Long Covid ECHO

Approach to Exercise Intolerance?

Dr. Jeff Ratushny

Learning Objectives:

- Describe the clinical concept of 'exertional intolerance' and recognize the value of advanced functional testing in its evaluation.
- Summarize the basic purpose and components of cardiopulmonary exercise testing (CPET) and how it differs from traditional tests of cardiac and respiratory function.
- Recognize underappreciated and emerging causes of exertional symptoms that may be overlooked in routine evaluation.

Conflict Disclosure

I have no conflicts to declare

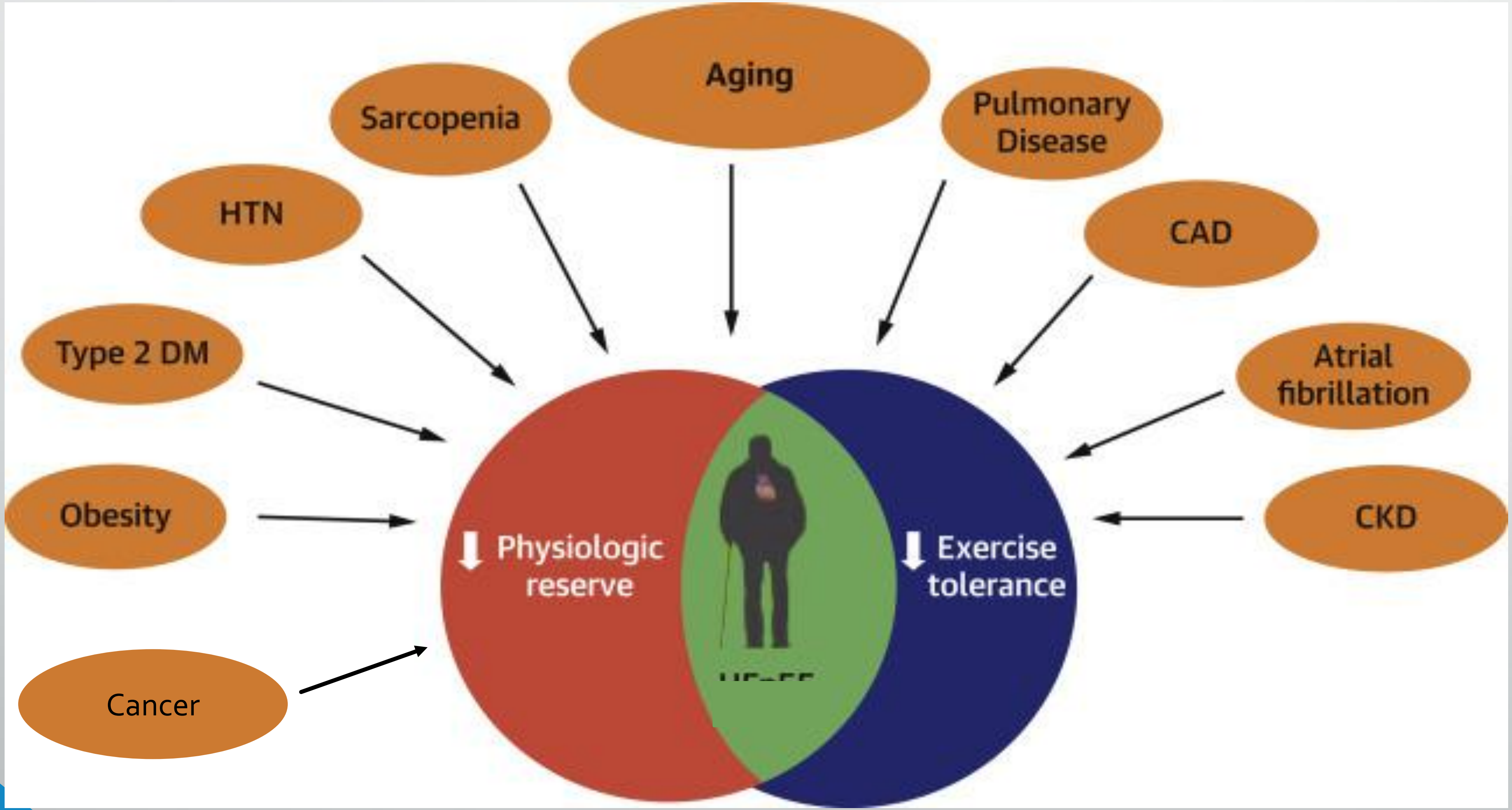
Exercise Intolerance

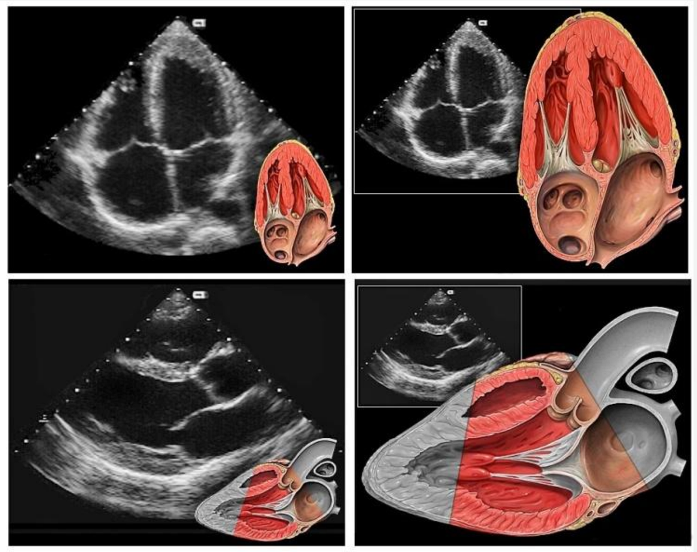
- Reduced ability to perform physical activity at a level expected of a person's age and size
- Not a disease itself
- A sign of an underlying medical condition
- Not explained by deconditioning

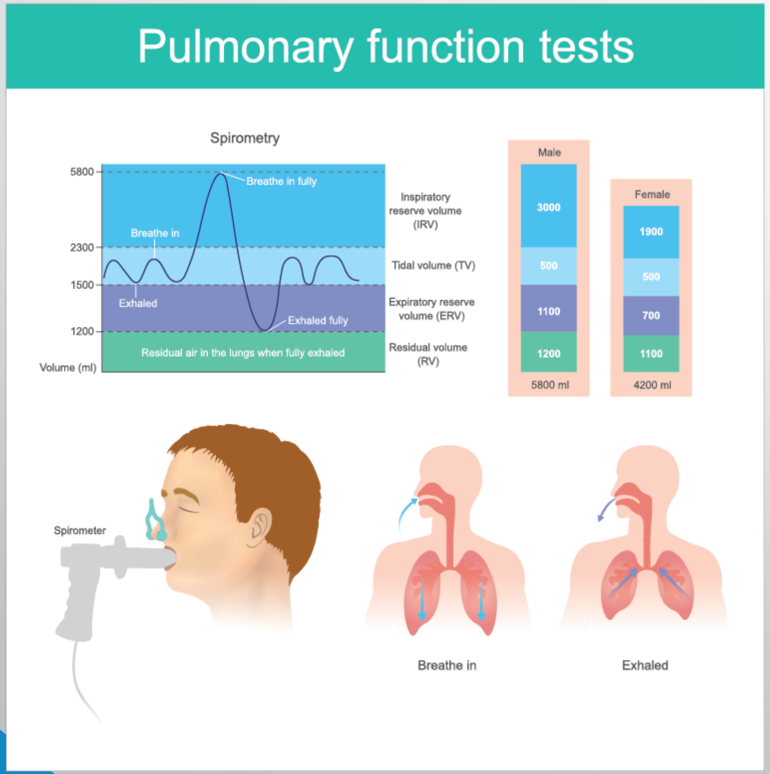
Symptoms

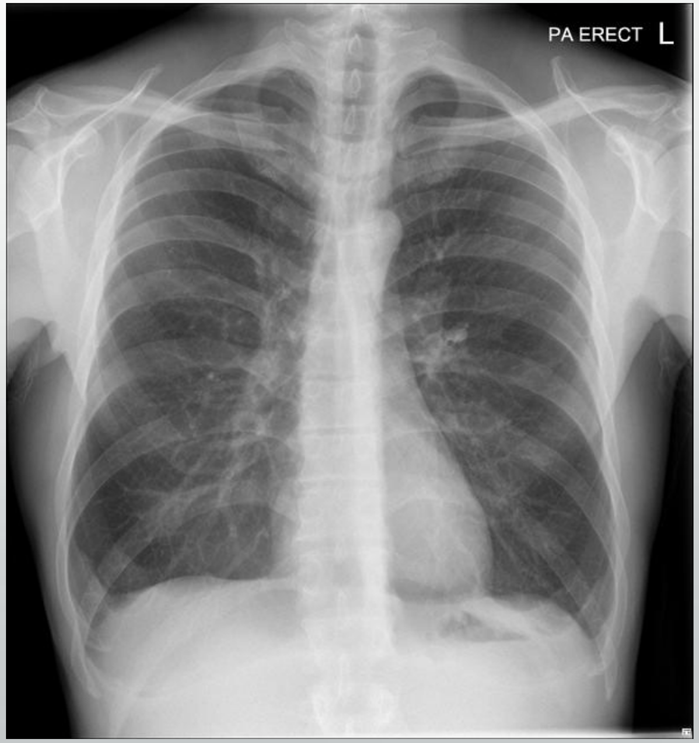
- Dyspnea
- Extreme fatigue
- Muscle pain or weakness
- Dizziness or lightheadedness
- Inappropriate rapid heart rate

Causes of Exercise Intolerance

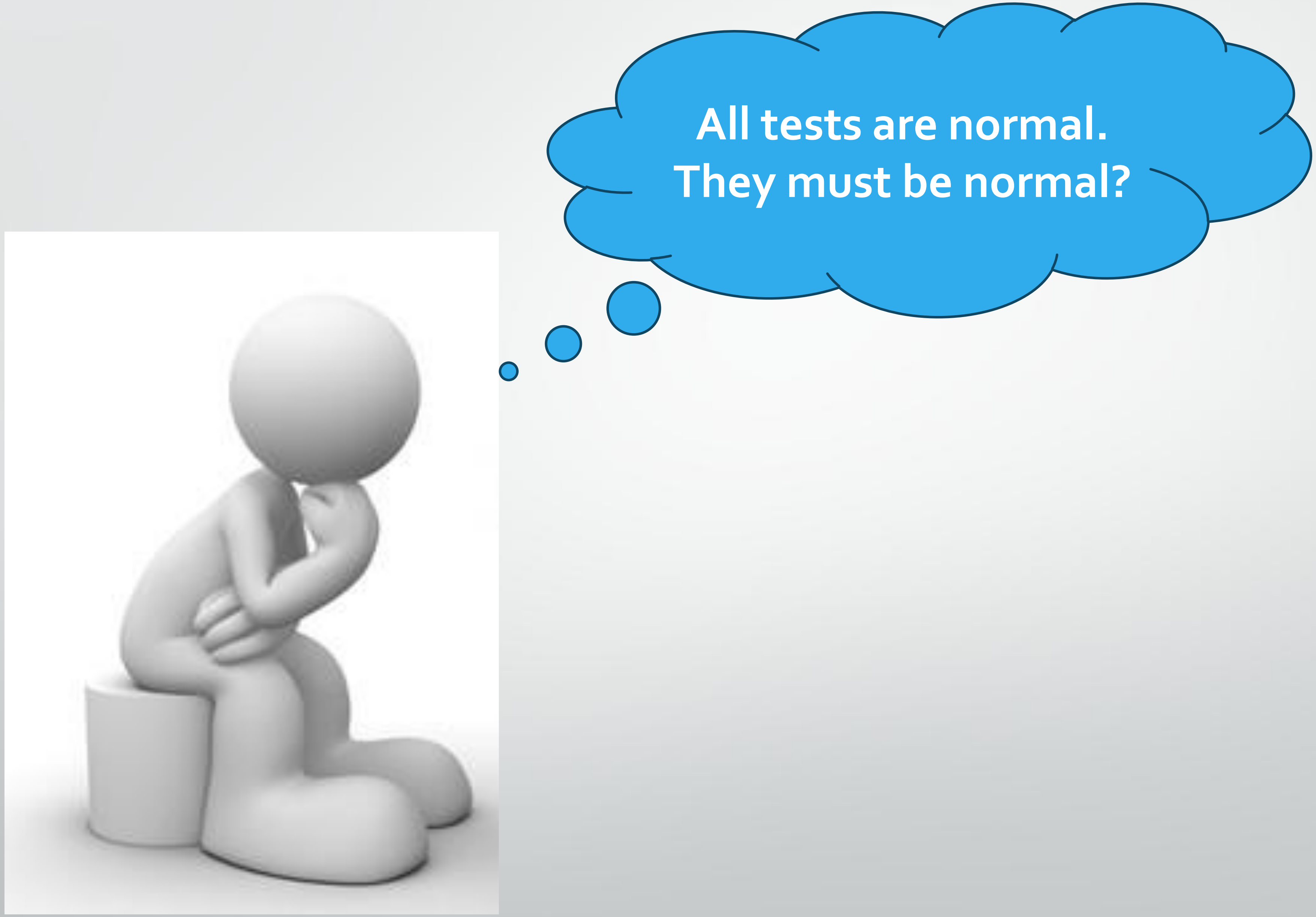





Pulmonary function tests
Spirometry
5800
2300
1500
1200
Volume (ml)
Breathe in fully
Breathe in
Exhaled
Exhaled fully
Residual air in the lungs when fully exhaled
Inspiratory reserve volume (IRV)
Tidal volume (TV)
Expiratory reserve volume (ERV)
Residual volume (RV)
Male
3000
500
1100
1200
5800 ml
Female
1900
500
700
1100
4200 ml
Spirometer
Breathe in
Exhaled


PA ERECT L

What do you do when you can’t find a cause?


