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

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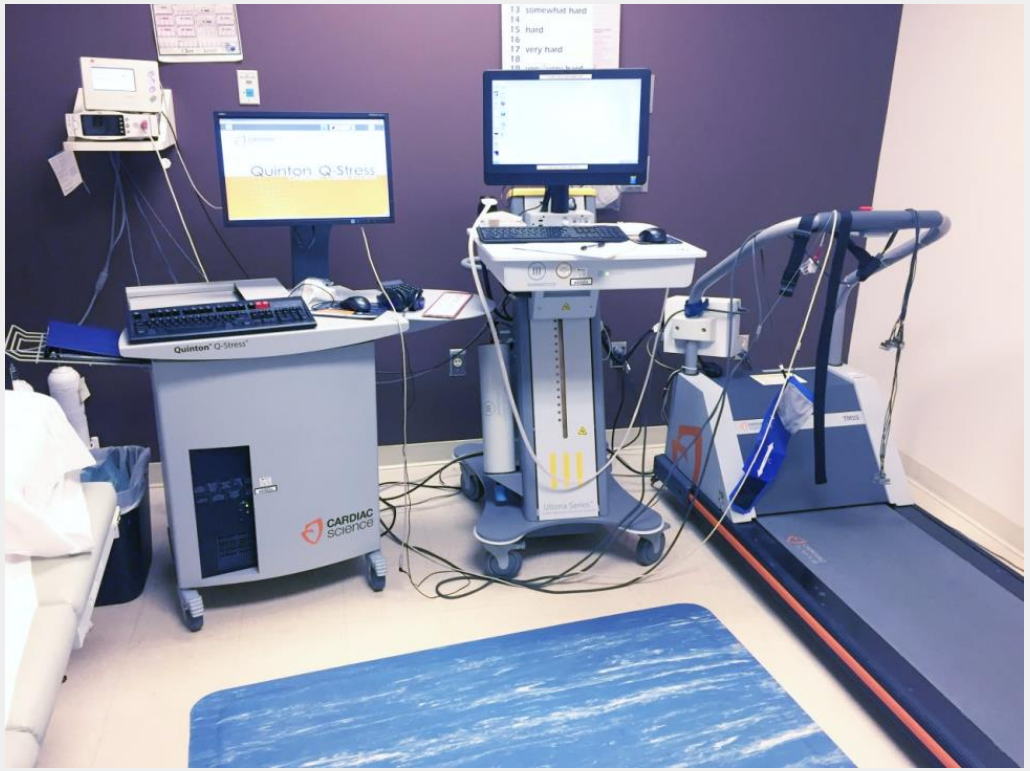
https://saliterman.umn.edu/physiology

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),tread mill 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

Tidal Volume: VT
Breathing frequency: Respiratory Rate (RR or f)
Minute Ventilation: V_E = VT × RR
Rate of O_2 consumption: O_2 uptake (V_{O2})
Maximal V_{O2}: $V_{O2\ max}$
Rate of CO_2 elimination: CO_2 output (V_{CO2})
Anaerobic threshold: AT , Also referred to as V_T, Ventilatory Threshold - gases or lactate
Respiratory Exchange ratio/ Respiratory Quotient (RER/RQ)
Heart Rate Reserve (HRR)
HR *vs.* V_{O2} slope
O2 pulse (V_{O2}/HR)
Ventilatory Reserve (VR)
Maximal ventilation (V_{Emax})
Ventilatory Equivalents for O_2 and CO_2 (V_E/ V_{O2} and V_E/V_{CO2})
End-tidal O_2: $PETO_2$ (partial pressure of end-tidal oxygen)
End-tidal CO_2: $PETCO_2$
Dead space/Tidal volume: V_D /V_T

Datta D, Normandin E, ZuWallack R. Cardiopulmonary exercise testing in the assessment of exertional dyspnea. *Ann Thorac Med.* 2015;10(2):77-86.

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*.

- V_E (minute ventilation): the *volume* of gas inhaled (inhaled minute volume) or exhaled (exhaled minute volume) from a person's lungs per minute.
- V_E/VO_2 and V_E/VCO_2: These are the *Ventilatory Equivalents* for O2 and CO2. They describes 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 V_T (Ventilatory Threshold): refers to the point during exercise at which ventilation starts to increase at a faster rate than VO_2 (volume of oxygen). Two thresholds;
  - V_{T1}
    - 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, V_{T1} can be identified at the point where the breathing rate begins to increase.
  - V_{T2}
    - At V_{T2}, 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 Vo_2

- *Global marker of fitness.* It represents the combination of ventricular systolic and diastolic function (cardiac output), vascular function (O_2 delivery), and peripheral skeletal muscle metabolic capacity (O_2 utilization).
- According to the Fick principle, 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).

Wagner J, Agostoni P, Arena R, et al. The Role of Gas Exchange Variables in Cardiopulmonary Exercise Testing for Risk Stratification and Management of Heart Failure with Reduced Ejection Fraction. *Am Heart J.* 2018;202:116-126.

Peak Vo_2, Vco_2 & Ventilatory Threshold...

Peak Vo_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_2 ≥ 85% of predicted is generally favorable; ≤ 14 mL/kg/min carries a poor prognosis in heart failure (≤ 10 if on beta-blockers)

Ventilatory threshold

Point at which anaerobic metabolism increases

Vo_2 at ventilatory threshold typically is 40%–60% of peak Vo_2

A low value is consistent with deconditioning or disease; a high value is consistent with athletic training

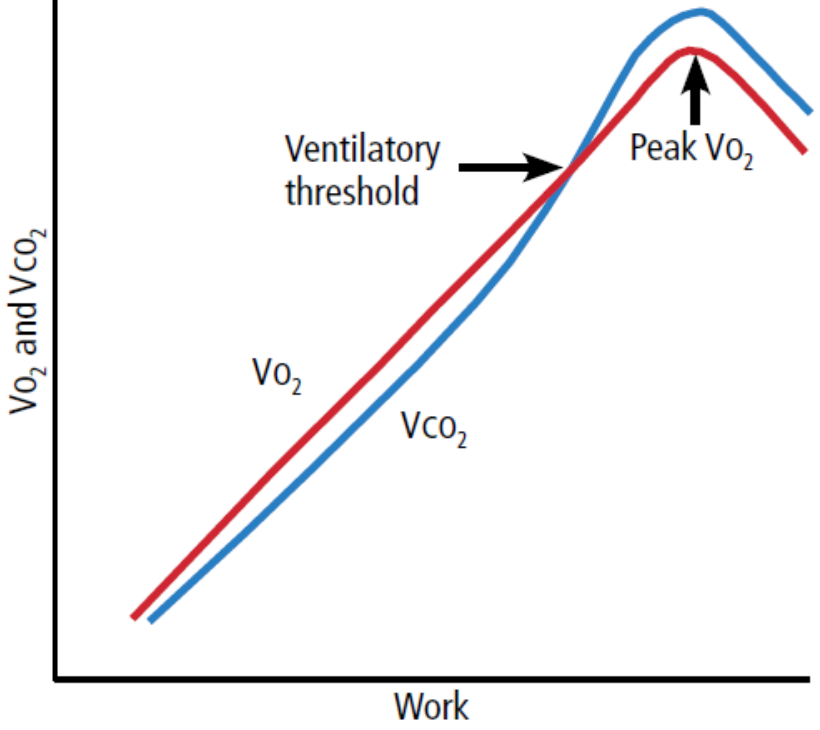


FIGURE 1. Diagram of response to work. Impairment from any cause will lower the peak Vo_2 and ventilatory threshold.

Leclerc K. Cardiopulmonary exercise testing: A contemporary and versatile clinical tool. *Cleve Clin J Med.* 2017;84(2):161-168.

