Brigham and Women's Hospital
Founding Member, Mass General Brigham

Interpretation of Integrated Cardiopulmonary Exercise Testing

David M Systrom, MD

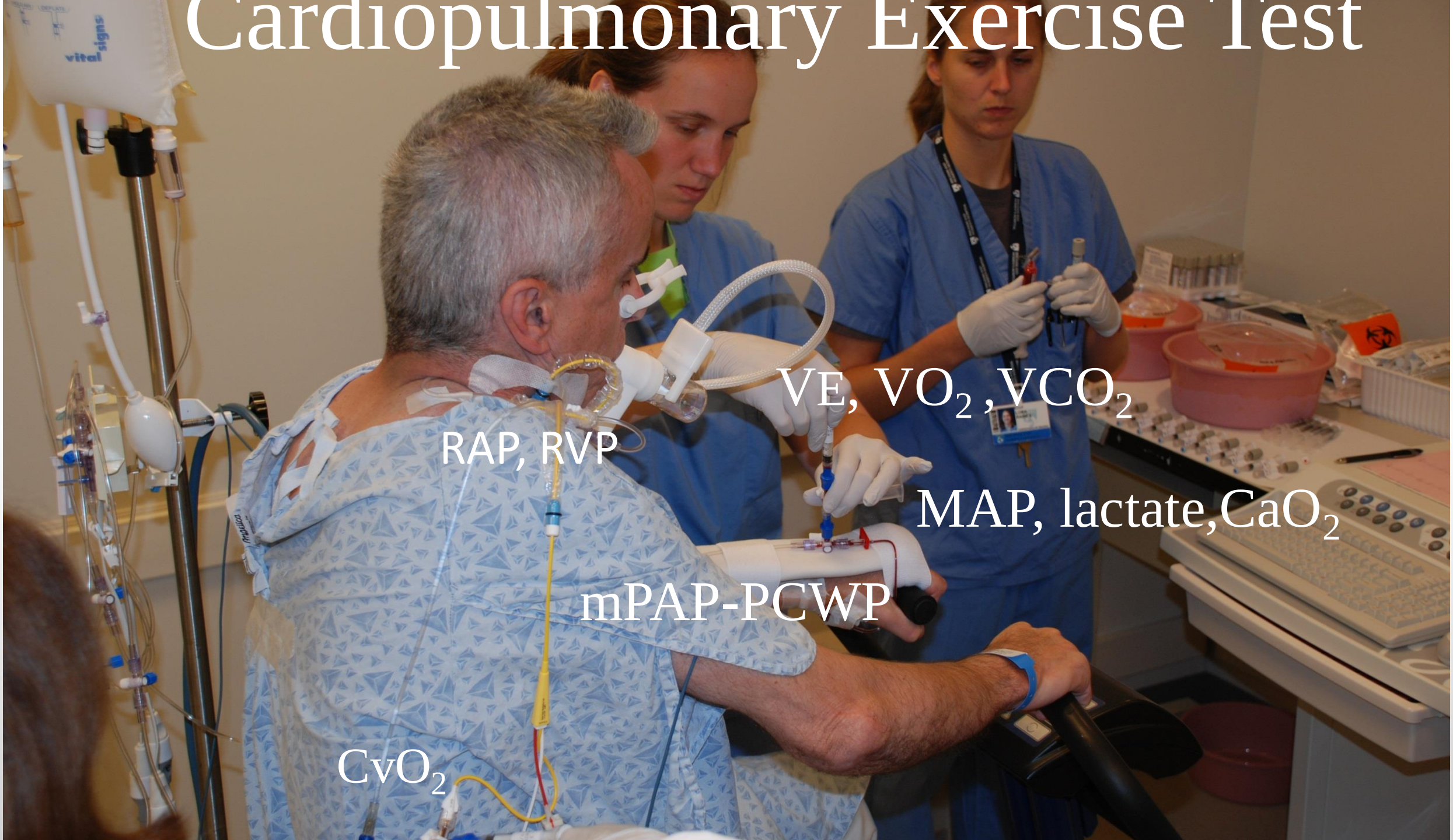
Disclosures

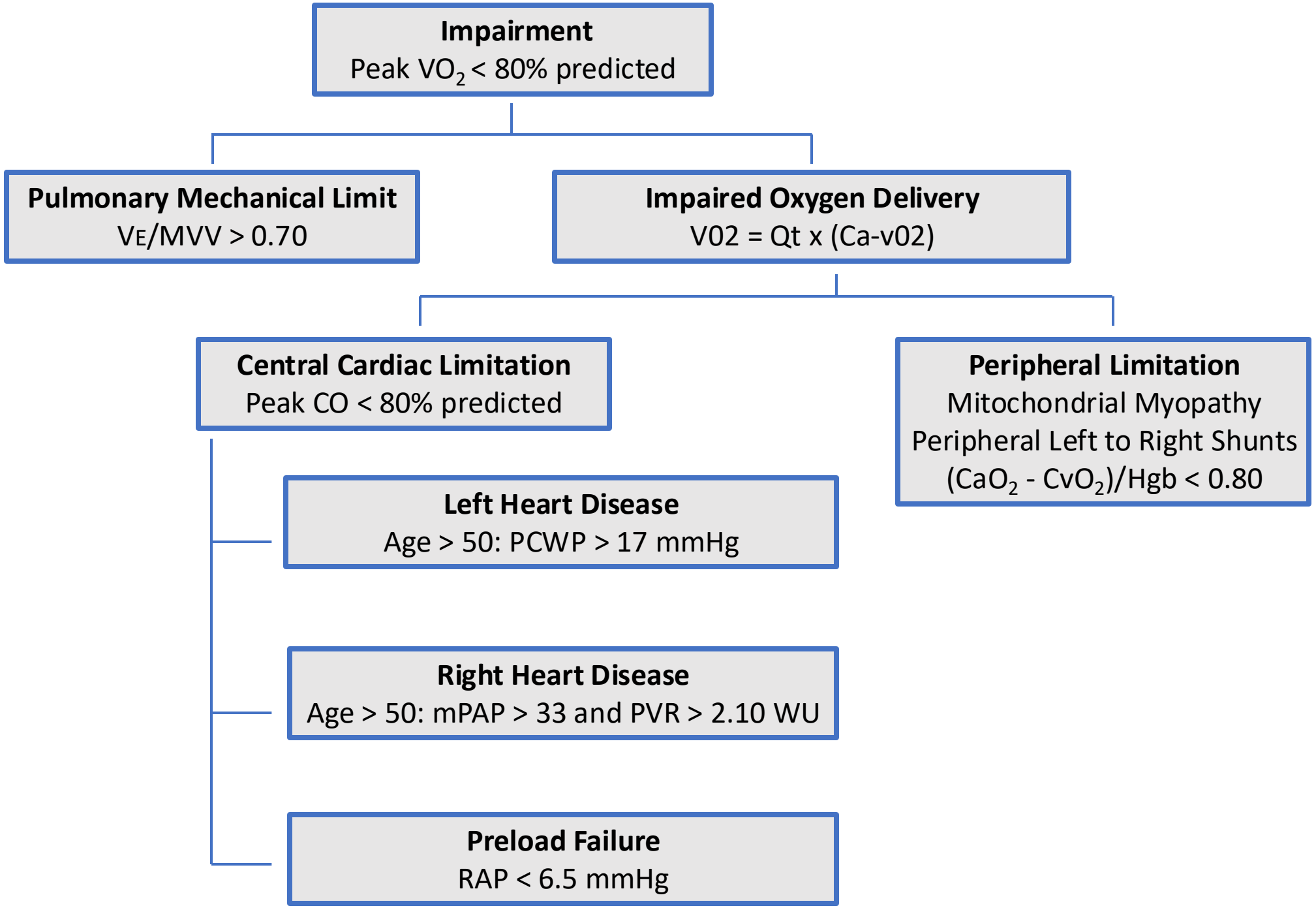
None

Harvard Fatigue Lab

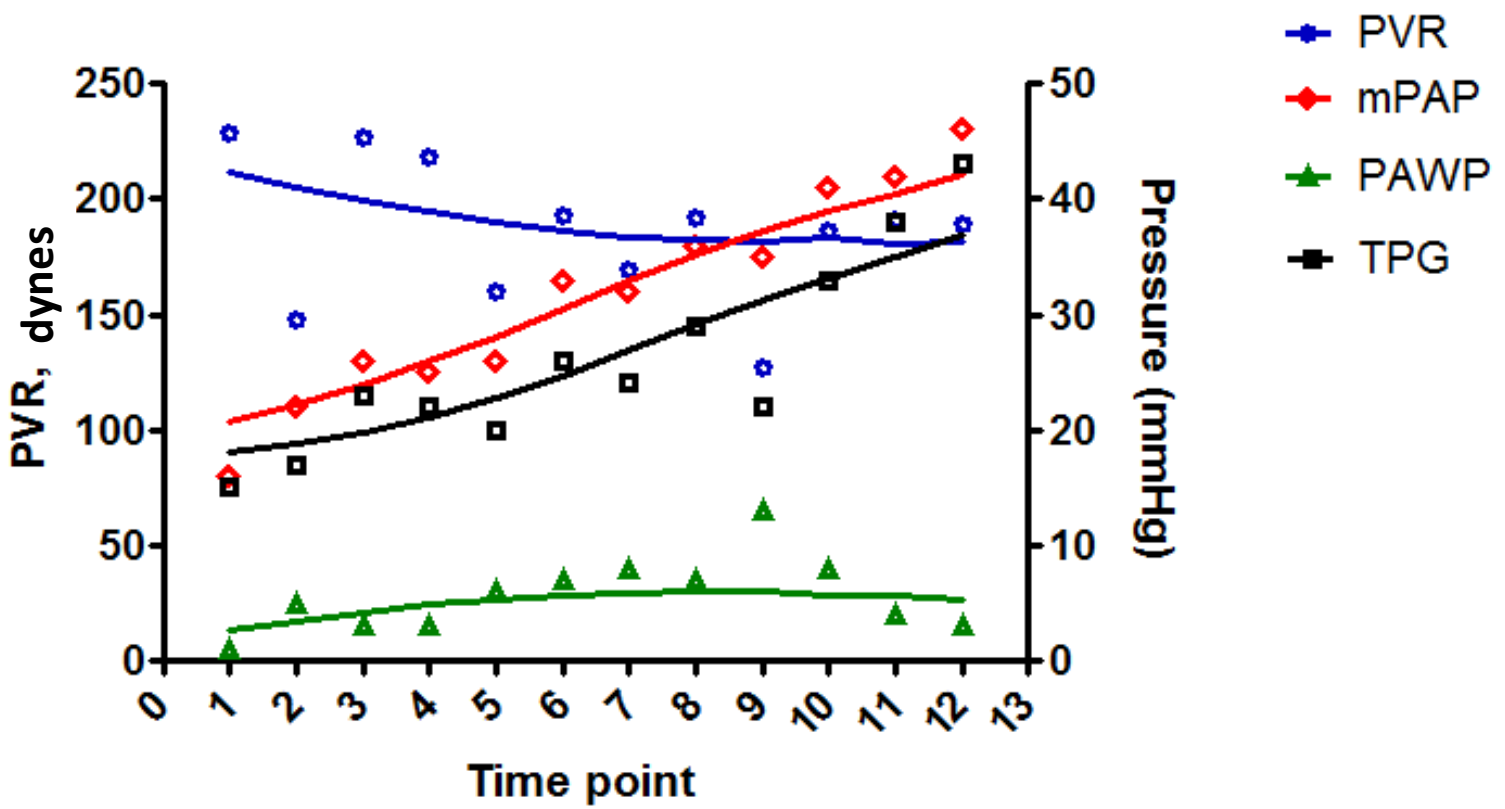
Cardiopulmonary Exercise Test

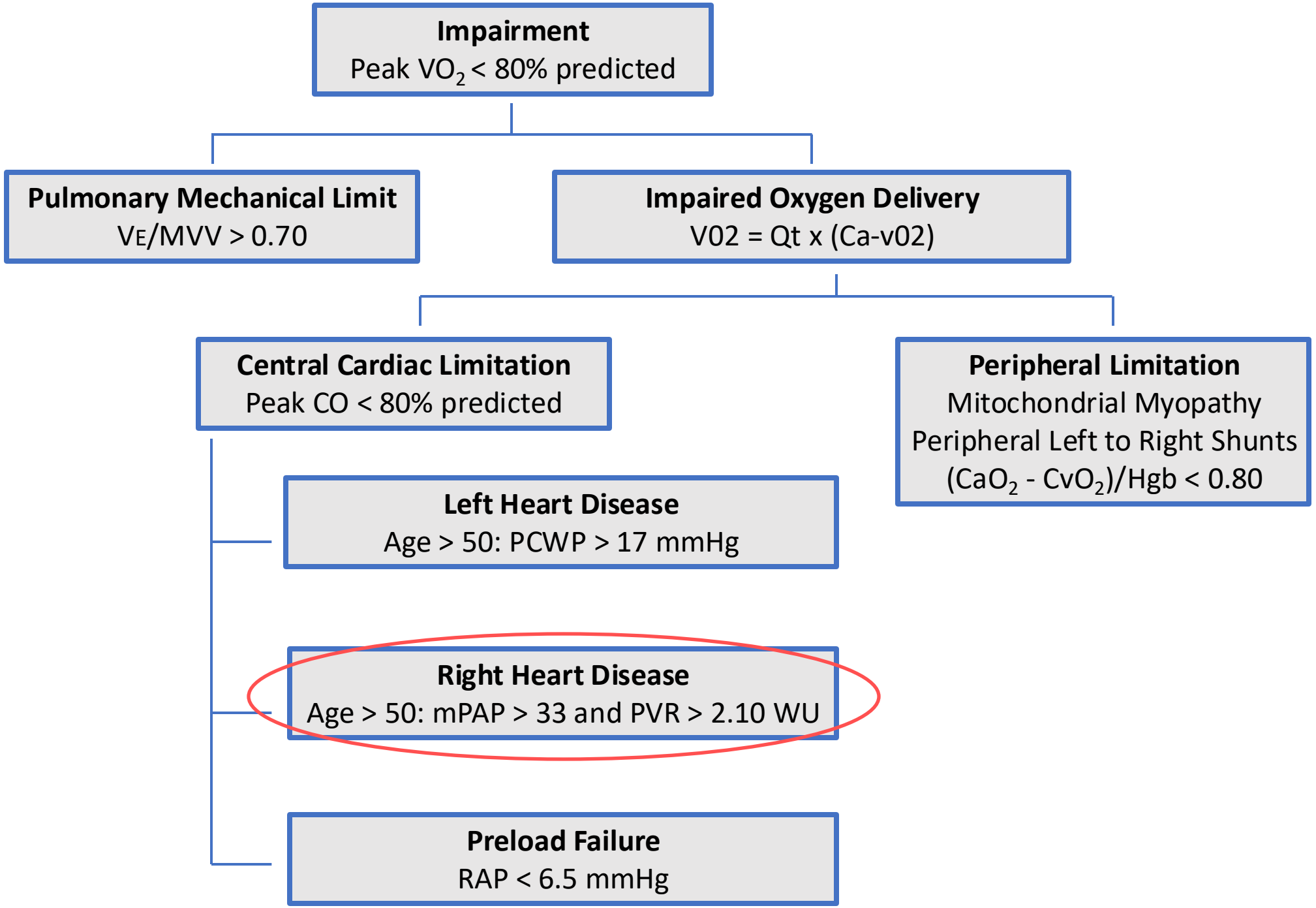
Cardiopulmonary Exercise Test




Impairment
Peak VO_2 < 80% predicted
Pulmonary Mechanical Limit
V_E/MVV > 0.70
Impaired Oxygen Delivery