All tests are normal.
They must be normal?

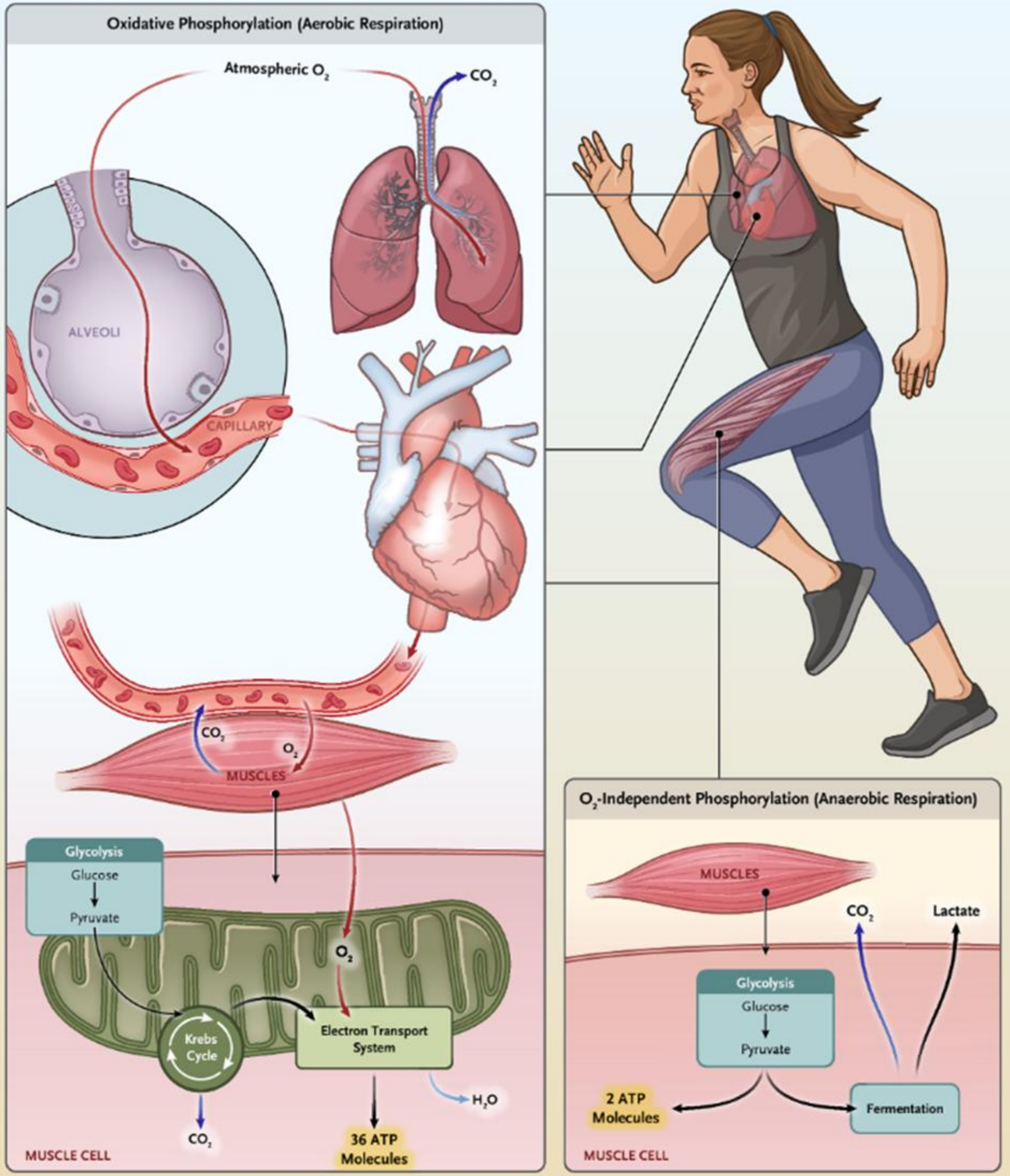
All tests are normal.
They must be normal?

Perform CPET

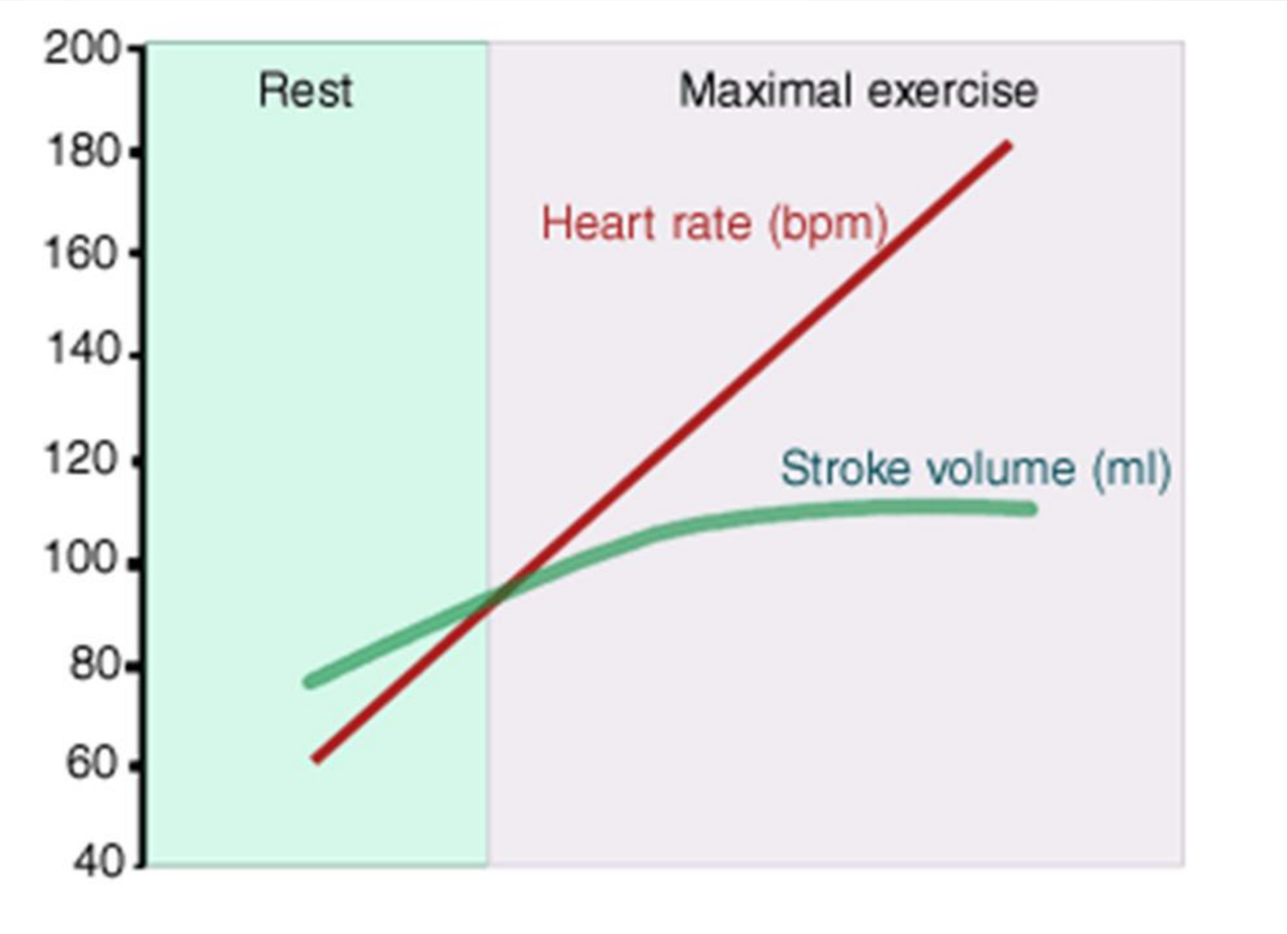
Cardiopulmonary Exercise Testing (CPET)

Simultaneous study of **cardiovascular** and **ventilatory** systems through the measurement of gas exchange at the airway