Ventilatory Threshold.....

Ventilatory threshold
Point at which anaerobic metabolism increases
V_{O_2} at ventilatory threshold typically is 40%–60% of peak V_{O_2}
A low value is consistent with deconditioning or disease; a high value is consistent with athletic training

Recall: V_E/VCO_2 or V_E/VO_2 (ventilatory equivalent): describes the ratio of ventilation (minute volume) to oxygen intake, or to carbon dioxide output.

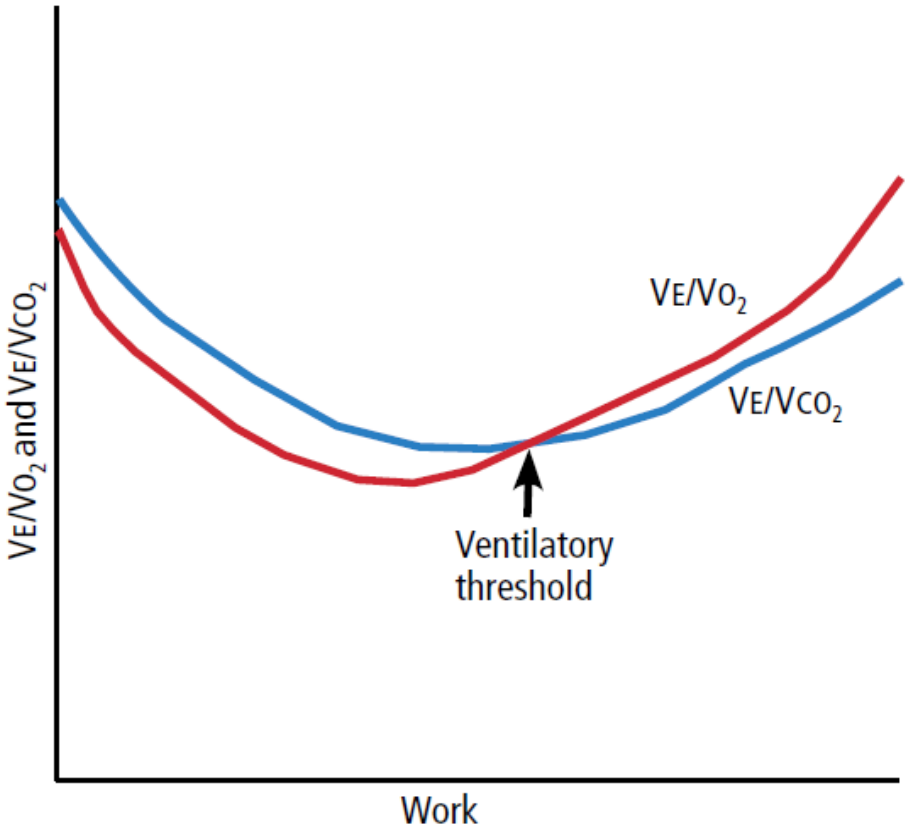


FIGURE 2. One method of determining the ventilatory threshold is to determine the intersection of the V_E/V_{O_2} and V_E/V_{CO_2} curves.

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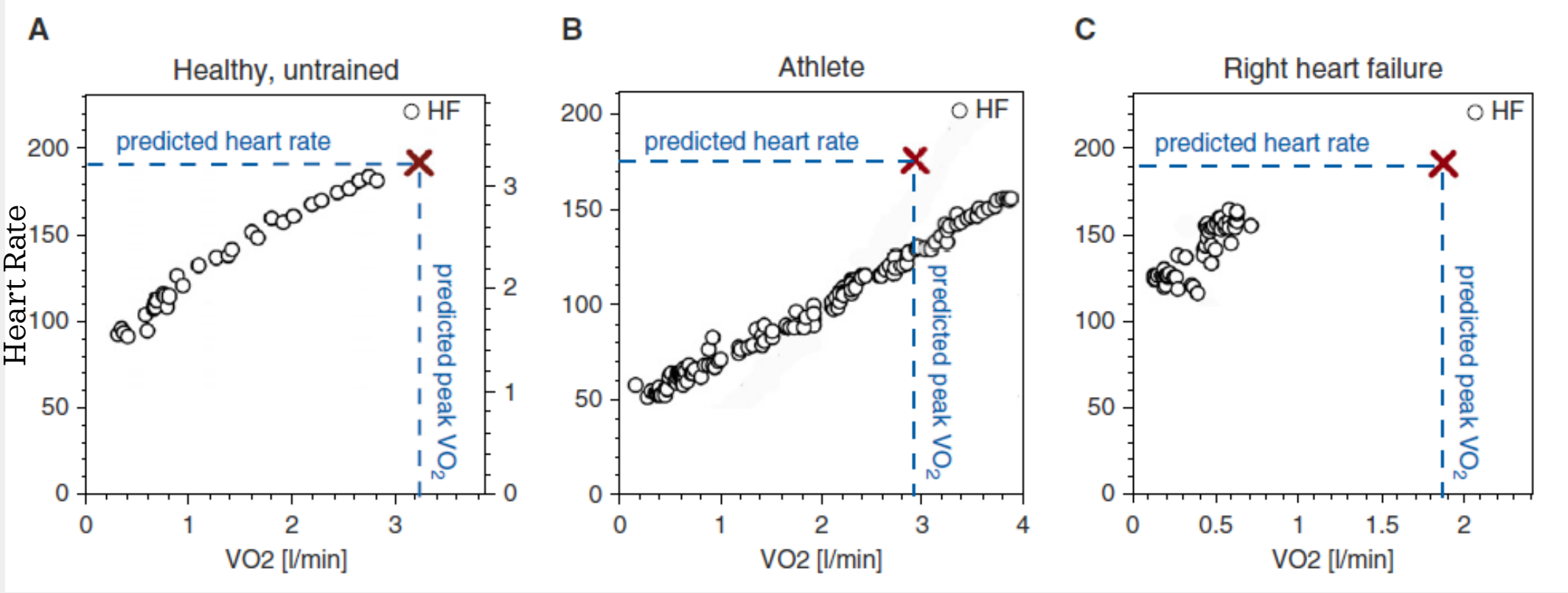
Vo_2 vs Heart Rate; Level of Conditioning & Heart Failure…

