CPET - VARIABLES, 9-PANEL DISPLAY, INTERPRETATION, AND LEVEL OF EVIDENCE

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Topics

- Indications
- Measured Parameters
- CPET Variables & Special Parameters
- Peak VO$_2$, VCO$_2$ & Ventilatory Threshold
- 9 Panel display
- Interpretation
- Clinical Stratification
- Assessment of CPET Variables
- Suitability of CPET Variables, Class Recommendations & Level of Evidence
Cardiopulmonary Exercise Testing*

*Abbreviated CPET or CPX

Metabolic cart (gas exchange), treadmill, and electrocardiogram monitor. Vyntus® CPX Metabolic Cart and pedal ergometer, showing mask with gas sensors.
Indications for CPET

- Evaluation of dyspnea of unclear etiology after routine cardiopulmonary testing.
- Determination of functional impairment in exercise intolerance.
- Heart failure.
- Evaluation for exercise-induced bronchospasm, and response to therapy.
- Preoperative evaluation prior to lung and/or heart surgery.
- Muscle-metabolic disorders.
- Athlete monitoring.
Table 1: Parameters measured during CPET

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal Volume</td>
<td>VT</td>
</tr>
<tr>
<td>Breathing frequency</td>
<td>Respiratory Rate (RR or f)</td>
</tr>
<tr>
<td>Minute Ventilation</td>
<td>$V_E = VT \times RR$</td>
</tr>
<tr>
<td>Rate of $O_2$ consumption</td>
<td>$O_2$ uptake ($V_{O_2}$)</td>
</tr>
<tr>
<td>Maximal $V_{O_2}$</td>
<td>$V_{O_2, max}$</td>
</tr>
<tr>
<td>Rate of $CO_2$ elimination</td>
<td>$CO_2$ output ($V_{CO_2}$)</td>
</tr>
<tr>
<td>Anaerobic threshold</td>
<td>AT, Also referred to as VT, Ventilatory Threshold - gases or lactate</td>
</tr>
<tr>
<td>Respiratory Exchange ratio/ RQ</td>
<td>$RER/RQ$</td>
</tr>
<tr>
<td>Heart Rate Reserve</td>
<td>(HRR)</td>
</tr>
<tr>
<td>HR vs. $V_{O_2}$ slope</td>
<td></td>
</tr>
<tr>
<td>$O_2$ pulse ($V_{O_2}/HR$)</td>
<td></td>
</tr>
<tr>
<td>Ventilatory Reserve</td>
<td>(VR)</td>
</tr>
<tr>
<td>Maximal ventilation</td>
<td>($V_{Emax}$)</td>
</tr>
<tr>
<td>Ventilatory Equivalents for $O_2$ and $CO_2$</td>
<td>($V_L/V_{O_2}$ and $V_L/V_{CO_2}$)</td>
</tr>
<tr>
<td>End-tidal $O_2$</td>
<td>$PETO_2$ (partial pressure of end-tidal oxygen)</td>
</tr>
<tr>
<td>End-tidal $CO_2$</td>
<td>$PETCO_2$</td>
</tr>
<tr>
<td>Dead space/Tidal volume</td>
<td>$V_D/V_T$</td>
</tr>
</tbody>
</table>

Special Parameters...

- **MET (metabolic equivalent):** The ratio of the *work metabolic rate* to the *resting metabolic rate*. One MET is defined as 1 kcal/kg/hour and is roughly equivalent to the energy cost of sitting quietly.

- **MMV (maximum voluntary ventilation):** A measure of the *maximum amount of air* that can be inhaled and exhaled within one minute.

- **RER (respiratory exchange ratio):** The respiratory exchange ratio is the ratio between the amount of *carbon dioxide* produced in metabolism and *oxygen* used. The ratio is determined by comparing *exhaled gases to room air*. 
- **VE (minute ventilation):** the *volume* of gas inhaled (inhaled minute volume) or exhaled (exhaled minute volume) from a person's lungs per minute.

- **VE/VO₂ and VE/VCO₂:** These are the *Ventilatory Equivalents* for O₂ and CO₂. They describe the ratio of ventilation (minute volume) to oxygen intake, or to carbon dioxide output.

  - A measure of instantaneous ventilatory and gas exchange efficiency.
  