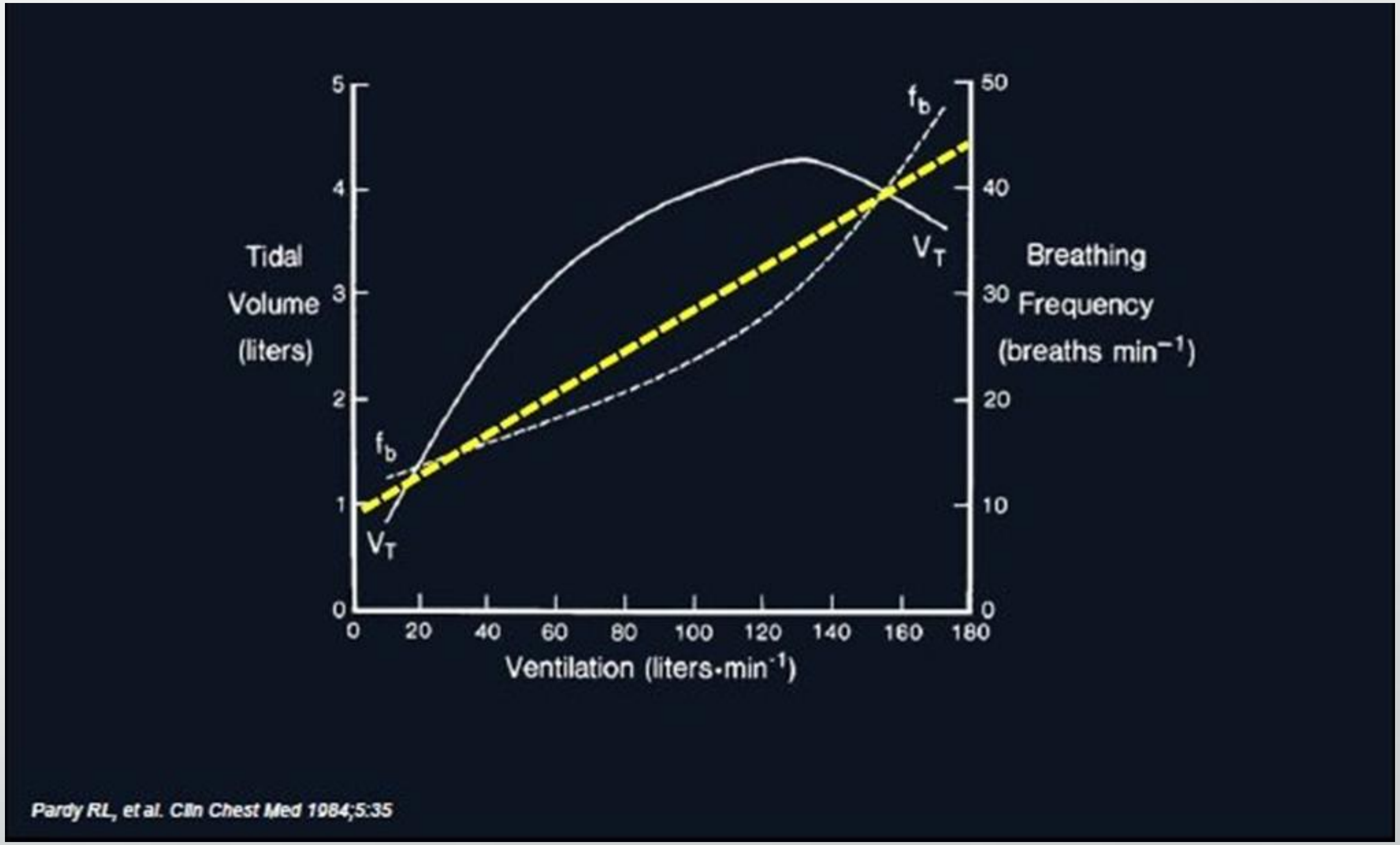
Exercise Physiology

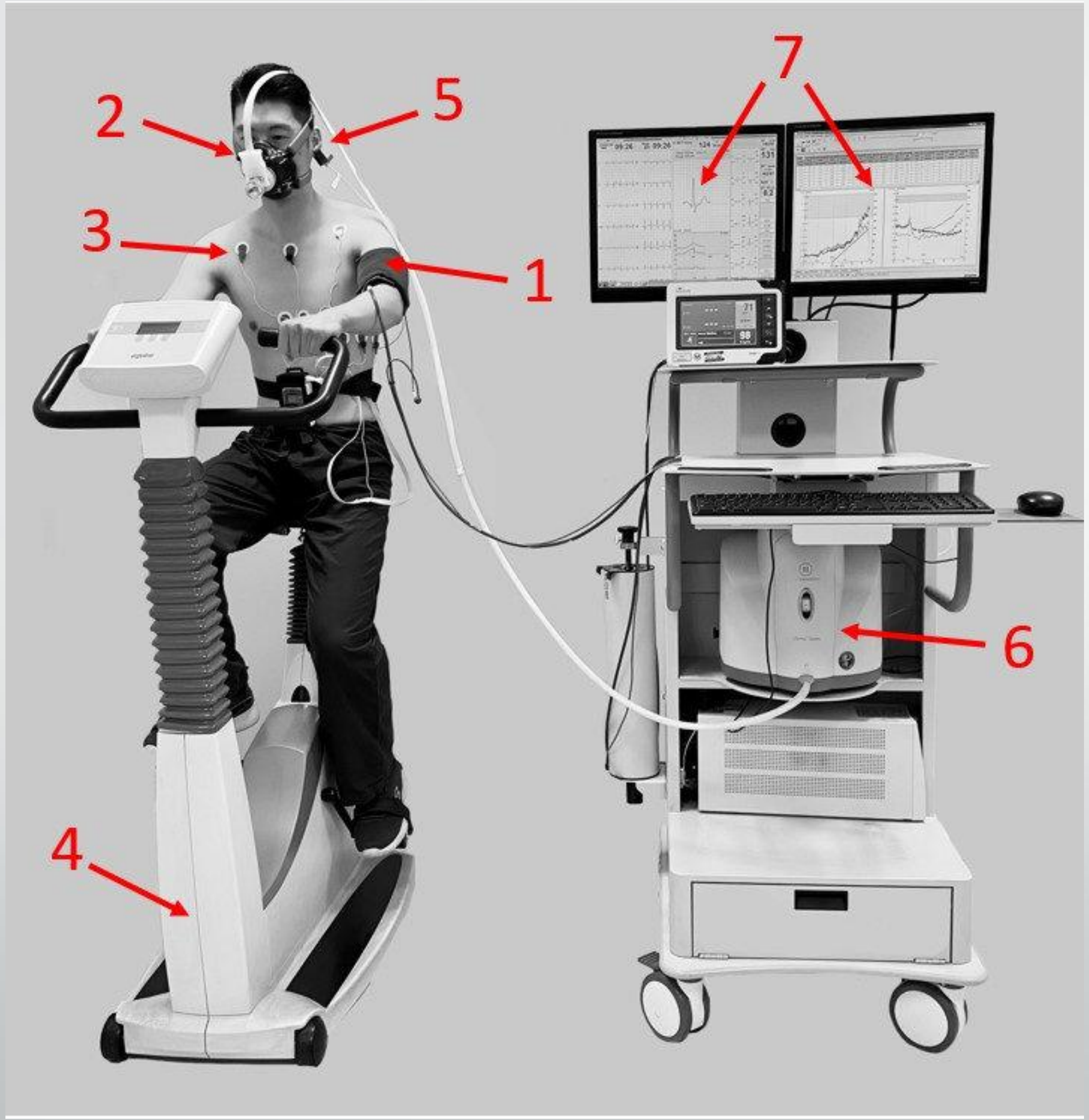


Cardiovascular Response to Exercise



Ventilatory Response to Exercise





1
2
3
4
5
6
7

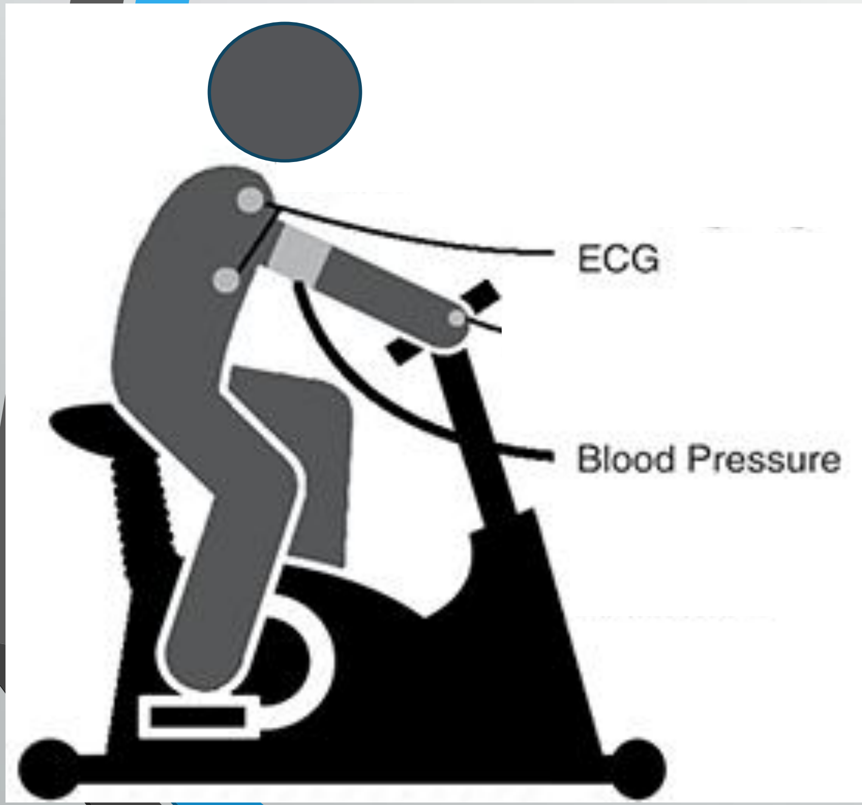
Additional Variables

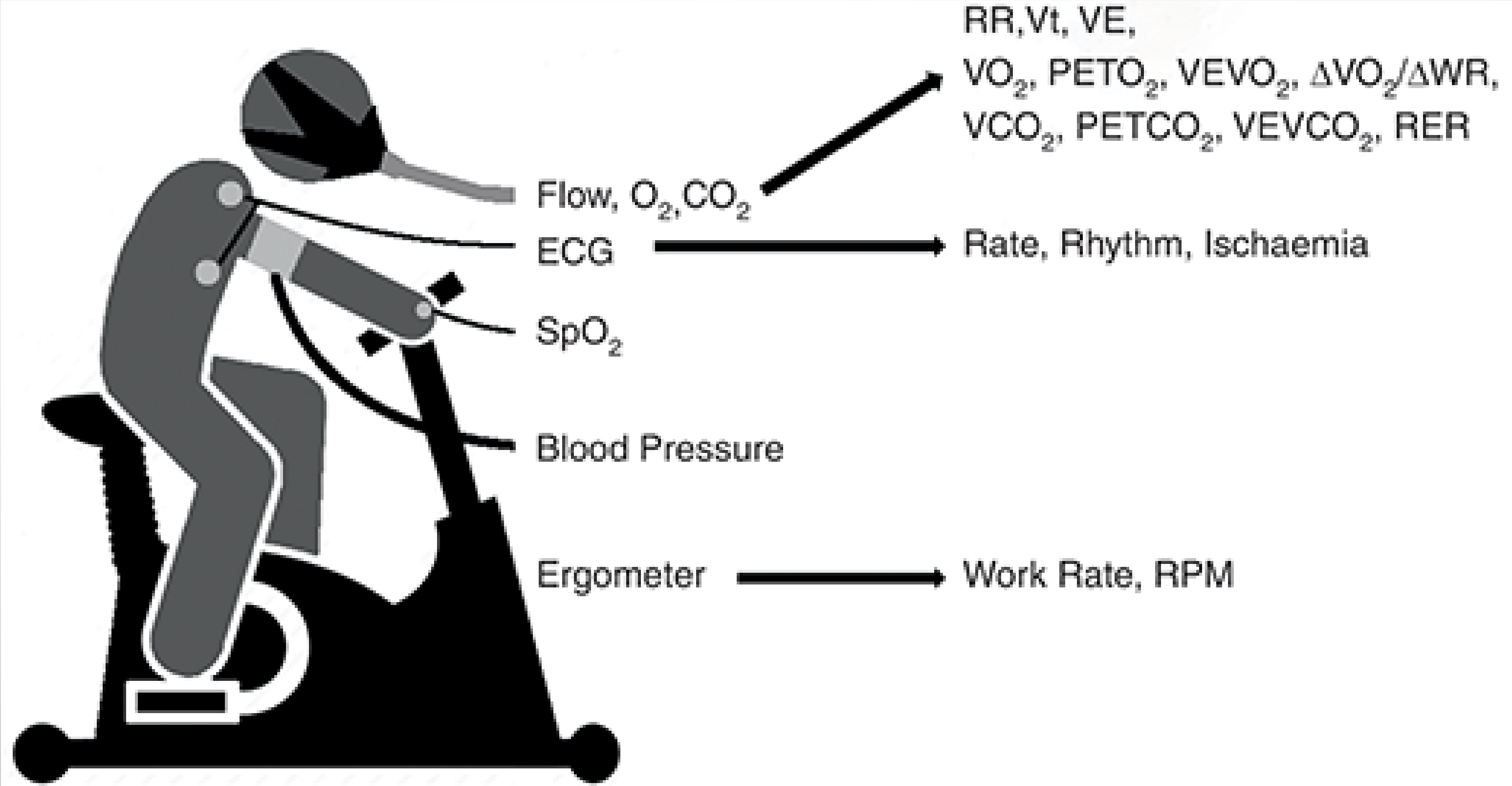
VO_2

VCO_2

Ve (RR x TV)

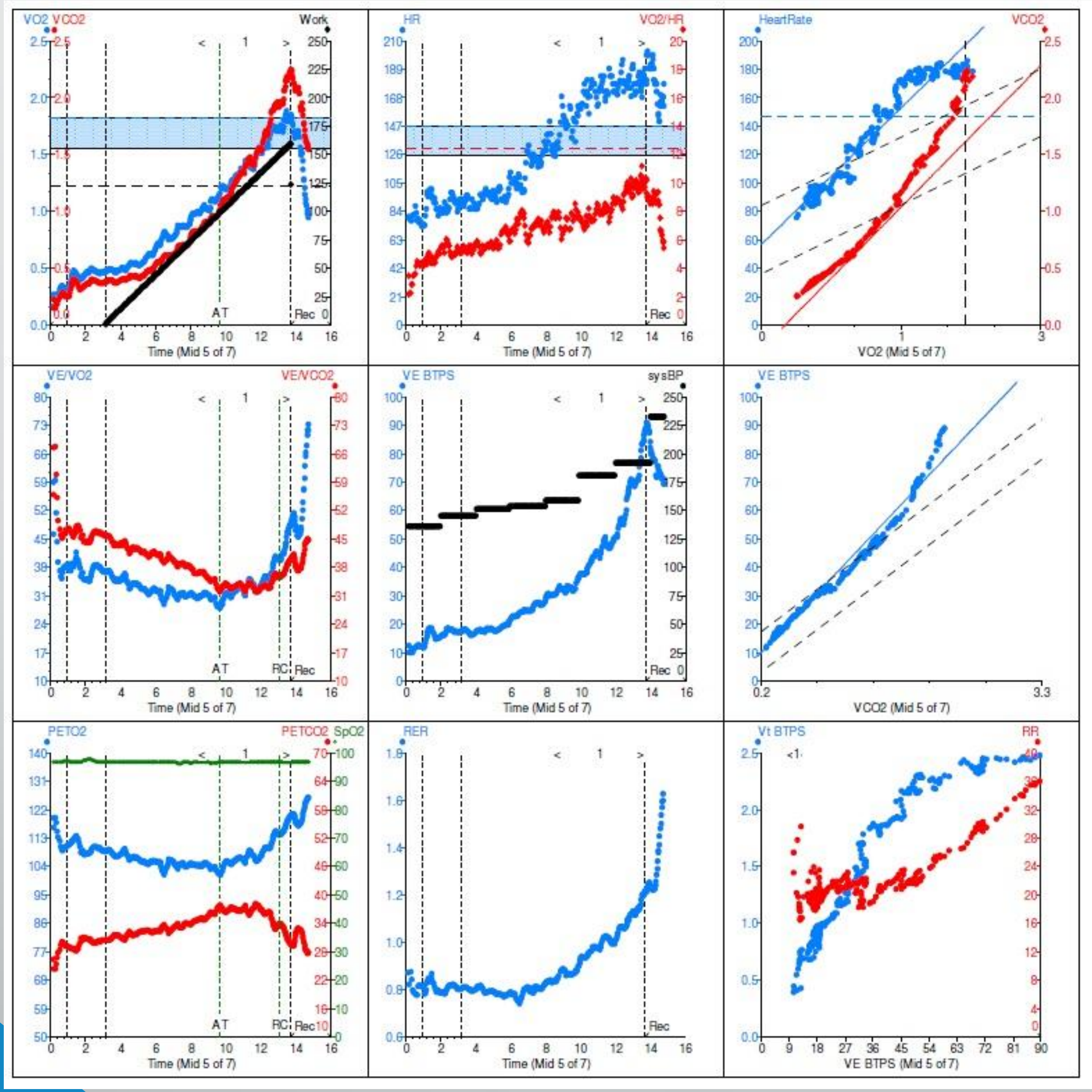
Which Would You Prefer?