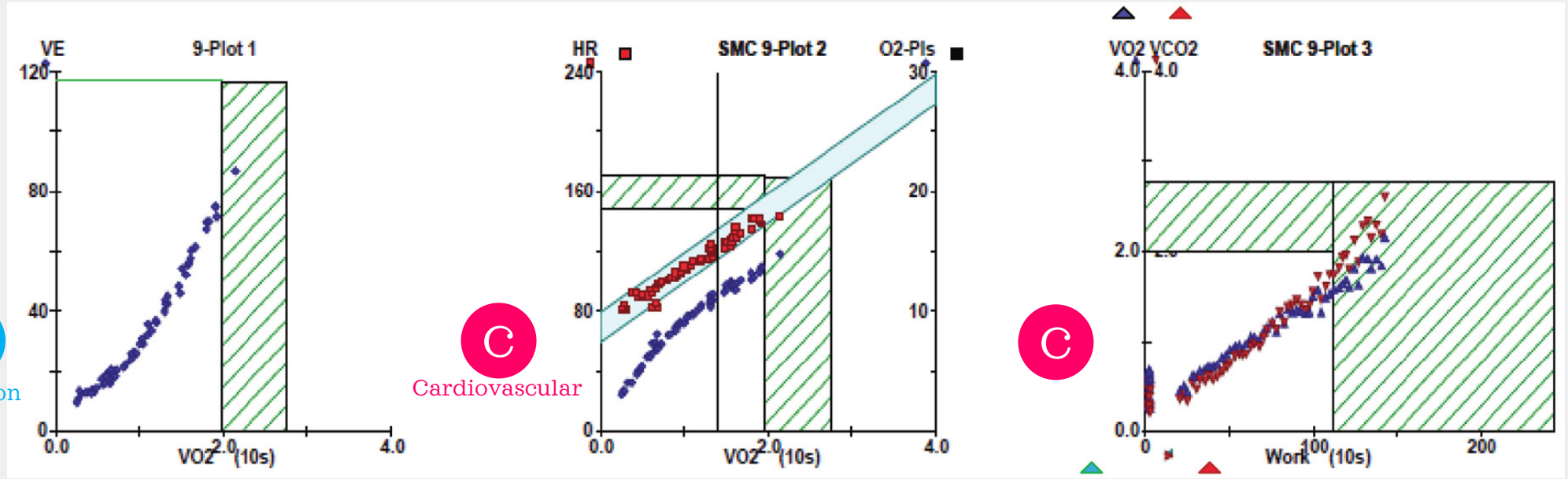


Note that Maximal Predicted HR = (220-Age) x 85%

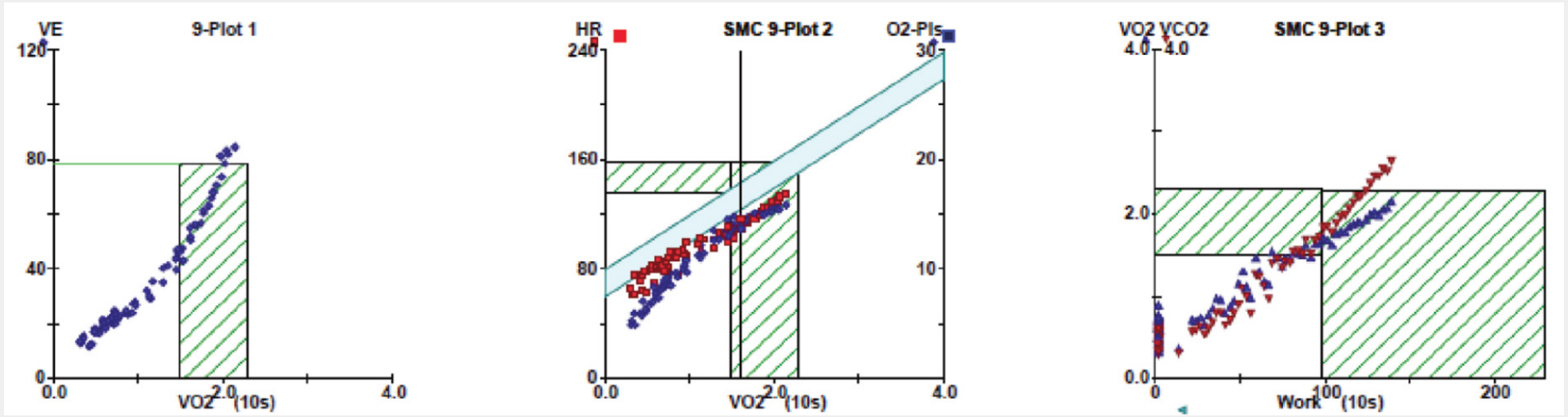
Dumitrescu D, Rosenkranz S. Graphical Data Display for Clinical Cardiopulmonary Exercise Testing. *Annals of the American Thoracic Society*. 2017;14(Supplement_1):S12-S21.

Plots 1-3

Normal



Lung Disease



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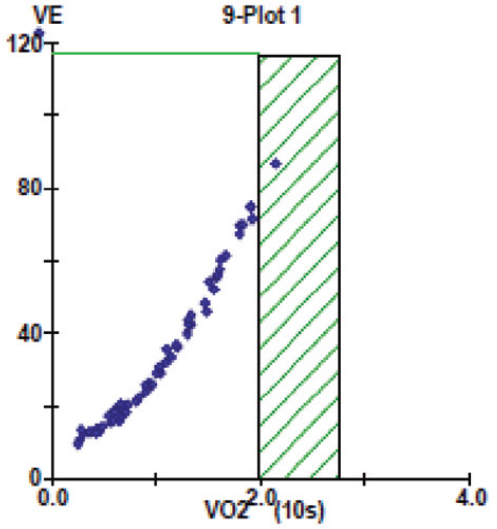
Plots 1-3

Normal

V



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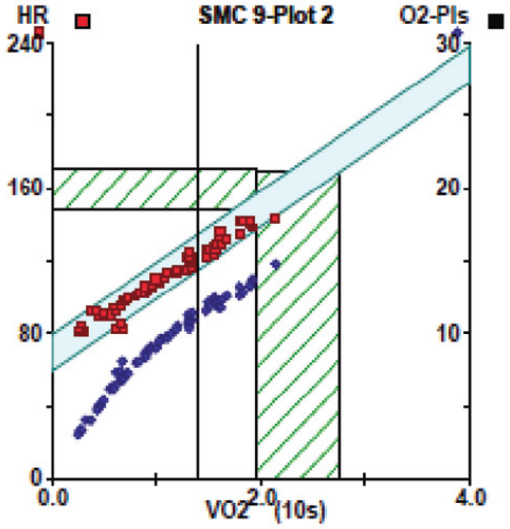

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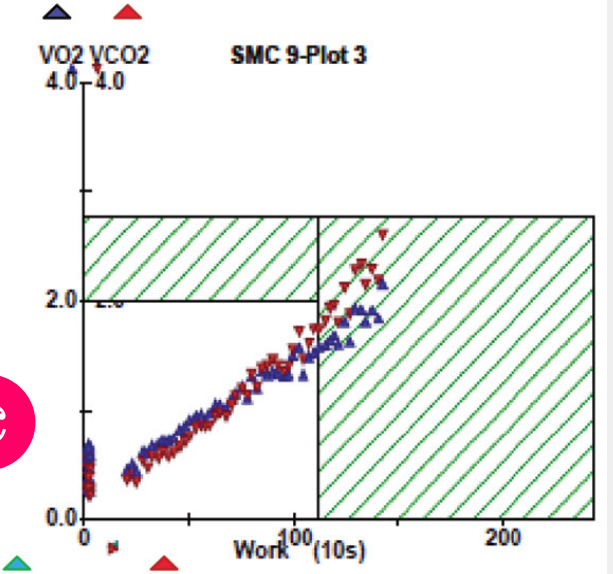
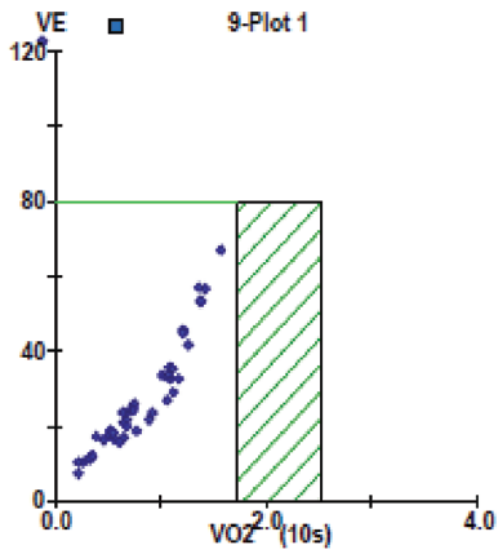
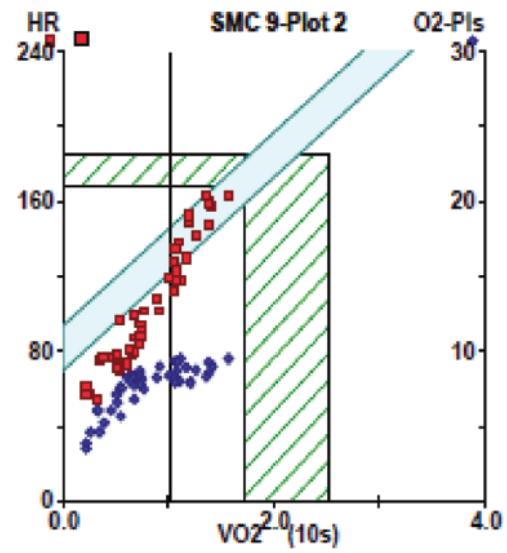
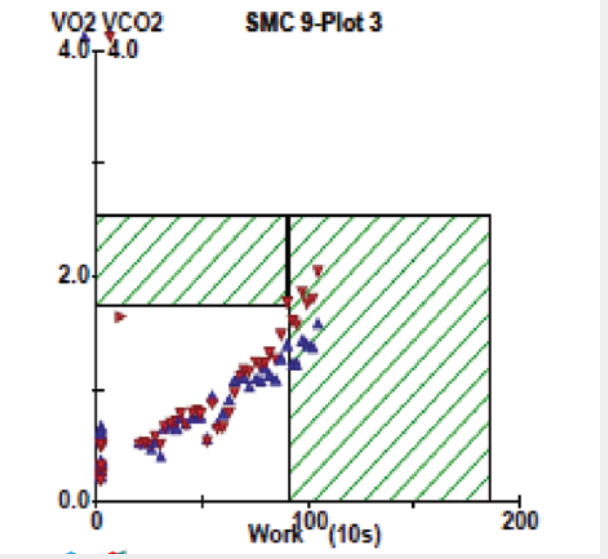