  - Tells how many liters does the patient have to breath in order to uptake 1 liter of oxygen or to produce 1 liter of carbon dioxide?
AT (Anaerobic Threshold) or VT (Ventilatory Threshold): refers to the point during exercise at which ventilation starts to increase at a faster rate than VO₂ (volume of oxygen). Two thresholds;

- VT₁
  - It is a marker of intensity that can be observed in a person's breathing at a point where lactate begins to accumulate in the blood.
  - As the intensity of the exercise begins to increase, VT₁ can be identified at the point where the breathing rate begins to increase.

- VT₂
  - At VT₂, lactate has quickly accumulated in the blood and the person needs to breathe heavily.
  - At this rapid rate of breathing, the exerciser can no longer speak.
Peak \( \text{Vo}_2 \)

- **Global marker of fitness.** It represents the combination of ventricular systolic and diastolic function (cardiac output), vascular function (\( \text{O}_2 \) delivery), and peripheral skeletal muscle metabolic capacity (\( \text{O}_2 \) utilization).

- According to the Fick principle, \( \text{VO}_2 \) is determined by
  - Heart rate, stroke volume, the concentration of hemoglobin and its capacity to transport oxygen.
  - Difference between arterial oxygen saturation (reflecting lung problems and other right-to-left shunts), and
  - Mixed venous oxygen saturation (reflecting peripheral blood flow distribution and oxygen extraction in the muscle).

Peak VO\textsubscript{2}, VCO\textsubscript{2} & Ventilatory Threshold...

**Peak VO\textsubscript{2}**
Highest oxygen uptake obtained (aerobic capacity)
Values vary widely with age, sex, activity level, weight, and disease (< 20 mL/kg/min in elderly; > 90 in elite athletes)
Nonspecific but starting point for interpretation and stratification
Peak VO\textsubscript{2} \geq 85\% of predicted is generally favorable; \leq 14 mL/kg/min carries a poor prognosis in heart failure (\leq 10 if on beta-blockers)

**Ventilatory threshold**
Point at which anaerobic metabolism increases
VO\textsubscript{2} at ventilatory threshold typically is 40\%–60\% of peak VO\textsubscript{2}
A low value is consistent with deconditioning or disease; a high value is consistent with athletic training

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*FIGURE 1. Diagram of response to work. Impairment from any cause will lower the peak VO\textsubscript{2} and ventilatory threshold.*

Recall: $VE/VCO_2$ or $VE/VO_2$ (ventilatory equivalent): describes the ratio of ventilation (minute volume) to oxygen intake, or to carbon dioxide output.
Vo2 vs Heart Rate; Level of Conditioning & Heart Failure...

Note that Maximal Predicted HR = (220-Age) x 85%

Plots 1-3

Normal

Plots 7-9

Normal

Heart Disease

**VE/VCO₂ (minute ventilation/CO₂ output)**

**VE/VCO₂ slope**
Ventilatory volume/carbon dioxide output; reflects ventilatory efficiency
Normal 25–30
May be slightly elevated in isolation in otherwise healthy elderly patients
Elevated value reflects ventilatory inefficiency or ventilation-perfusion mismatch
Values ≥ 34 indicate clinically significant cardiopulmonary disease (heart failure, pulmonary hypertension, chronic obstructive pulmonary disease
Higher values = worse prognosis

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### Cardiopulmonary exercise testing scoring system for patients with heart failure

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<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Points</th>
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<tr>
<td>Ventilation/carbon dioxide (Ve/Vco₂) slope</td>
<td>≥ 34</td>
<td>7</td>
</tr>
<tr>
<td>Heart rate recovery</td>
<td>≤ 6 bpm</td>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Oxygen uptake efficiency slope</td>
<td>≤ 1.4</td>
<td>2</td>
</tr>
<tr>
<td>Peak Vo₂</td>
<td>≤ 14 mL/kg/min</td>
<td>2</td>
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</table>

Score > 15 points: annual mortality rate 12.2%; relative risk > 9 for transplant, left ventricular assist device, or cardiac death.
Score < 5 points: annual mortality rate 1.2%.

<sup>a</sup> Maximum heart rate minus heart rate at 1 minute in recovery.

<sup>b</sup> 2 points if on a beta-blocker.