Exercise Modality

VO2 Max usually 5-10% higher on the treadmill

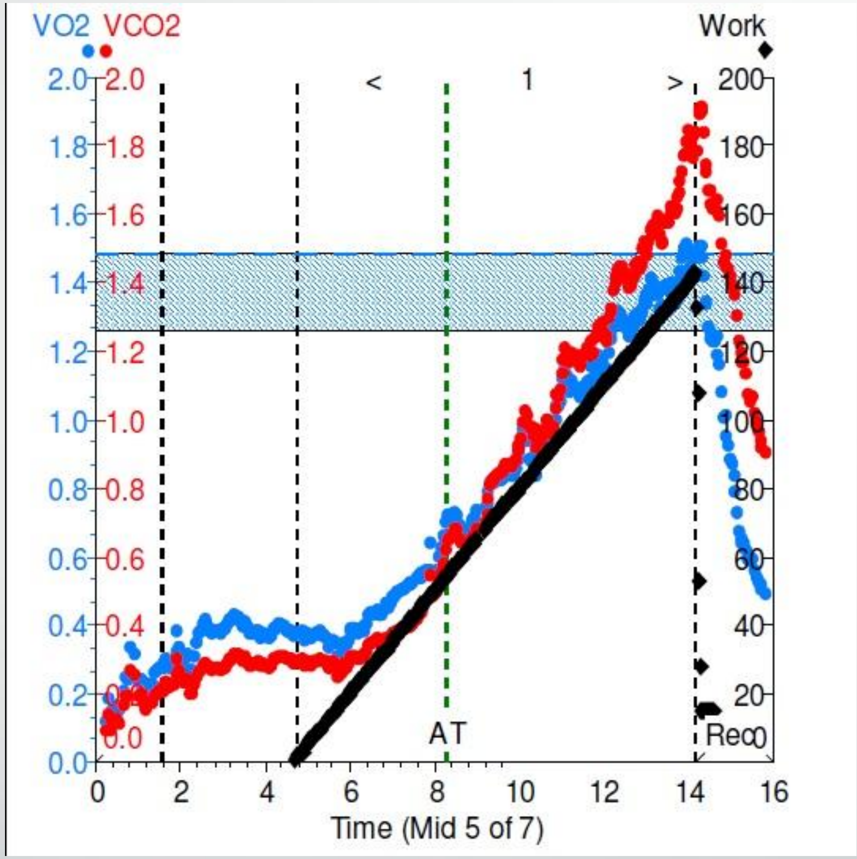


9 Panel Plot

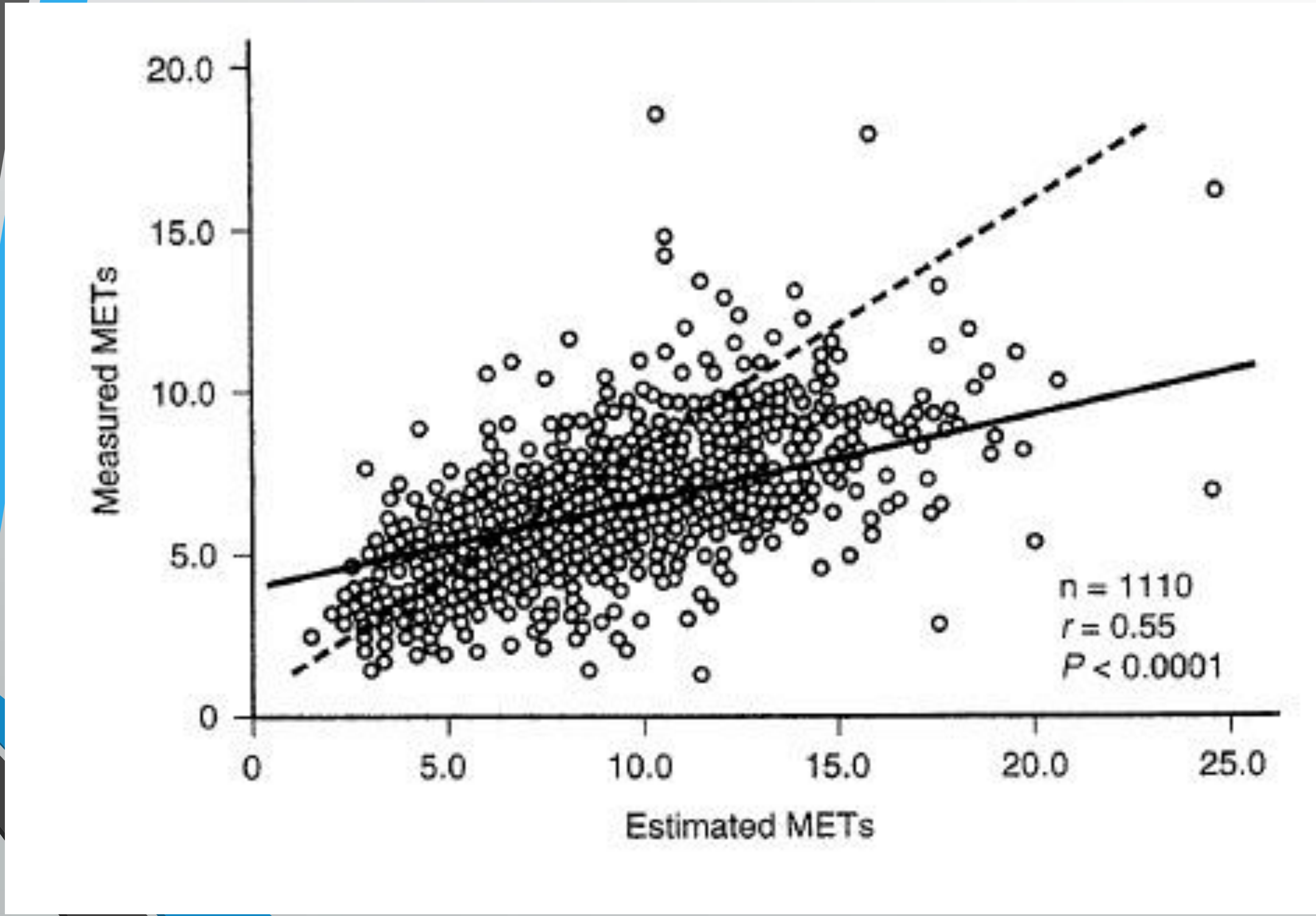
Integrated cardiovascular, pulmonary, metabolic responses to exercise

Pre-Test Spirometry

Aerobic Function Normal?



What are we really measuring without gas exchange?



Systematically overestimating patient's abilities

=

<u>Missing disease</u>

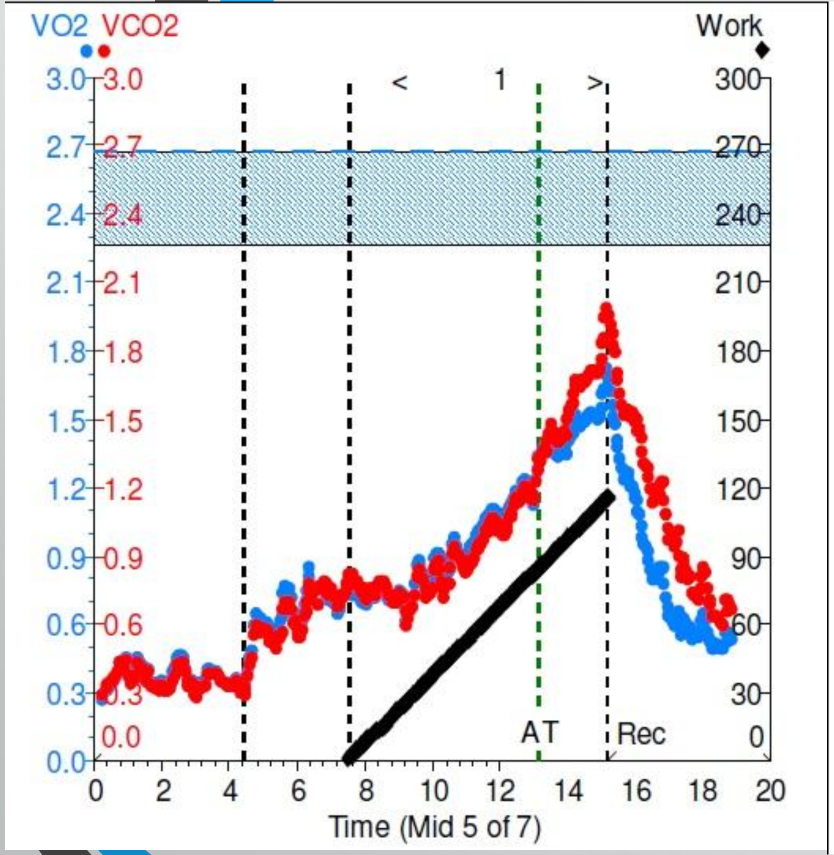
Int J Sports Med 2005; 26:1-7).

Case 1

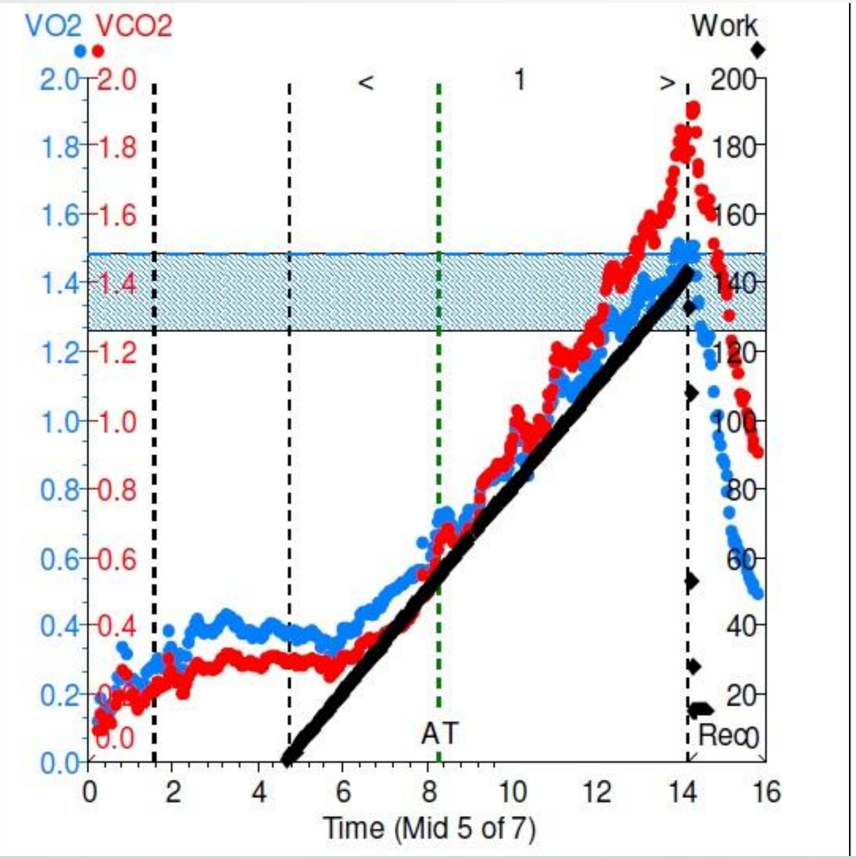
Ms. RB

22 year old female with
fatigue, dyspnea, dizziness

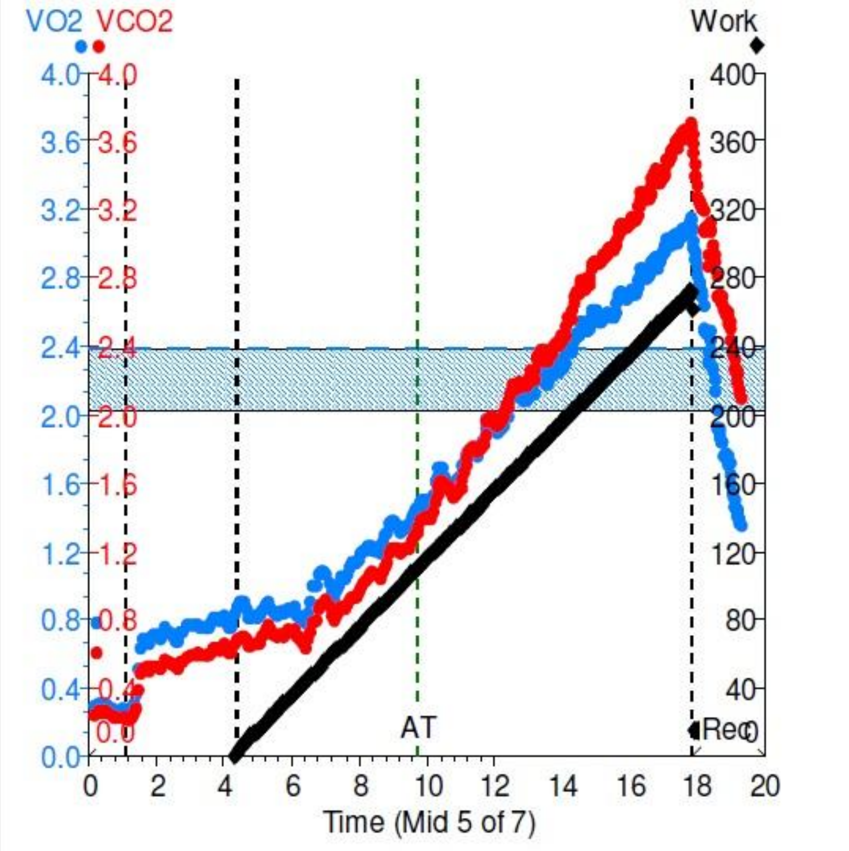
Aerobic Function Normal?