Heart Disease







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Plots 4-6

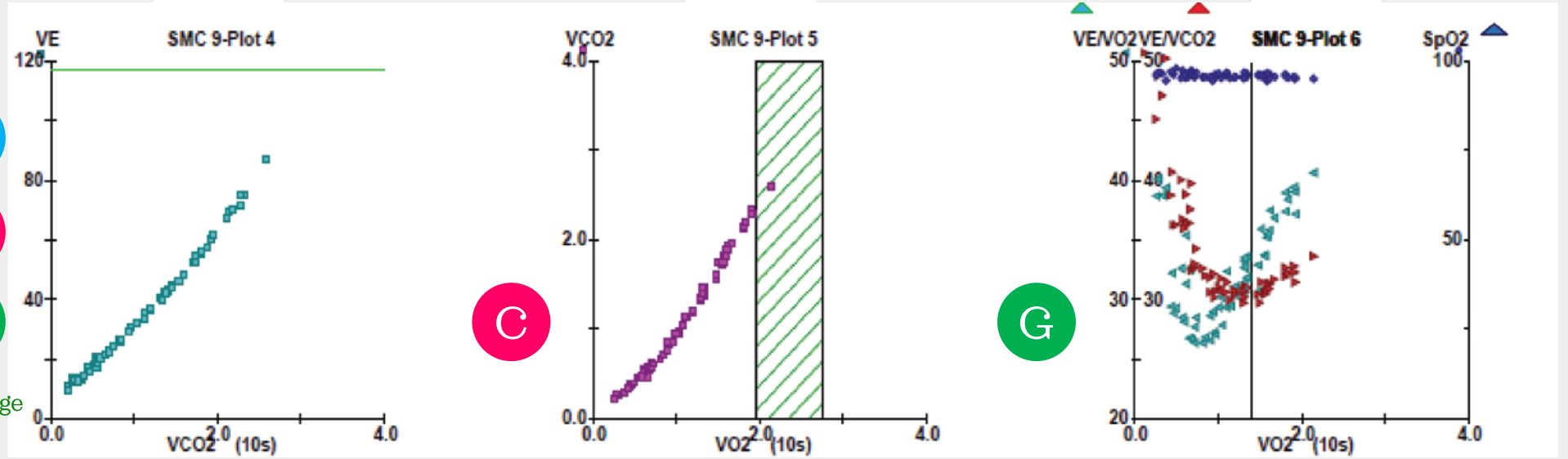
V

C

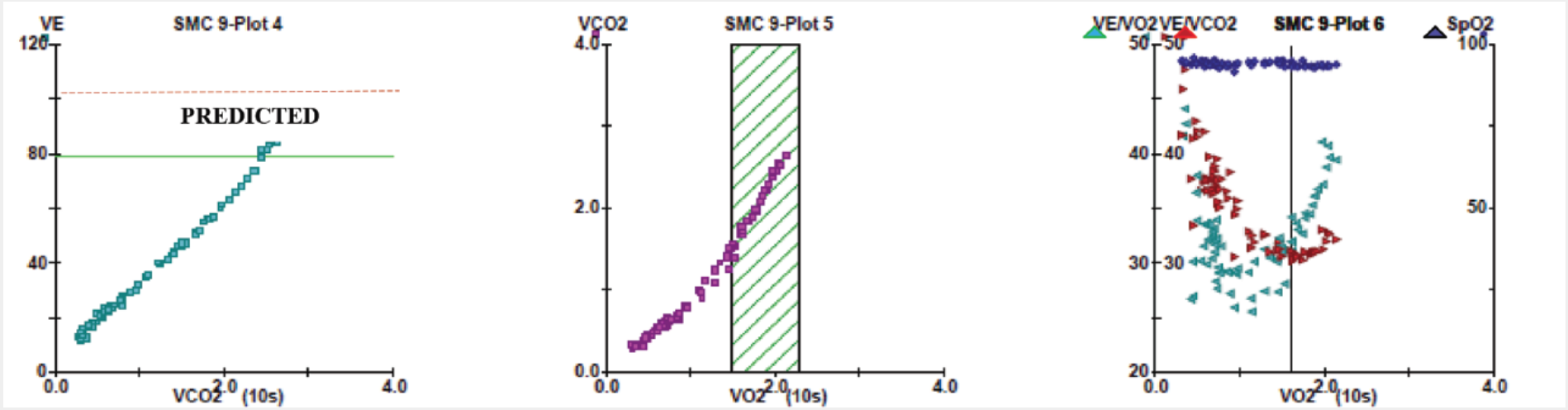
G

Gas Exchange

Normal



Lung Disease



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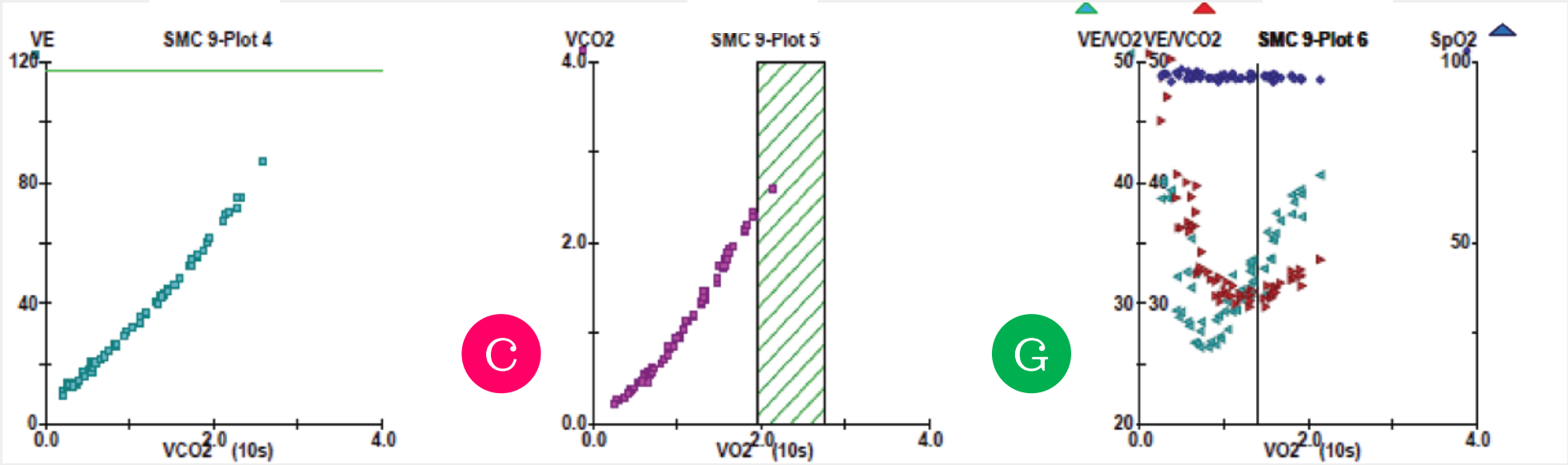
Plots 4-6