Recall: $\frac{VE}{VCO_2}$ (ventilatory equivalent): describes the ratio of ventilation (minute volume) to carbon dioxide output.

**Ve/VCO₂ slope**
- Ventilatory volume/carbon dioxide output; reflects ventilatory efficiency
- Normal 25–30
- May be slightly elevated in isolation in otherwise healthy elderly patients
- Elevated value reflects ventilatory inefficiency or ventilation-perfusion mismatch
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- Higher values = worse prognosis


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Score > 15 points: annual mortality rate 12.2%; relative risk > 9 for transplant, left ventricular assist device, or cardiac death.
Score < 5 points: annual mortality rate 1.2%.
a Maximum heart rate minus heart rate at 1 minute in recovery.
b 2 points if on a beta-blocker.
What cardiopulmonary exercise test patterns suggest

Nonspecific: suggest significant cardiopulmonary or metabolic impairment of any sort
Peak VO₂ < 80% of predicted
VE/VCO₂ slope > 34
Ventilatory (anaerobic) threshold < 40% of peak VO₂

Deconditioning
Low-normal peak VO₂
Low ventilatory (anaerobic) threshold
Absence of any other abnormal responses

Obesity
Increased VO₂/work slope
Indexed peak VO₂ (mL/kg/min) less than predicted
Absolute VO₂ (L/min) normal or greater than predicted
Oxygen indexed to lean body mass normal or greater than predicted

continued...
Cardiac limitations
Oxygen pulse ($O_2$-pulse) < 80% predicted or flattened or falling curve
Chronotropic incompetence
Heart rate recovery ≤ 12 beats per minute after 1 minute of recovery
Standard electrocardiographic criteria for ischemia

Pulmonary limitations
Peak exercise respiratory rate > 50 per minute
Ventilatory reserve (peak $V_e/M_vv$) < 15%
Oxygen desaturation by pulse oximetry
Abnormal results on pretest screening spirometry
Abnormal exercise flow-volume loops

Muscular disease
Submaximal cardiac and respiratory responses
Ventilatory (anaerobic) threshold < 40% of peak $V_o_2$
Elevated lactate at any given level of submaximal work
Heart Rate
(beats per min.)

VO₂ and VCO₂
(Rate of O₂ uptake and CO₂ output in L/min.)

VE and RER
(Minute ventilation and Respiratory Exchange Ratio. Ratio between the amount of carbon dioxide produced in metabolism and oxygen used.)

(VO₂/HR) or O₂ Pulse
(ml/beat)

PetO₂
(Partial Pressure of End Tidal O₂)

PetCO₂

(VO₂/HR) or O₂ Pulse
(ml/beat)

Ventilatory Threshold or AT
Exercise oscillatory breathing
Abnormal breathing pattern often seen in heart failure; no universal definition
Sustained visible fluctuations in ventilations support a poorer prognosis


### TABLE 1 Clinical Stratification for Patients With HF

<table>
<thead>
<tr>
<th>Primary CPET Variables</th>
<th>EDV</th>
<th>(P_{ET}CO_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventilatory Class I</strong></td>
<td>Peak (V_{O_2}) &gt;20.0 ml·kg(^{-1})·min(^{-1})</td>
<td>Not Present</td>
</tr>
<tr>
<td>VE/(V_{O_2}) slope &lt;30.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ventilatory Class II</strong></td>
<td>Peak (V_{O_2}) = 16.0-20.0 ml·kg(^{-1})·min(^{-1})</td>
<td>Present</td>
</tr>
<tr>
<td>VE/(V_{O_2}) slope 30.0-35.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ventilatory Class III</strong></td>
<td>Peak (V_{O_2}) = 10.0-15.0 ml·kg(^{-1})·min(^{-1})</td>
<td></td>
</tr>
<tr>
<td>VE/(V_{O_2}) slope 36.0-44.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ventilatory Class IV</strong></td>
<td>Peak &lt;10.0 ml·kg(^{-1})·min(^{-1})</td>
<td></td>
</tr>
<tr>
<td>VE/(V_{O_2}) slope ≤45.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Standard ET Variables