LC - POTS

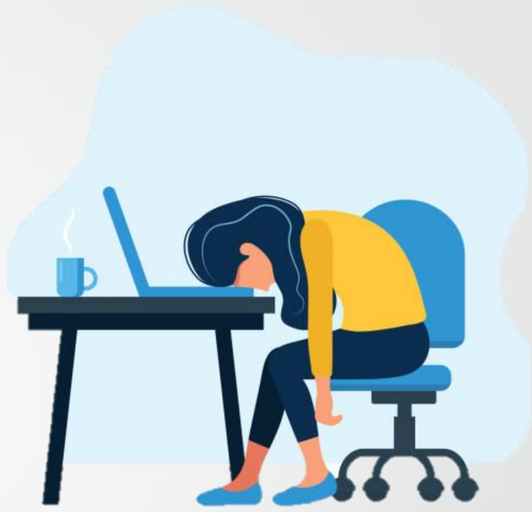


DCM: EF 30%



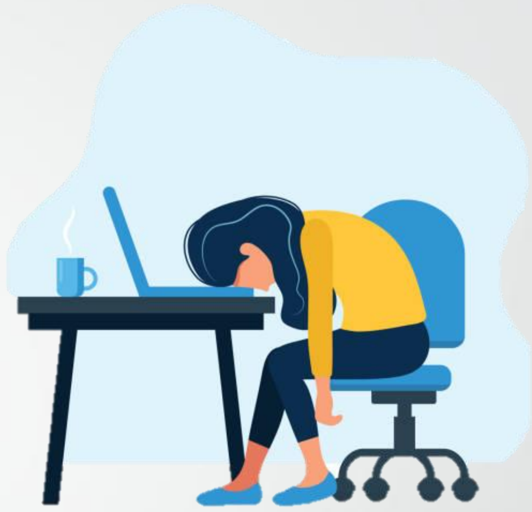
Internal Medicine Physician (Cyclist)

Case 1



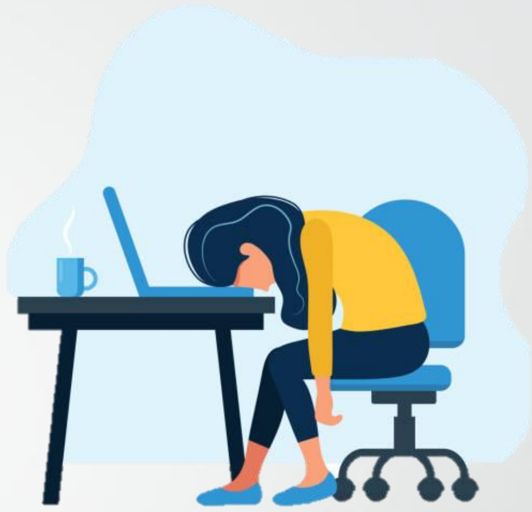
- Unwell x 3 years
- Abrupt onset of symptoms
  - Fatigue, dyspnea, dizziness
- Began after COVID 19
  - Mild illness, no hospitalization
- + Chest pain and palpitations
- No cough, sputum, wheeze
- Difficulty walking to bus stop, standing in cafeteria line

Case 1

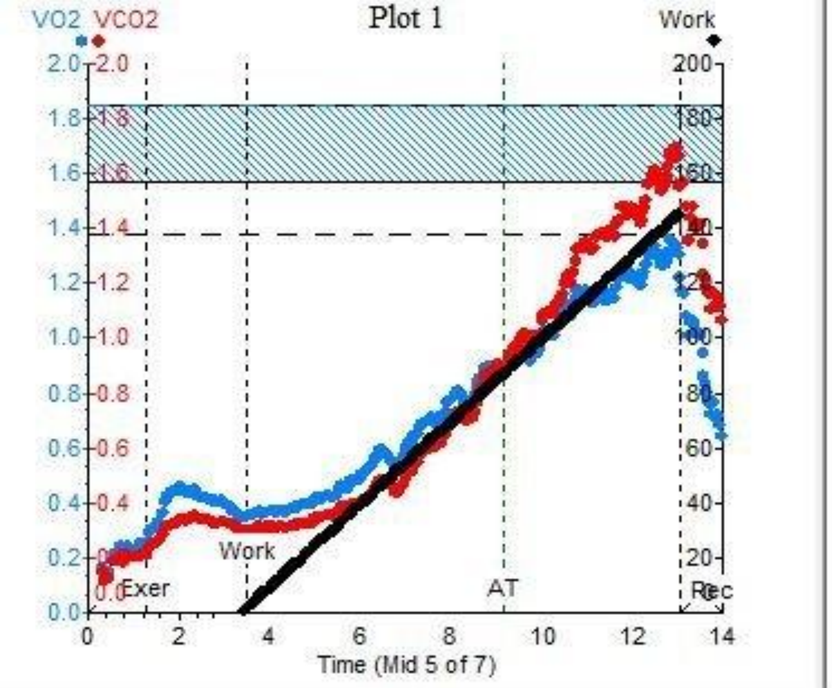


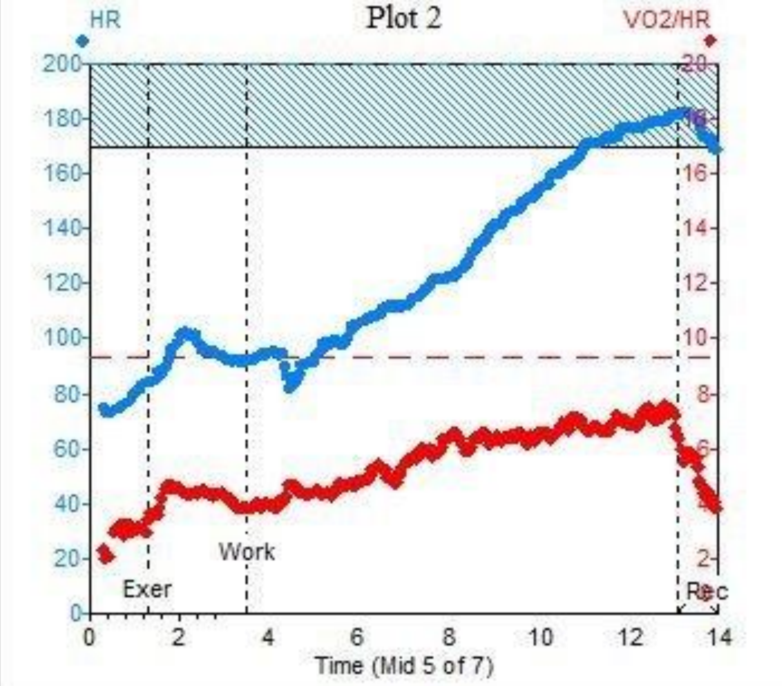
- PMH: nil
- Med: none
- SHx:
  - No tobacco, drugs or alcohol, University student – on leave due to illness
- Training history:
  - X-country high school runner, 5K: 20:30

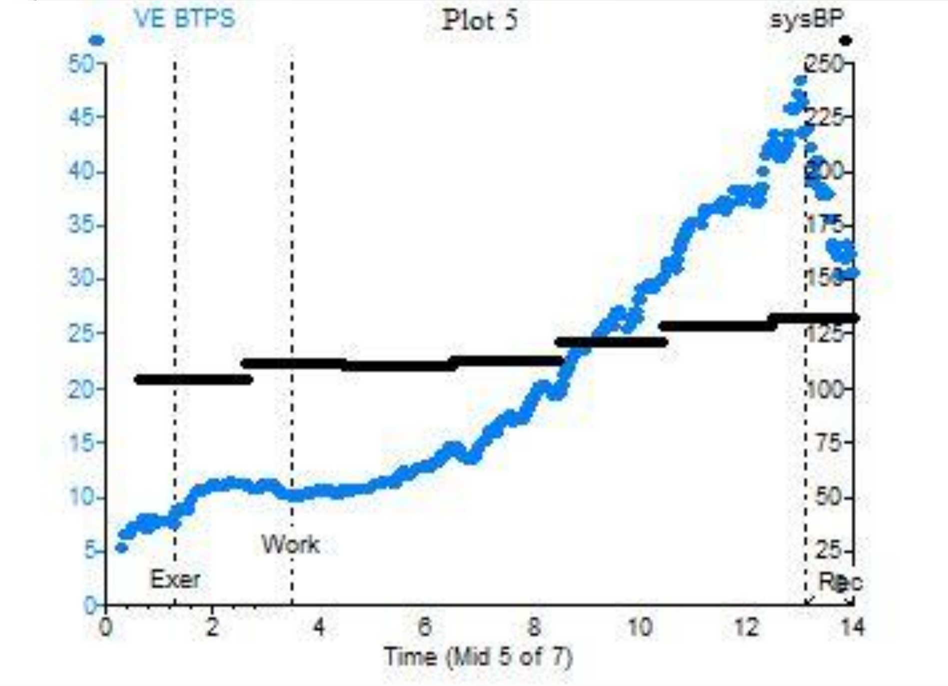
Case 1



- Exam:
  - Appeared well, BMI 21
  - Afebrile, HR 102, BP 102/75, SpO_2 96%
  - CV and pulm: normal
- Labs:
  - WBC 6.1, Hgb 121, Plt 229
  - Na 138, K 4.5, Creatinine 70, TSH 0.426
  - hsTrop I < 1.5, D-Dimer negative
- EKG – Sinus tach (101 bpm)
- CXR – Normal
- Echo – Normal







- Peak VO2 = 25 ml/kg/min
  - 72% predicted
- Peak RER = 1.25

- Peak HR – 180 bpm
  - 91% predicted
  - left shifted
- O2 pulse – 7 ml/beat
  - 77% predicted

Case 1
CPET

1. Mildly Impaired Aerobic Capacity

2. Cardiocirculatory limitation likely on the basis of a low SV state

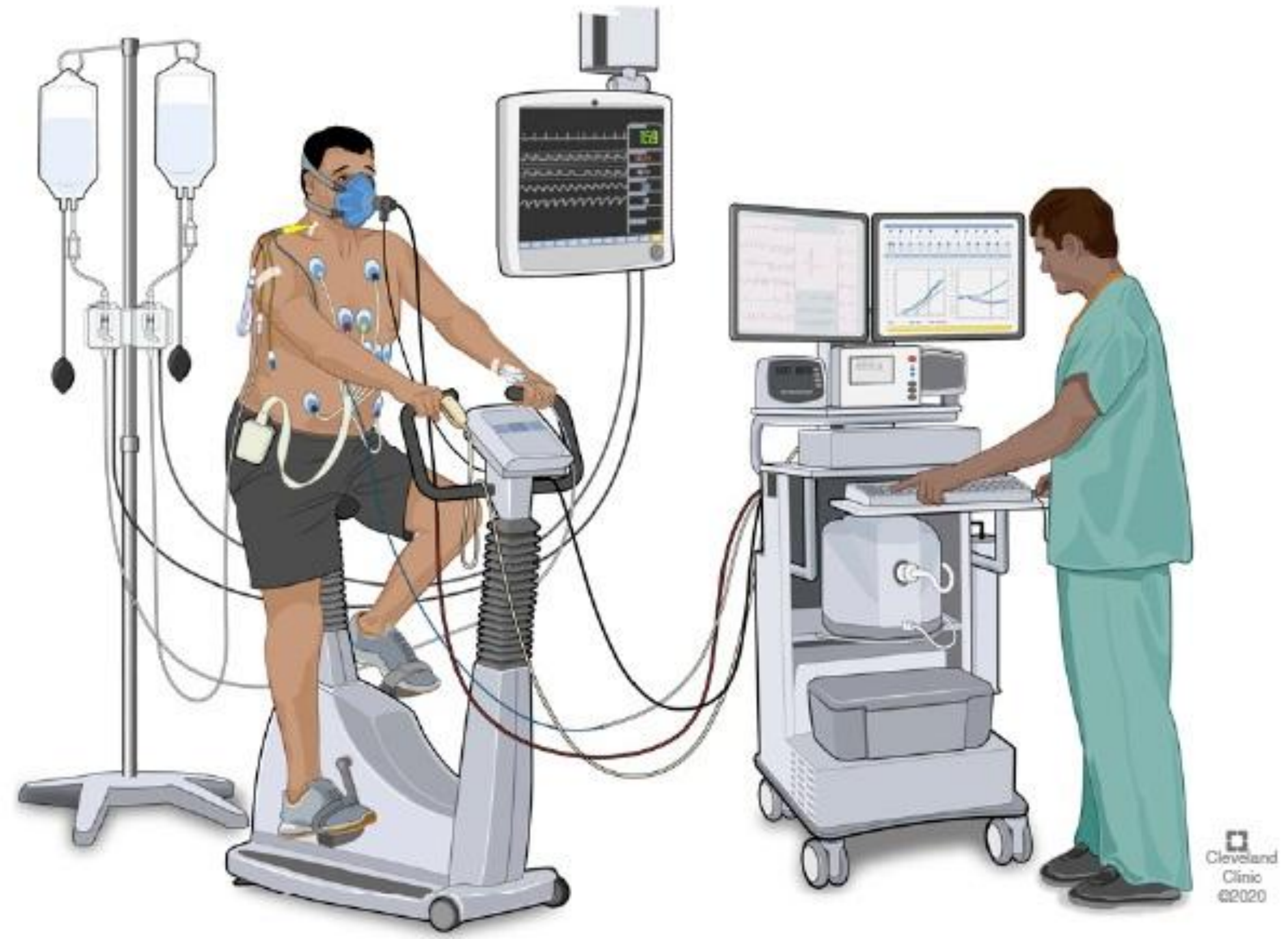


Figure 2. Invasive cardiopulmonary exercise testing. Invasive hemodynamic measurements are done via pulmonary arterial and radial arterial catheters. These measurements are monitored while a patient is at rest and during incremental upright exercise. Reprinted by permission from the Cleveland Clinic Center for Medical Art and Photography, 2020. All Rights Reserved. Illustration by David R. Schumick, B.S., C.M.I.