Normal

V

C

G



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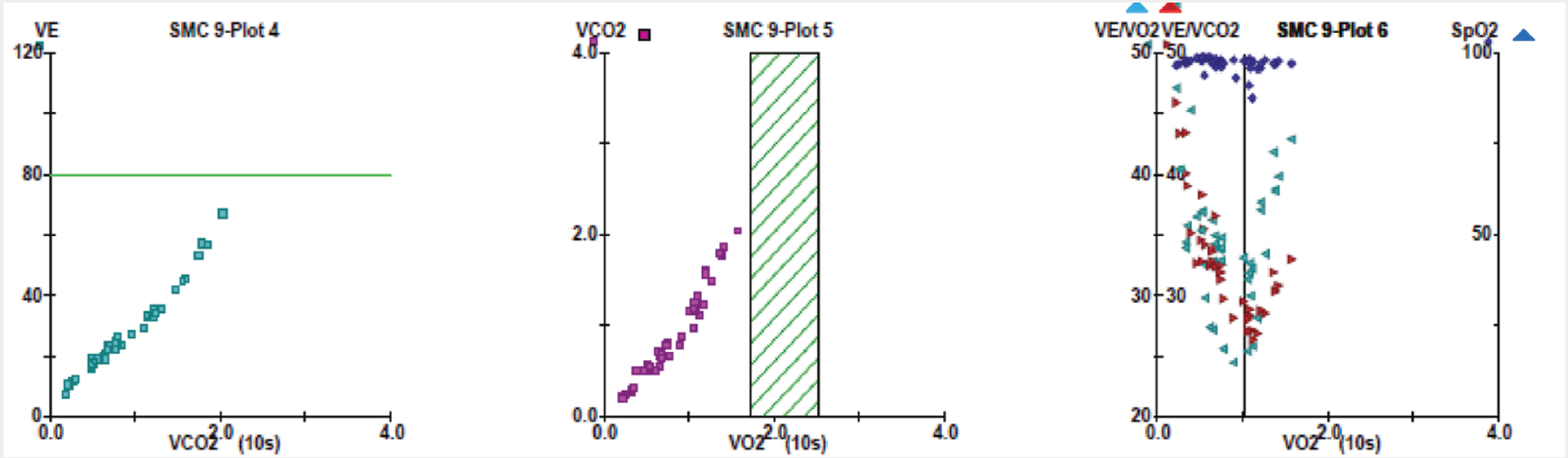

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Plots 7-9

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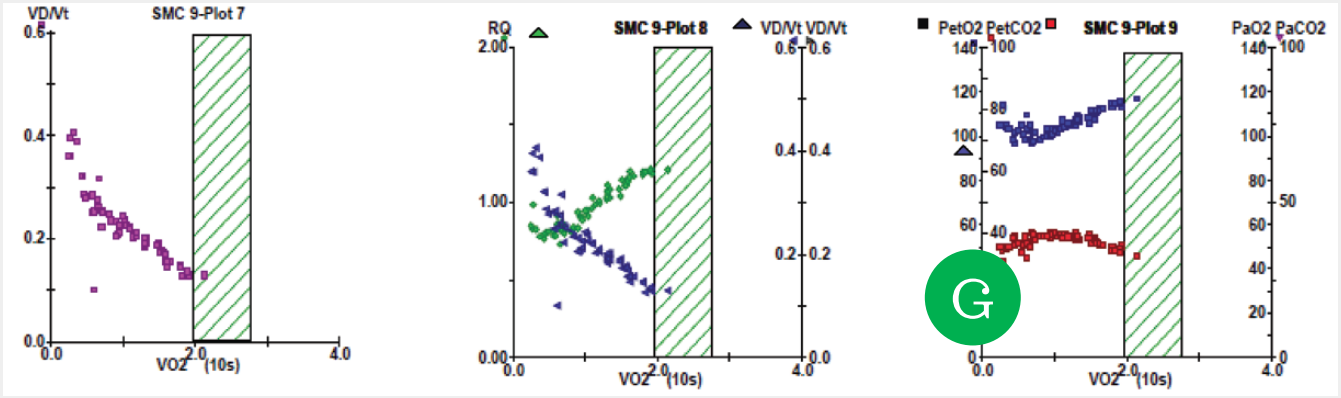

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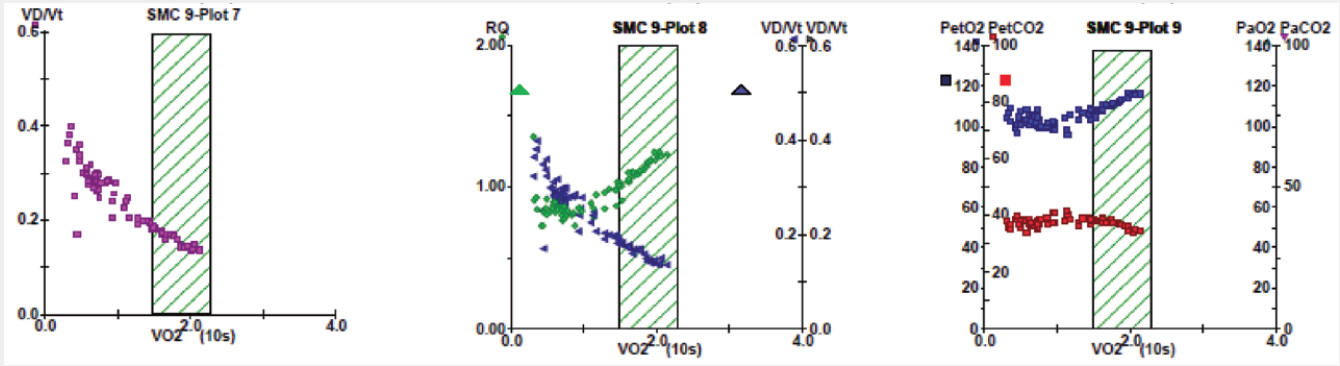