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>ECG</th>
<th>HRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rise in systolic BP during ET</td>
<td>No sustained arrhythmias, ectopic foci, and/or ST-segment changes during ET and/or in recovery</td>
<td>&gt;12 beats at 1 min recovery</td>
</tr>
<tr>
<td>Flat systolic BP response during ET</td>
<td>Altered rhythm, ectopic foci, and/or ST-segment changes during ET and/or in recovery, did not lead to test termination</td>
<td>&lt;12 beats at 1 min recovery</td>
</tr>
<tr>
<td>Drop in systolic BP during ET</td>
<td>Altered rhythm, ectopic foci, and/or ST-segment changes during ET and/or in recovery, led to test termination</td>
<td></td>
</tr>
</tbody>
</table>

### Patient Reason for Test Termination

- Lower extremity muscle fatigue
- Angina
- Dyspnea

### Interpretation

- All variables in green: excellent prognosis in the next 1-4 years (>90% event-free)
  - Maintain medical management and retest in 4 years
- Greater number of CPET and standard ET variables in red/yellow/orange indicative of progressively worse prognosis.
  - All CPET variables in red: risk for major adverse event extremely high in next 1-4 years (>50%)
- Greater number of CPET and standard ET variables in red/yellow/orange indicative of increasing HF disease severity.
  - All CPET variables in red: expected significantly diminished cardiac output, elevated neurohormones, higher potential for secondary PH.
- Greater number of CPET and standard ET variables in red/yellow/orange warrants strong consideration of more aggressive medical management and surgical options.
Table 1
Assessment of CPET variables

<table>
<thead>
<tr>
<th></th>
<th>Peak $\dot{V}_{O_2}$</th>
<th>$\dot{V}<em>{E}/\dot{V}</em>{CO_2}$ slope</th>
<th>EOV</th>
<th>OUES</th>
<th>$P_{ET/CO_2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% predicted peak $\dot{V}_{O_2}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proof of concept</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Prospective validation</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Incremental value</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+/−</td>
<td>+/−</td>
</tr>
<tr>
<td>Clinical utility</td>
<td>++</td>
<td>+++</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Clinical outcomes</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Ease of use</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Methodological consensus</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Reference values</td>
<td>Yes</td>
<td>Yes</td>
<td>Not necessary</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Peak $\dot{V}_{O_2}$ = peak oxygen uptake; $\dot{V}_{E}/\dot{V}_{CO_2}$ slope = minute ventilation to carbon dioxide production slope; EOV = exercise oscillatory ventilation; OUES = oxygen uptake efficiency slope; $P_{ET/CO_2}$ = the partial pressure of end-tidal CO₂

+++ = criteria fully met, very large evidence base
+++ = criteria fully met, large evidence base
++ = criteria met, moderate evidence base
+ = minimal requirements of criteria met, small evidence base
+/− = criteria partly met and/or contradictory literature
− = criteria not met


<table>
<thead>
<tr>
<th>Table II</th>
<th>Suitability of CPET variables for primary and secondary HFREF prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recommendation</td>
</tr>
<tr>
<td>Peak (\dot{V}O_2)/</td>
<td>I</td>
</tr>
<tr>
<td>% predicted peak (\dot{V}O_2)</td>
<td>I</td>
</tr>
<tr>
<td>(\dot{V}_E-\dot{V}CO_2) slope</td>
<td>Ila</td>
</tr>
<tr>
<td>EOV</td>
<td>IIb</td>
</tr>
<tr>
<td>OUES</td>
<td>IIb</td>
</tr>
<tr>
<td>(P_{ET}CO_2)</td>
<td>IIb</td>
</tr>
</tbody>
</table>

Class recommendations system used by Arena et al.\(^7\):
- I = CPET is clearly prognostic/diagnostic & gauges therapeutic efficacy;
- IIa = CPET is likely prognostic/diagnostic & likely gauges therapeutic efficacy;
- IIb = CPET may be prognostic/diagnostic & may gauge therapeutic efficacy;
- III = CPET is not prognostic/diagnostic & does not gauge therapeutic efficacy.

Level of evidence ratings used by Arena et al.\(^7\):
- Level A = Multiple investigations, possibly one or more meta-analyses, prospective study design
- Level B = Several investigations, total number of studies not considered definitive because of total number and/or study quality, mix of retrospective and prospective designs
- Level C = Scientific evidence, limited, expert opinions
Summary

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