Hemodynamic measures

- RAP
- mPAP
- PCWP
- CO (Fick's)

Blood gas measures

- SaO_2
- SvO_2
- AVO_2 Diff

Case 1

	Cardiac Output (l/min)	HR (bpm)	SV (ml)	RAP (mmHg)	ScvO2	Lactate
Rest	5.0	101	49	0	68	1.3
Peak	9.8 (72% pred)	180	54	2	25	8.2

Low RAP at rest with minimal increase with exercise

+

Low peak CO

Case 1

1. Mildly Impaired Aerobic Capacity

2. Cardiocirculatory limitation likely on the basis of a low SV state

3. Preload failure

Case 1

Orthostatic Vital Signs/The NASA 10-minute Lean Test

	Blood Pressure (BP)		Pulse
	Systolic	Diastolic	
Supine 1 minute	91	54	60
Supine 2 minute	91	52	63
Standing 0 minute			103
Standing 1 minute	93	64	104
Standing 2 minute			105
Standing 3 minute			108
Standing 4 minute	97	65	95
Standing 5 minute			97
Standing 6 minute			104
Standing 7 minute	97	71	99
Standing 8 minute			106
Standing 9 minute			93
Standing 10 minute	95	63	101

Delta HR: ~46 bpm
No orthostatic hypotension

Dx: **POTS**

Unexplained exertional dyspnea caused by low ventricular filling pressures: results from clinical invasive cardiopulmonary exercise testing

William M. Oldham,[1,2,3] Gregory D. Lewis,[3,4] Alexander R. Opotowsky,[2,3,5] Aaron B. Waxman,[1,2,3] David M. Systrom[1,2,3]

[1]Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; [2]Heart and Vascular Center, Brigham and Women's Hospital, Boston, Massachusetts, USA; [3]Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA; [4]Pulmonary and Critical Care Unit and Cardiology Division, Medical Services, Massachusetts General Hospital, Boston, Massachusetts, USA; [5]Department of Cardiology, Boston Children's Hospital, and Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

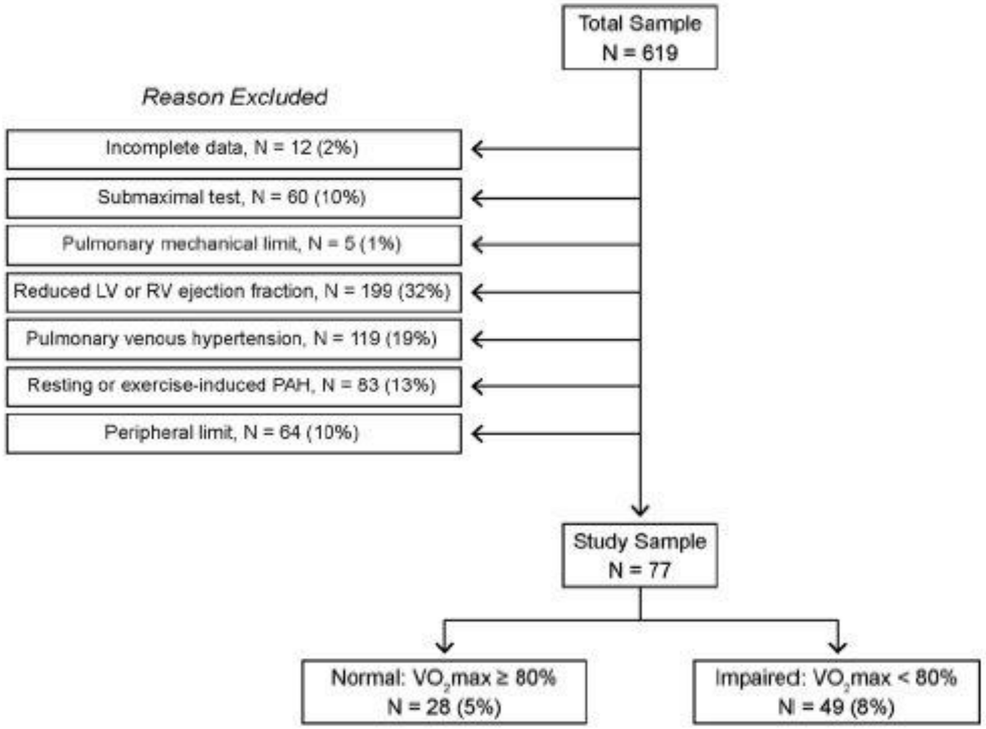


Table 1. Demographic variables and baseline characteristics

Characteristic	Single-test cohort: Normal (N = 28)	Single-test cohort: Impaired (N = 49)	Sequential-testing cohort (N = 21)
Age, median (IQR), years	45 (40–60)	46 (31–63)	44 (25–58)
Male sex, no. (%) of patients	11 (39.3)	8 (16.3)	6 (28.6)
BMI, median (IQR), kg/m^2	27.3 (25.2–29.9)	24.9 (21.1–28.3)	23.0 (20.9–24.6)
Medications, no. (%) of patients			
Diuretic	3 (10.7)	6 (12.2)	2 (0.7)
BB	4 (14.3)	8 (16.3)	2 (0.7)
CCB	5 (17.9)	12 (24.5)	3 (14.3)
ACE inhibitor/ARB	4 (14.3)	8 (16.3)	2 (0.7)
[Hb], median (IQR), g/dL	12.8 (12.1–13.7)	11.9 (11.1–13.5)	13.9 (13.6–14.5)
$\dot{V}O_2$max, mean ± SD, mL/kg/min	24.4 ± 9.4	16.6 ± 5.0	23.2 ± 7.2[a]
$\dot{V}O_2$max, median (IQR), % pred.	86 (84–97)	53 (47–64)	80 (70–102)[a]
Preexercise fluid, median (IQR), L	0 (0–0.75)	0.1 (0–0.9)	2.0 (1.9–2.3)[b]

Note: BMI: body mass index; BB: β-adrenergic receptor antagonist; CCB: calcium channel blocker; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; [Hb]: hemoglobin concentration; IQR: interquartile range; $\dot{V}O_2$max: maximum aerobic capacity; SD: standard deviation; % pred.: percent of predicted value.

[a] $\dot{V}O_2$max from the first invasive cardiopulmonary exercise test (iCPET).

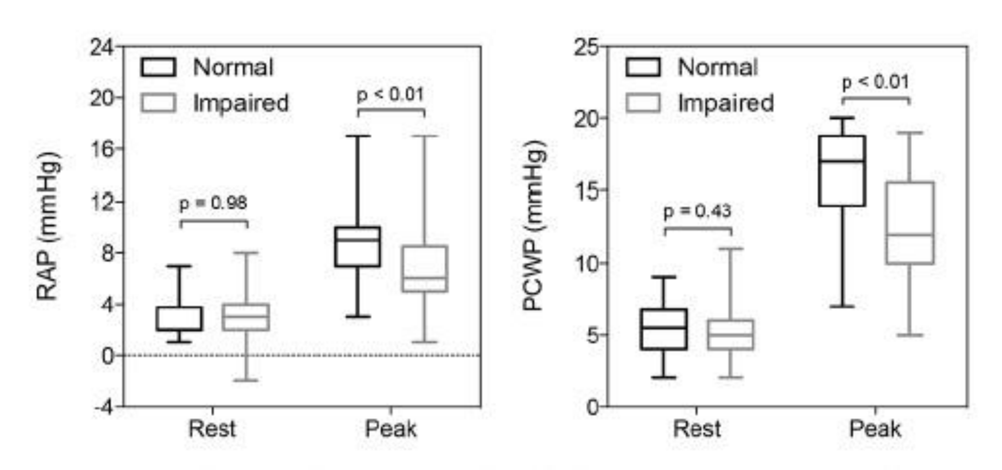
[b] Volume of normal saline infused between iCPETs.

Pulm Circ 2016;6(1):55-62. DOI: 10.1086/685054.

Unexplained exertional dyspnea caused by low ventricular filling pressures: results from clinical invasive cardiopulmonary exercise testing

William M. Oldham,[1,2,3] Gregory D. Lewis,[3,4] Alexander R. Opotowsky,[2,3,5] Aaron B. Waxman,[1,2,3] David M. Systrom[1,2,3]

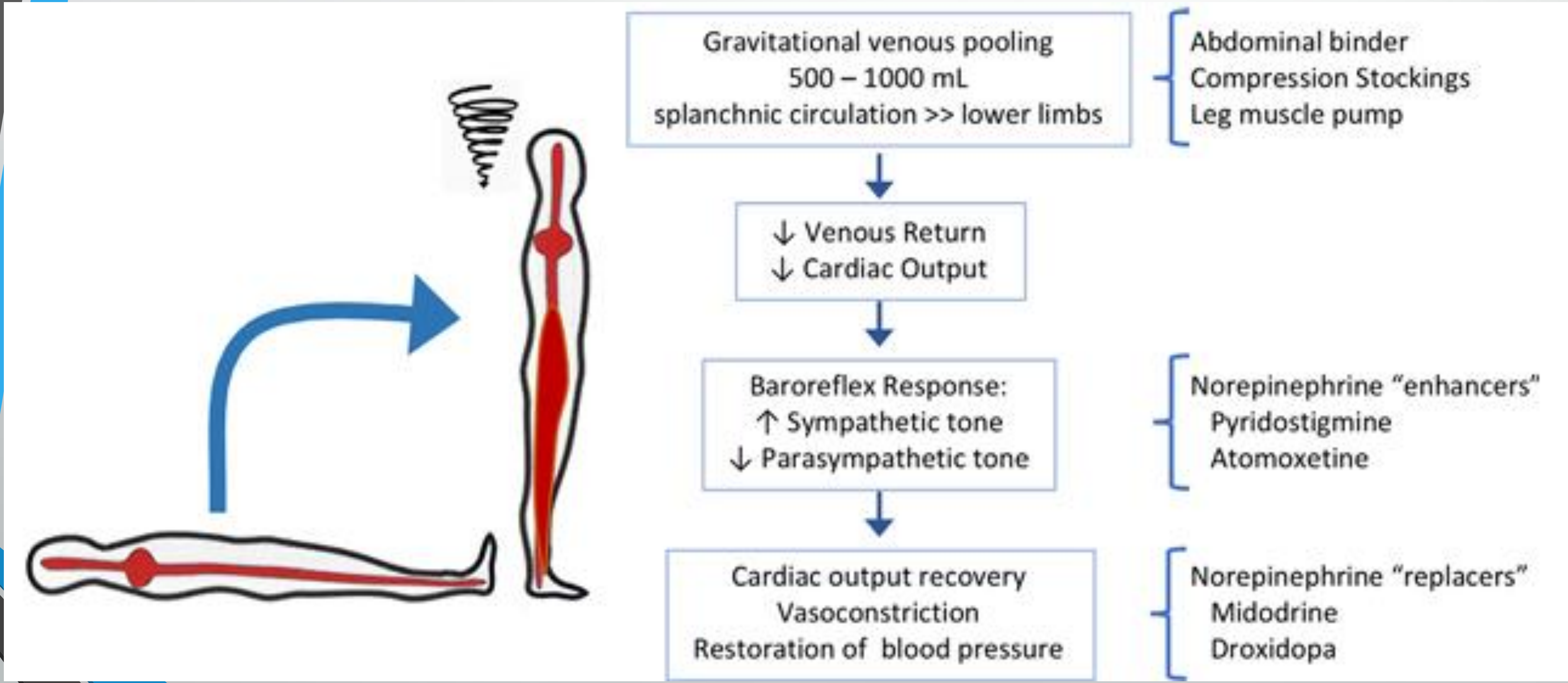
Variable	Normal Rest	Normal Peak	Impaired Rest	Impaired Peak
Cardiac index, L/min/m^2	2.7 (2.2–3.5)	8.6 (6.9–10.2)	2.6 (1.9–3.2)	6.3 (5.2–7.1)
Cardiac output, % predicted		108 (97–115)		72 (62–76)
Heart rate, bpm	78 ± 13	153 ± 20	85 ± 17	141 ± 28
Heart rate, % predicted		92 ± 10		84 ± 13
SV index, mL/m^2	37 ± 12	56 ± 10	32 ± 9	44 ± 9
MAP, mmHg	101 ± 14	124 ± 16	93 ± 13	112 ± 16
SVR index, dyn·s/cm^5/m^2	2,666 (2,220–3,691)	1,067 (868–1,322)	2,832 (2,190–3,801)	1,369 (1,148–1,698)
Mean PA pressure, mmHg	15 (12–17)	29 (26–31)	14 (12–16)	24 (22–27)
PVR index, dyn·s/cm^5/m^2	257 (198–350)	130 (99–155)	285 (182–422)	148 (105–198)
Ca-$\bar{v}O_2$, mL O_2/dL	5.5 (5.0–6.4)	12.5 (11.1–13.0)	5.7 (4.7–6.5)	10.1 (9.0–11.4)
RVEDV index, mL/m^2	70 (61–85)	79 (71–97)	70 (62–82)	81 (69–95)
LVEDV index, mL/m^2	58 (51–69)	64 (59–81)	56 (50–66)	64 (53–80)