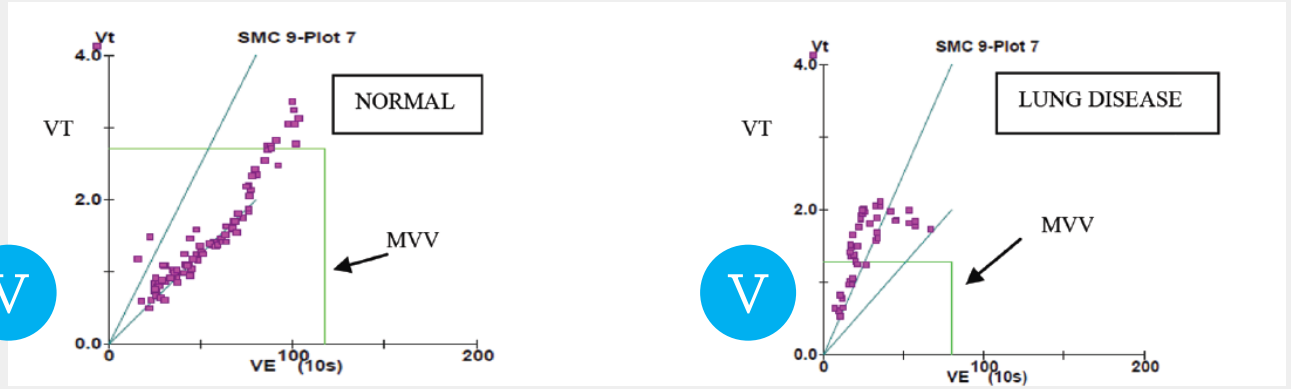

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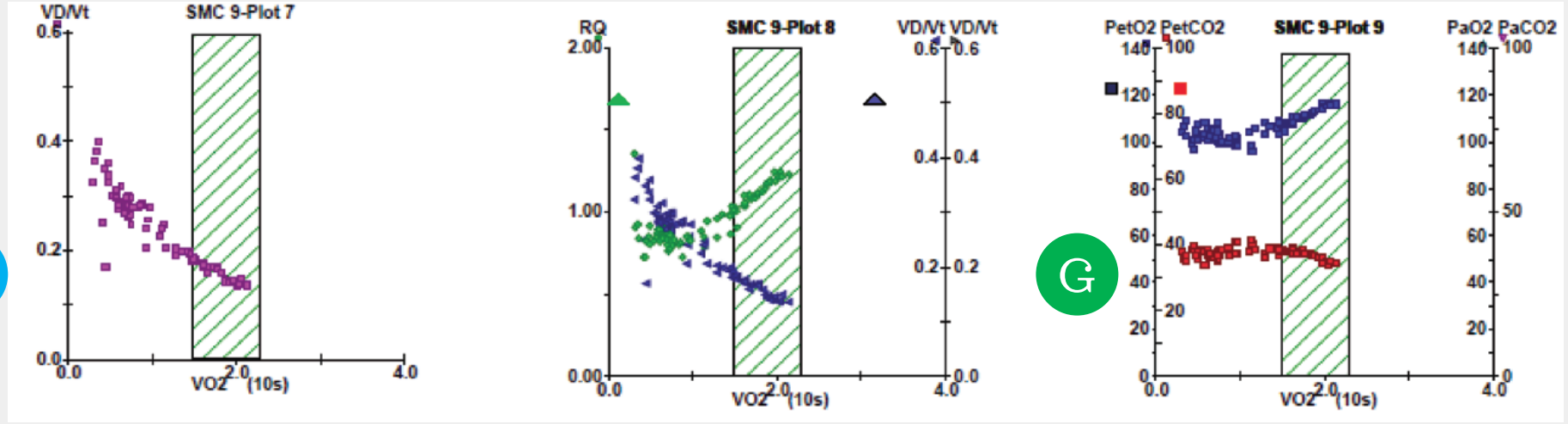
V



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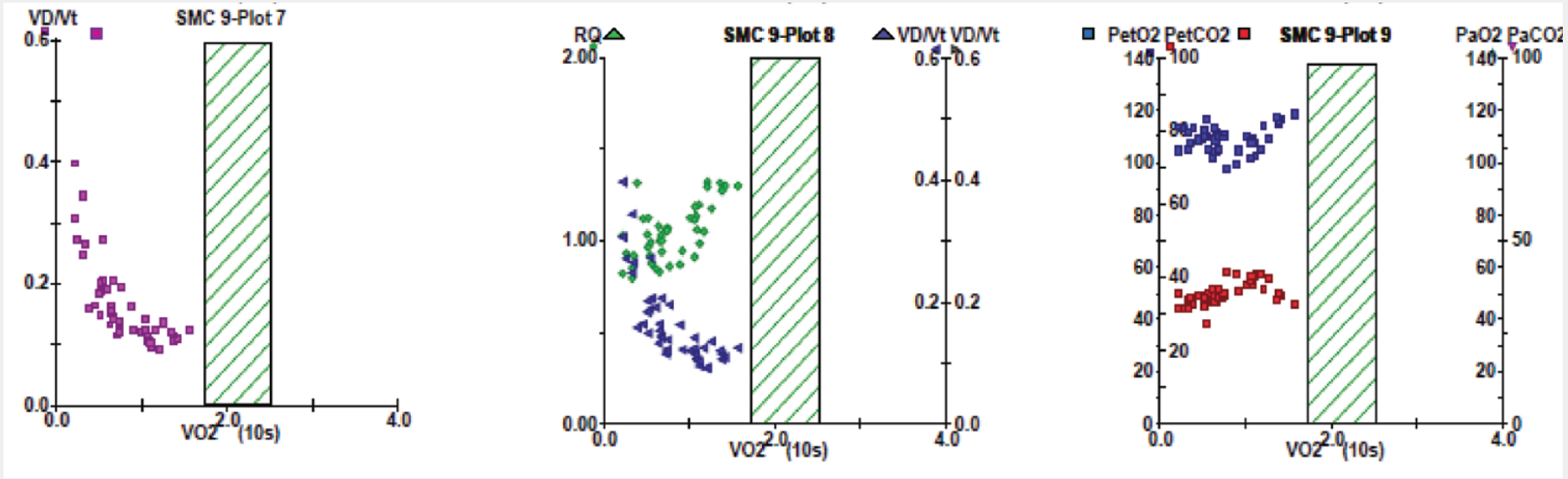

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V_E/V_{CO_2} (minute ventilation/CO_2 output)…

V_E/V_{CO_2} slope

Ventilatory volume/carbon dioxide output; reflects ventilatory efficiency

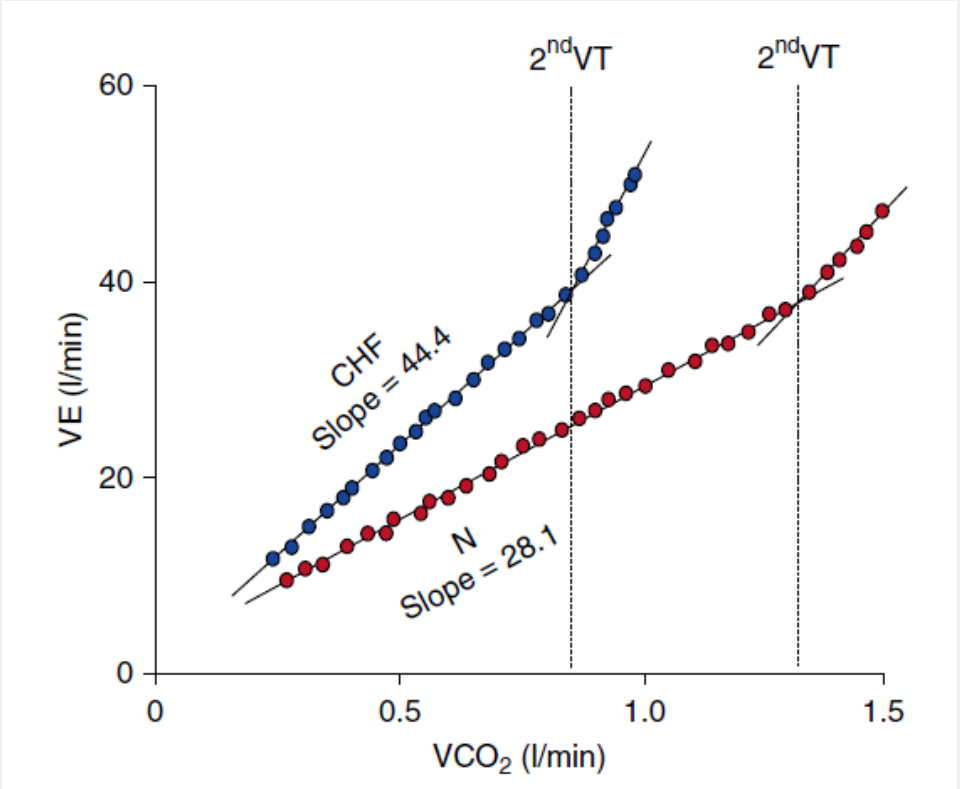
Normal 25–30

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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Mezzani A. Cardiopulmonary Exercise Testing: Basics of Methodology and Measurements. *Annals of the American Thoracic Society.* 2017;14(Supplement_1):S3-S11.