V02 = Qt x (Ca-v02)
Central Cardiac Limitation
Peak CO < 80% predicted
Peripheral Limitation
Mitochondrial Myopathy
Peripheral Left to Right Shunts
(CaO_2 - CvO_2)/Hgb < 0.80
Left Heart Disease
Age > 50: PCWP > 17 mmHg
Right Heart Disease
Age > 50: mPAP > 33 and PVR > 2.10 WU
Preload Failure
RAP < 6.5 mmHg

Pt MR


PVR
mPAP
PAWP
TPG
PVR, dynes
Pressure (mmHg)
Time point
250
200
150
100
50
0
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13


Impairment
Peak VO_2 < 80% predicted
Pulmonary Mechanical Limit
V_E/MVV > 0.70
Impaired Oxygen Delivery
V02 = Qt x (Ca-v02)
Central Cardiac Limitation
Peak CO < 80% predicted
Peripheral Limitation
Mitochondrial Myopathy
Peripheral Left to Right Shunts
(CaO_2 - CvO_2)/Hgb < 0.80
Left Heart Disease
Age > 50: PCWP > 17 mmHg
Right Heart Disease
Age > 50: mPAP > 33 and PVR > 2.10 WU
Preload Failure
RAP < 6.5 mmHg

Circulation. 2008 Nov 18;118(21):2183-9. doi: 10.1161/CIRCULATIONAHA.108.787101. Epub 2008 Nov 3.

Exercise-induced pulmonary arterial hypertension.