Low biventricular filling pressures
+
Low stroke volume

Pulm Circ 2016;6(1):55-62. DOI: 10.1086/685054.

Preload Failure



Preload Failure

Table 1. Etiologies of low preload

Decreased Intravascular Volume	Venous Obstruction/Restriction	Reduction of Venous Tone
• Reduced fluid intake • Excessive perspiration • Chronic diarrhea • Hemorrhage • Endocrinopathies • Medication side effects	• Thrombosed inferior vena cava • Deep vein thrombosis • Dysfunctional venous valves • Congenital heart disease	• Postural orthostatic tachycardia syndrome • Orthostatic hypotension • Orthostatic intolerance • Small-fiber neuropathy

Case 2

Ms. DV

53 year old female with dyspnea and fatigue

Case 2

- Started 9 months ago
- Slow progressive exertional dyspnea – mMRC 2
- Associated dizziness
- No chest pain, orthopnea, PND, edema
- No cough, sputum, hemoptysis
- + Covid 19 - ?around the time of onset of symptoms

Case 2

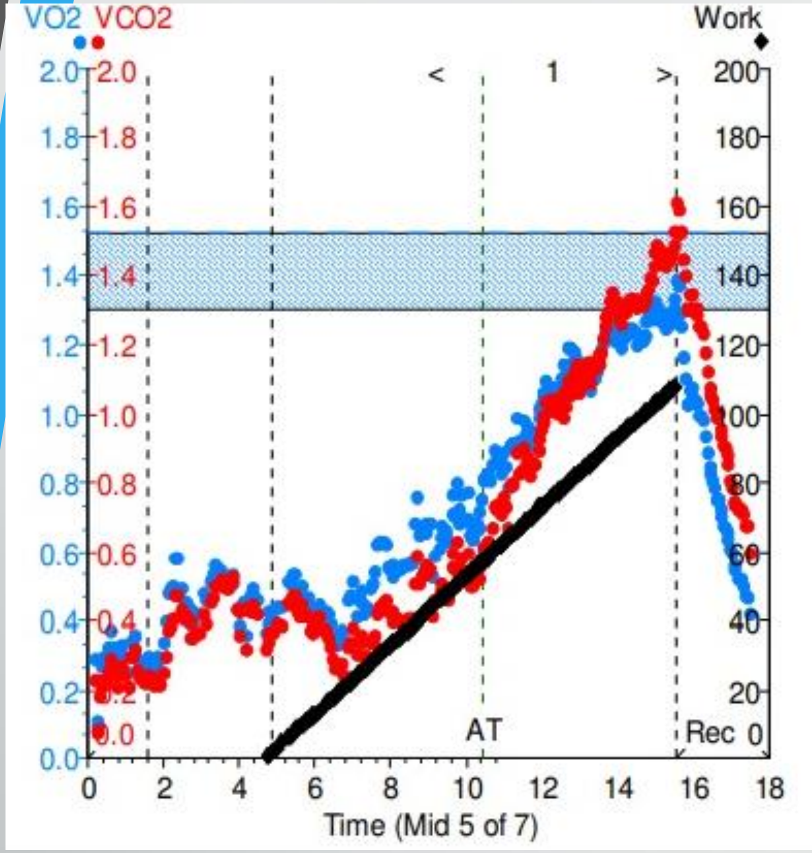
- PMH: HTN, s/p bariatric Sx, depression, anxiety
- Med: amlodipine, abilify, omeprazole
- SHx: No tobacco, drugs. Alcohol – 1 bottle wine / d

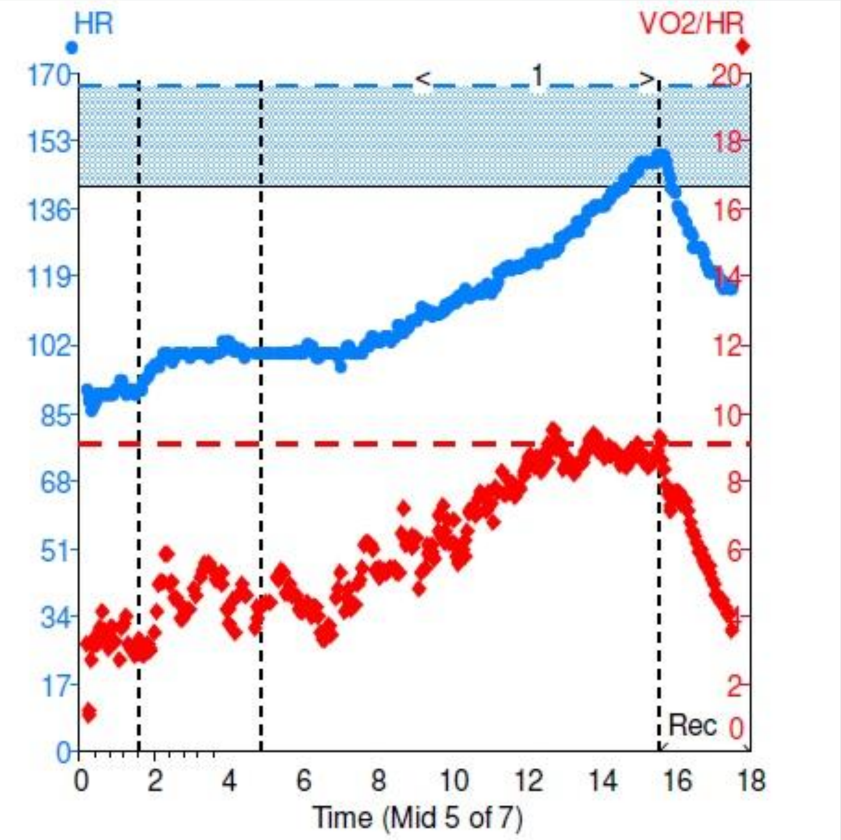
Case 2

- Exam:
  - Appeared well, BMI 30.1
  - Afebrile, HR 91, BP 146/90, SpO_2 97%
  - CV and pulm: normal
- Labs: Normal
- Normal EKG and Normal CXR
- Echo: Normal
- Spirometry: Normal

Case 2

CPET





- Peak VO2 = 17.1 ml/kg/min
  - 86% predicted
- Peak RER = 1.12
  - Endpoint – leg fatigue

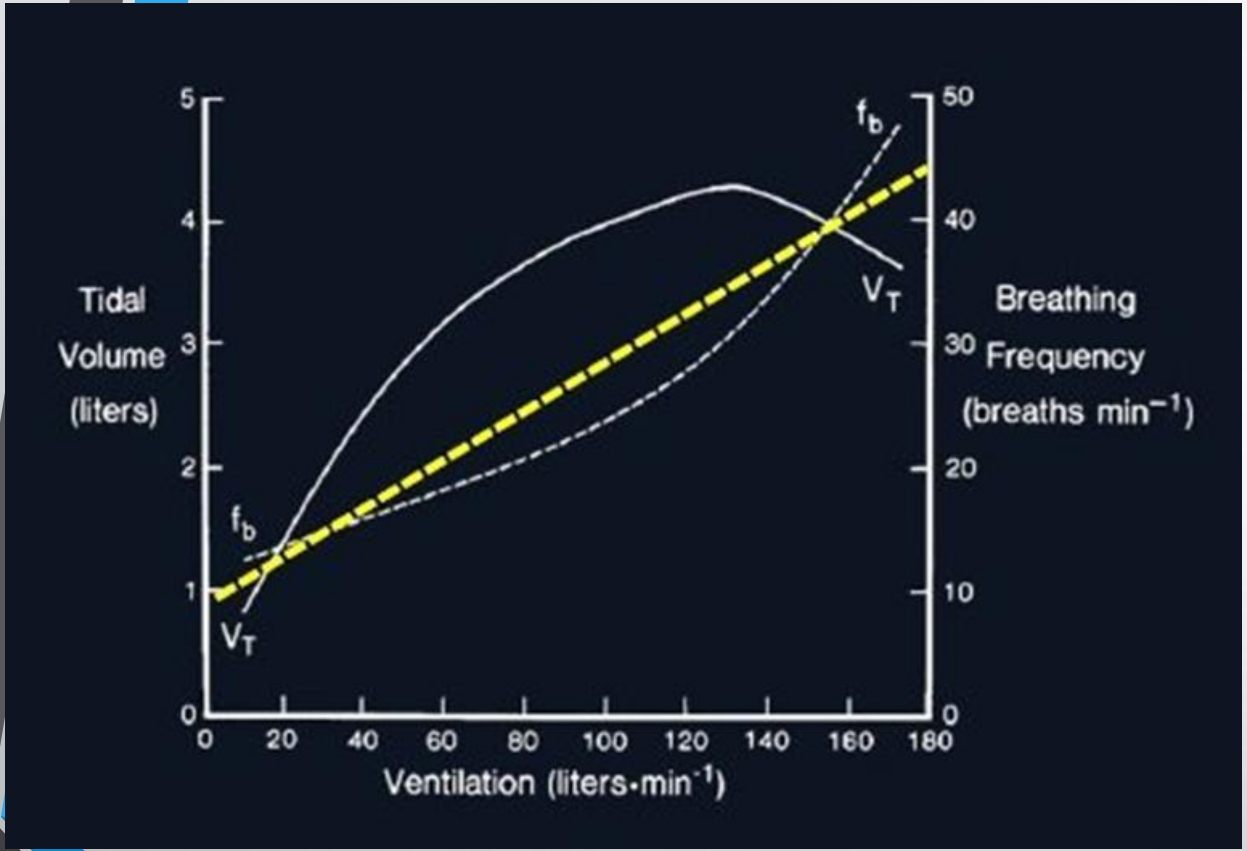
- Peak HR – 148 bpm
  - 89% predicted
- O2 pulse – 9 ml/beat
  - 98% predicted

Case 2

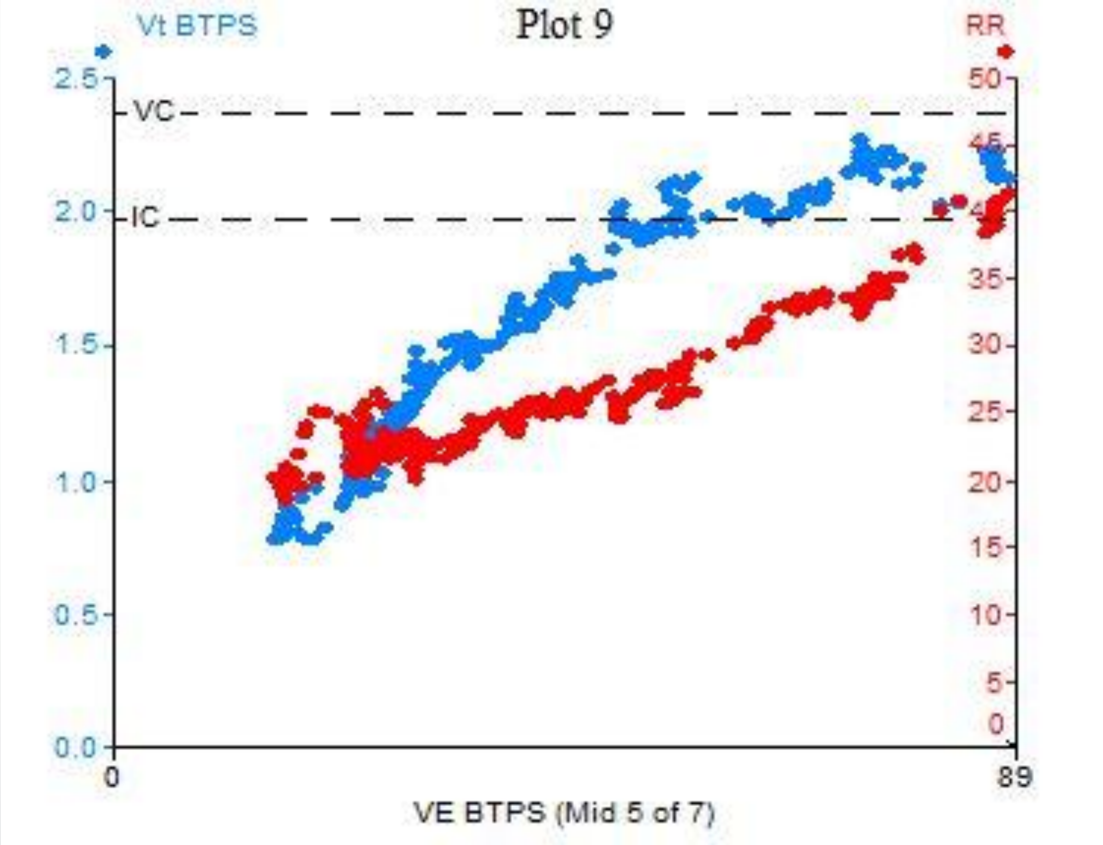
CPET

1. Low Normal Aerobic Function
2. Normal CV responses to exercise

?What about the ventilatory response ?