Scoring for Heart Failure …

Cardiopulmonary exercise testing scoring system for patients with heart failure

Variable	Value	Points
Ventilation/carbon dioxide (V_E/V_{CO_2}) slope	≥ 34	7
Heart rate recovery [a]	≤ 6 bpm	5[b]
Oxygen uptake efficiency slope	≤ 1.4	2
Peak V_{O_2}	≤ 14 mL/kg/min	2

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.

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V_E/V_{CO_2}.....

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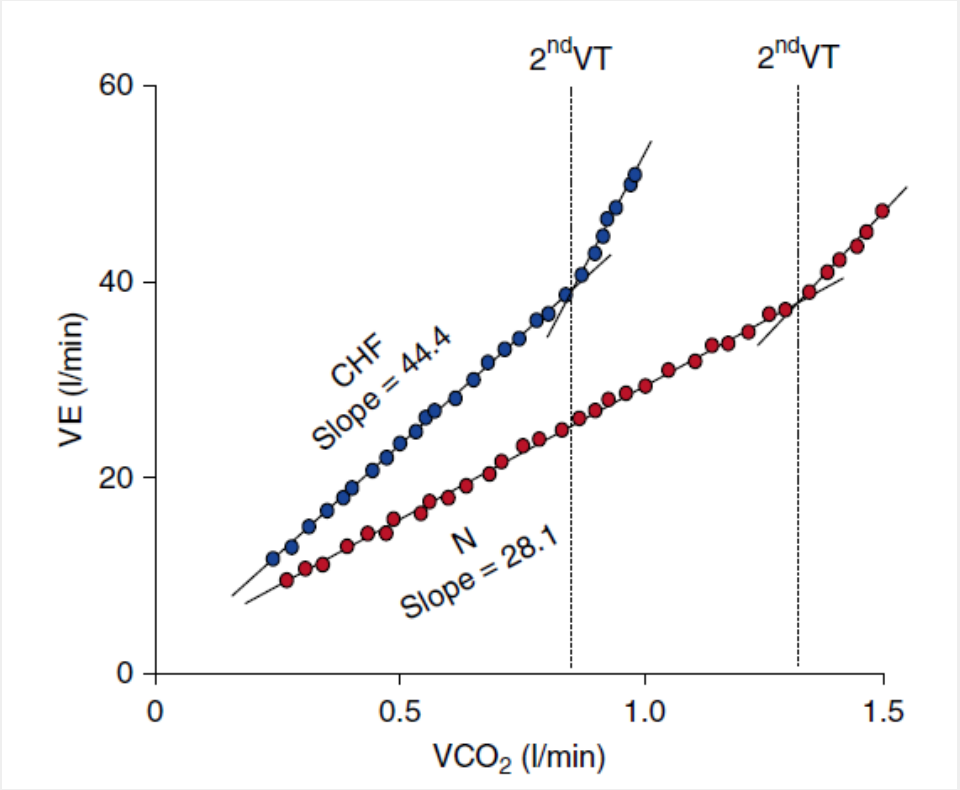

Recall: V_E/V_{CO_2} (ventilatory equivalent): describes the ratio of ventilation (minute volume) to carbon dioxide output.

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What cardiopulmonary exercise test patterns suggest

Nonspecific: suggest significant cardiopulmonary or metabolic impairment of any sort

Peak Vo_2 < 80% of predicted
V_E/Vco_2 slope > 34
Ventilatory (anaerobic) threshold < 40% of peak Vo_2

Deconditioning

Low-normal peak Vo_2
Low ventilatory (anaerobic) threshold
Absence of any other abnormal responses

Obesity

Increased Vo_2/work slope
Indexed peak Vo_2 (mL/kg/min) less than predicted
Absolute Vo_2 (L/min) normal or greater than predicted
Oxygen indexed to lean body mass normal or greater than predicted

continued...

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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/MVV) < 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

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$\dot{V}O_2$ and $\dot{V}CO_2$

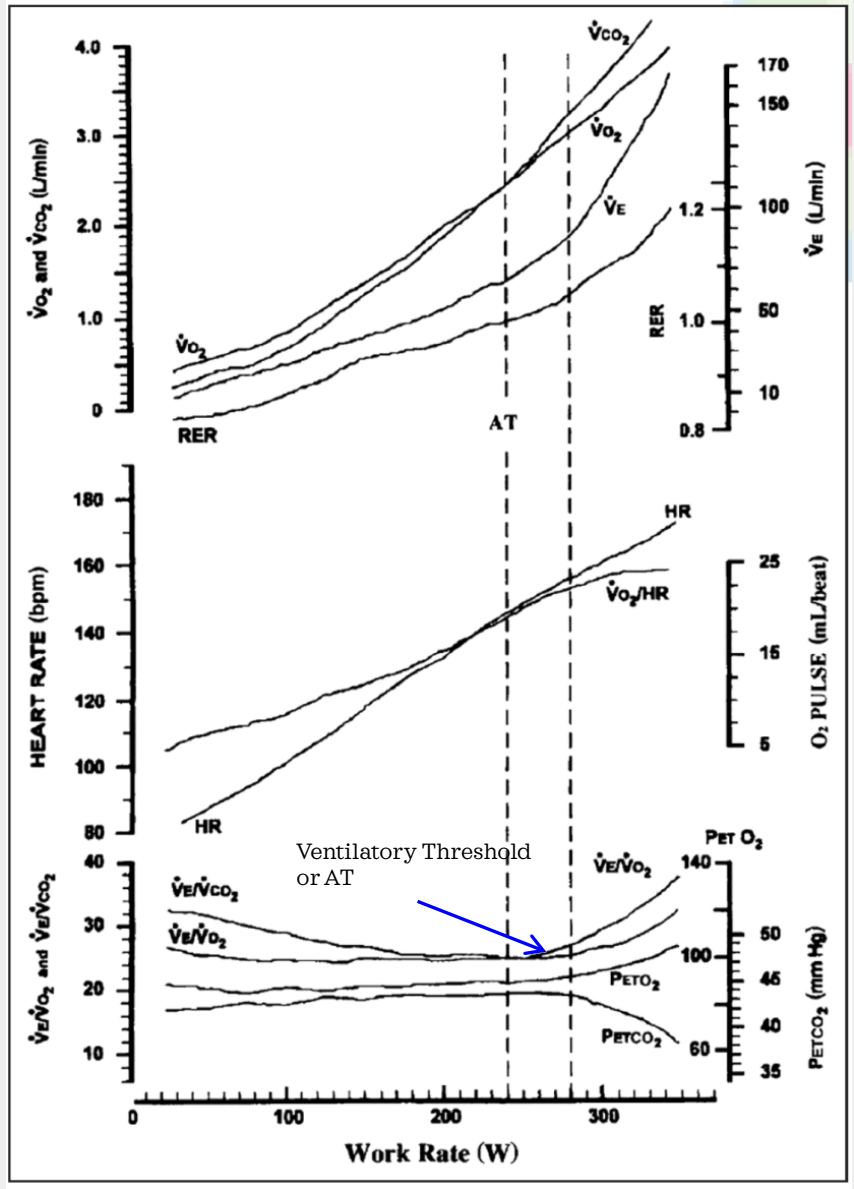
(O_2 uptake and CO_2 output in L/min.)