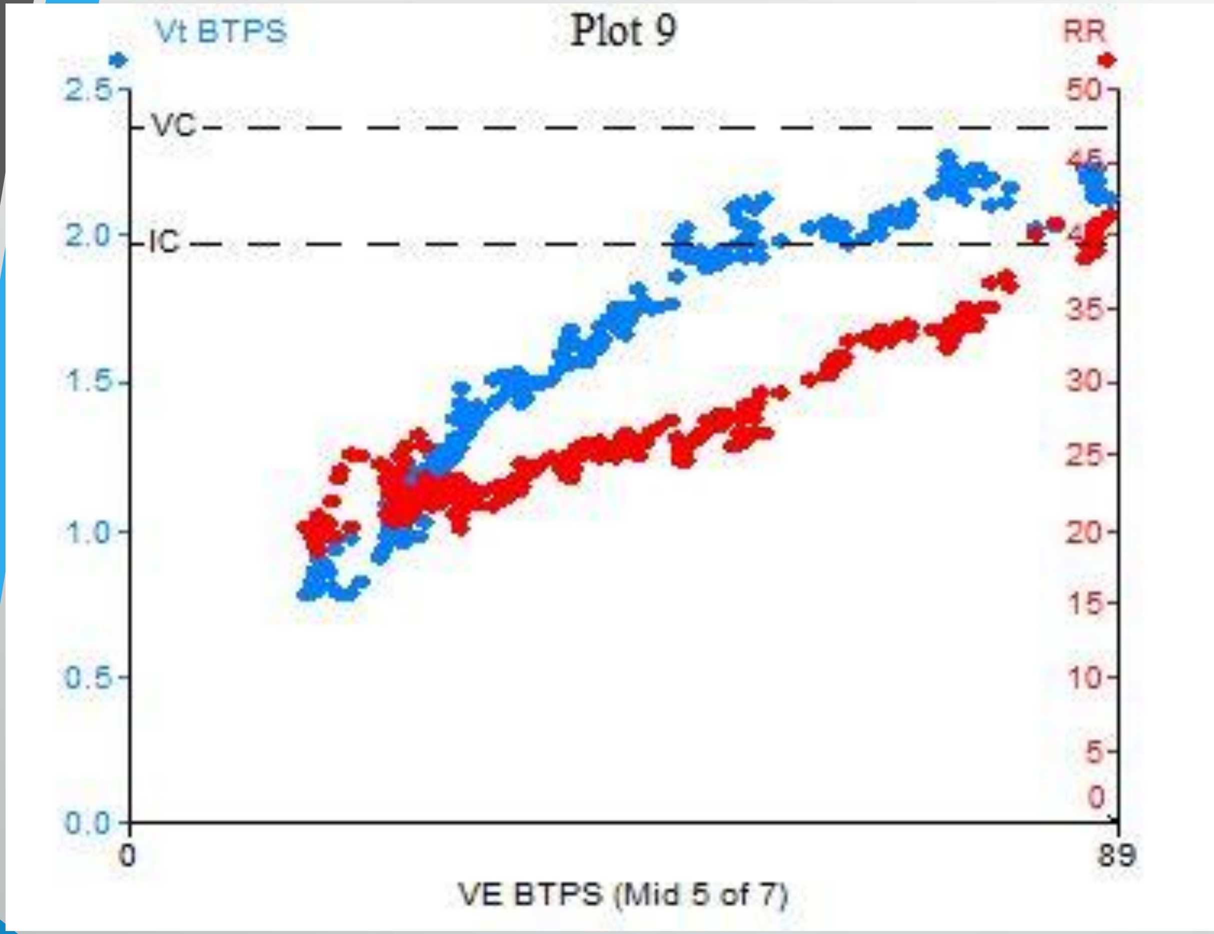


Tidal Volume (liters)
Breathing Frequency (breaths min^{-1})
Ventilation (liters·min^{-1})
f_b
V_T
0 1 2 3 4 5
0 10 20 30 40 50
0 20 40 60 80 100 120 140 160 180

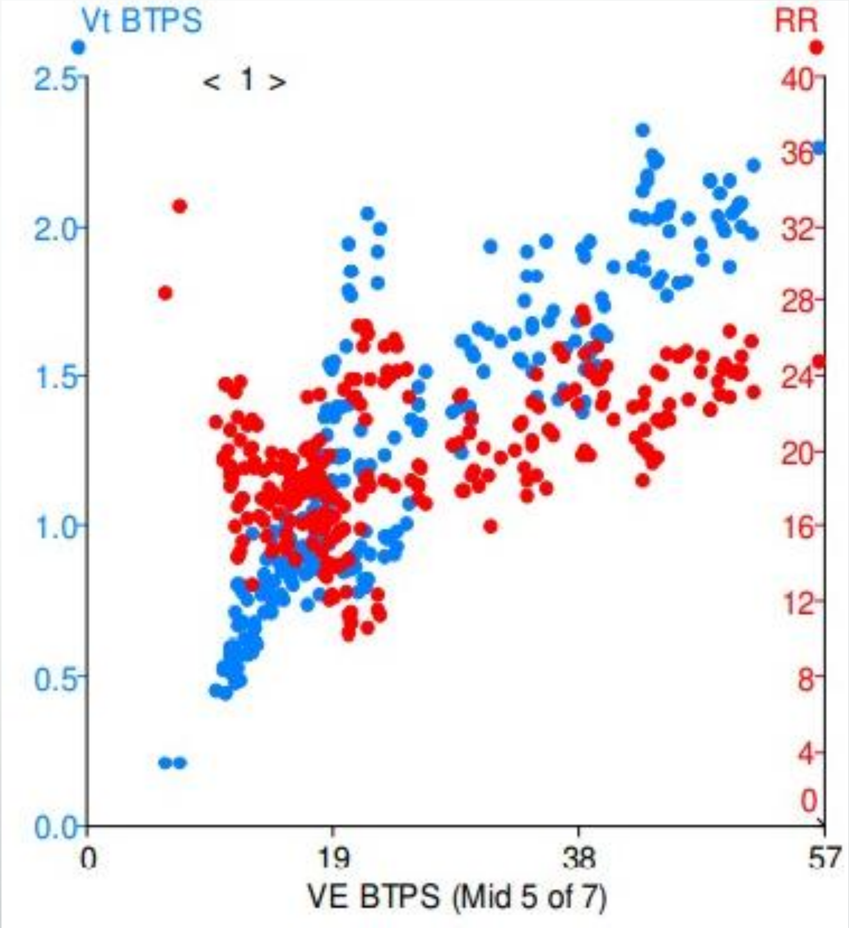


Plot 9
Vt BTPS
RR
VC
IC
0.0 0.5 1.0 1.5 2.0 2.5
0 5 10 15 20 25 30 35 40 45 50
0
89
VE BTPS (Mid 5 of 7)

Normal



Case 3



Resting PETCO2: 29 mmHg

Breathing Pattern Disorder (BPD) / Dysfunctional Breathing

WHAT IS BPD / DYSFUNCTIONAL BREATHING?

A GROUP OF DISORDERS WHERE THERE ARE CHRONIC CHANGES IN BREATHING PATTERN

RESULTING IN:

- Dyspnoea
- Chest tightness
- Chest pain
- Deep sighing
- Exercise-induced dyspnoea
- Frequent yawning
- Hyperventilation

PREVALENCE:

8

8% GENERAL POPULATION

TREATMENT OPTIONS:

NOTE: BPD DOES NOT RESPOND TO ASTHMA TREATMENTS

- Breathing retraining by a qualified professional (e.g. physiotherapist) is recommended
- Having patients differentiate symptoms of BPD and asthma is an important goal

Breathing Pattern Disorder

- Also referred to as dysfunctional breathing (DB)
- Identified on CPET by one or more of the following:
  - Erratic tidal volume (TV) – respiratory rate (RR) response to exercise
  - Low end-tidal CO_2 ($PETCO_2$) at rest and / or failure to rise with exercise
  - Isolated ventilatory inefficiency – high $VE\text{-}VCO_2$
- Treated with breathing retraining

Original Investigation | Cardiology

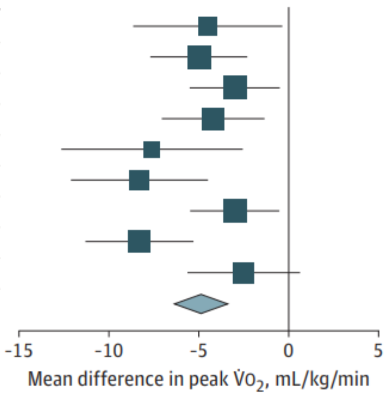
Use of Cardiopulmonary Exercise Testing to Evaluate Long COVID-19 Symptoms in Adults

A Systematic Review and Meta-analysis

Matthew S. Durstenfeld, MD, MAS; Kaiwen Sun, MD; Peggy Tahir, MLIS, MA; Michael J. Peluso, MD, MHS, MPhil, DTMH; Steven G. Deeks, MD; Mandar A. Aras, MD, PhD; Donald J. Grandis, MD; Carlin S. Long, MD; Alexis Beatty, MD; Priscilla Y. Hsue, MD

Figure 2. Meta-analysis of Peak Oxygen Consumption ($\dot{V}O_2$) Among Studies Comparing Patients With and Without Long COVID-19 (LC) Symptoms

Source	No. of participants/mean (SD): LC symptoms	No. of participants/mean (SD): No LC symptoms	Mean difference (95% CI)	Weight, %
Schaeffer et al,[58] 2022	34/19.9 (7.1)	15/24.4 (6.7)	-4.5 (-8.6 to -0.4)	8.22
Aparisi et al,[47] 2021	41/17.8 (4)	29/22.8 (6.6)	-5.0 (-7.7 to -2.3)	13.04
Barbagelata et al,[38] 2022	112/25.8 (8.1)	88/28.8 (9.6)	-3.0 (-5.5 to -0.5)	13.85
Brown et al,[44] 2022	20/14.9 (2.3)	20/19.1 (6.1)	-4.2 (-7.1 to -1.3)	12.38
Durstenfeld et al,[26] 2022	23/21.2 (8.2)	16/28.8 (7.7)	-7.6 (-12.6 to -2.6)	6.28
Ladlow et al,[31,69] 2022	61/32.4 (6.7)	26/40.7 (8.9)	-8.3 (-12.1 to -4.5)	9.12
Margalit et al,[37] 2022	66/27.7 (7.5)	75/30.7 (7.5)	-3.0 (-5.5 to -0.5)	13.96
Skjørten et al,[33] 2021	59/23.6 (7.9)	67/31.9 (9.3)	-8.3 (-11.3 to -5.3)	11.81
Szekely et al,[29] 2021	48/18.8 (6.3)	23/21.3 (6.3)	-2.5 (-5.6 to 0.6)	11.34
Heterogeneity: $\tau^2 = 2.51$; $I^2 = 50.28\%$			-4.9 (-6.4 to -3.4)	



By random-effects meta-analysis of 9 studies that included 464 individuals with LC symptoms and 359 individuals without LC symptoms (as defined by each study), the mean difference in peak $\dot{V}O_2$ was −4.9 (95% CI, −6.4 to −3.4) mL/kg/min.

38 studies
2160 patients

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"All truth passes through three stages.
First, it is ridiculed.
Second, it is violently opposed.
Third, it is accepted as
being self-evident."
-Arthur Schopenhauer