Heart Rate

(beats per min.)

$\dot{V}E/\dot{V}O_2$
$\dot{V}E/\dot{V}CO_2$

(Ventilatory Equivalents)



$\dot{V}E$ and RER

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

($\dot{V}O_2$/HR) or O_2 Pulse

(ml/beat)

$PETO_2$
$PETCO_2$

(Partial Pressure of End Tidal O_2 and CO_2)

Weisman, IM et al. , Clinical exercise testing. *Clinics in Chest Medicine* 2001, 22:4: 679.

Exercise oscillatory breathing

Abnormal breathing pattern often seen in heart failure; no universal definition

Sustained visible fluctuations in ventilations support a poorer prognosis

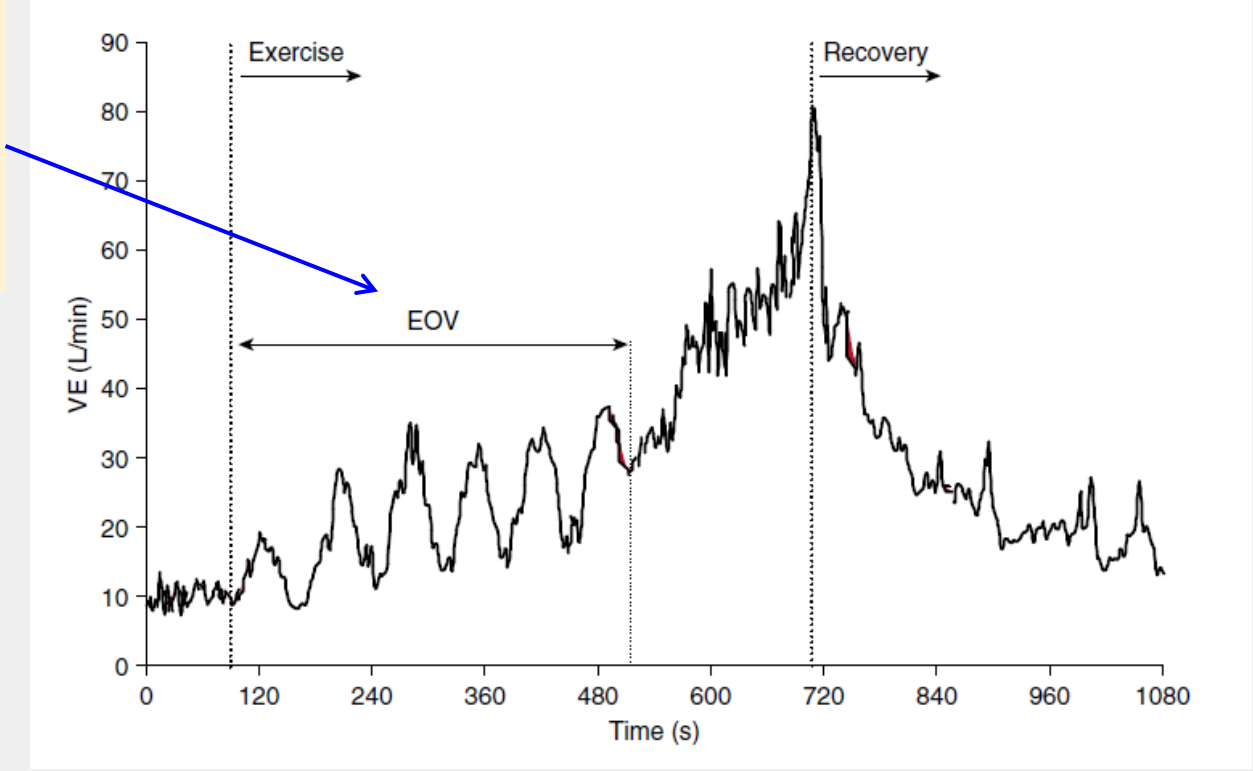


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TABLE 1 Clinical Stratification for Patients With HF

Primary CPET Variables

VE/Vco_2 Slope	Peak Vo_2	EOV	$P_{ET}CO_2$
Ventilatory Class I VE/Vco_2 slope <30.0	Ventilatory Class A Peak Vo_2 >20.0 $ml \cdot kg^{-1} \cdot min^{-1}$	Not Present	Resting $P_{ET}CO_2$ ≥33.0 mm Hg 3-8 mm Hg increase during ET
Ventilatory Class II VE/Vco_2 slope 30.0-35.9	Ventilatory Class B Peak Vo_2 = 16.0-20.0 $ml \cdot kg^{-1} \cdot min^{-1}$		
Ventilatory Class III VE/Vco_2 slope 36.0-44.9	Ventilatory Class C Peak Vo_2 = 10.0-15.9 $ml \cdot kg^{-1} \cdot min^{-1}$	Present	Resting $P_{ET}CO_2$ <33.0 mm Hg <3 mm Hg increase during ET
Ventilatory Class IV VE/Vco_2 slope ≥45.0	Ventilatory Class D Peak <10.0 $ml \cdot kg^{-1} \cdot min^{-1}$		

Standard ET Variables

Hemodynamics	ECG	HRR
Rise in systolic BP during ET	No sustained arrhythmias, ectopic foci, and/or ST-segment changes during ET and/or in recovery	>12 beats at 1 min recovery
Flat systolic BP response during ET	Altered rhythm, ectopic foci, and or ST-segment changes during ET and/or in recovery: did not lead to test termination	≤12 beats at 1 min recovery
Drop in systolic BP during ET	Altered rhythm, ectopic foci, and/or ST-segment changes during ET and/or in recovery: led to test termination	

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.

Guazzi M, Bandera F, Ozemek C, Systrom D, Arena R. Cardiopulmonary Exercise Testing: What Is its Value? *J Am Coll Cardiol.* 2017;70(13):1618-1636.

Table I
Assessment of CPET variables

	Peak $\dot{V}O_2$/ % predicted peak $\dot{V}O_2$	$\dot{V}_E$-$\dot{V}CO_2$ slope	EOV	OUES	$P_{ET}CO_2$
Proof of concept	+++	+++	+++	+	+++
Prospective validation	+++	+++	+++	+	+
Incremental value	++	+++	+++	+/-	+/-
Clinical utility	++	+++	-	+	-
Clinical outcomes	+++	+++	++	+	-
Cost-effectiveness	+	-	-	-	-
Ease of use	++	++	++	++	++
Methodological consensus	-	-	-	+	-
Reference values	Yes	Yes	Not necessary	Yes	Yes

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 CO_2
++++ = 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

Wagner J, Agostoni P, Arena R, et al. The Role of Gas Exchange Variables in Cardiopulmonary Exercise Testing for Risk Stratification and Management of Heart Failure with Reduced Ejection Fraction. *Am Heart J.* 2018;202:116-126.

Table II
Suitability of CPET variables for primary and secondary HFrEF prevention

(For Heart Failure and reduced Ejection Fraction)

	Recommendation	Level of evidence
Peak $\dot{V}O_2$/ % predicted peak $\dot{V}O_2$	I	A
$\dot{V}_E$-$\dot{V}CO_2$ slope	I	A
EOV	IIa	B
OUES	IIb	B
$P_{ET}CO_2$	IIb	B

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 disgns
Level C = Scientific evidence, limited, expert opinions

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Summary

- 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