Tolle JJ[1], Waxman AB, Van Horn TL, Pappagianopoulos PP, Systrom DM.

	Normal (n=16)	EIPAH (n=78)	RPAH (n=15)
mPAP rest (mmHg)	13.9±2.9	18.6±3.2 *	30.9±8.9 *, †
mPAP max (mmHg)	27.4±3.7	36.6±5.7 *	48.4±11.1 *, †
PVR rest (dynes-sec/cm^5)	154±61	223±82 *	352±141 *, †
PVR max (dynes-sec/cm^5)	62±20	161±60 *	294±158 *, †

Circulation. 2008 Nov 18;118(21):2183-9. doi: 10.1161/CIRCULATIONAHA.108.787101. Epub 2008 Nov 3.

Exercise-induced pulmonary arterial hypertension.

Tolle JJ[1], Waxman AB, Van Horn TL, Pappagianopoulos PP, Systrom DM.

	Normal (n=16)	EIPAH (n=78)	RPAH (n=15)
Age (years)	45.9±14.9	58.8±15.1 *	58.5±15.7 *
Female gender (%)	68.8	65.8	46.7
BMI	25.5±4.2	30.2±5.3 *	28.1±6.2
Work max (watts)	155.5±43.1	90.3±41.7 *	70.0±41.5 *
VO_2 max (ml/min)	2022±468	1284±58 *	1127±507 *
VO_2 max (% predicted)	91.7±13.7	66.5±16.3 *	55.8±20.3 *, †
Q_t max (% predicted)	99.4±11.1	83.1±18.9 *	71.8±22.4 *, †

Age Related Upper Limit of Normal Exercise Pulmonary Hemodynamics to Diagnosis Exercise PH

	≤ 50 years	> 50 years
Subjects	25	41
RAP, mmHg	13	13
mPAP, mmHg	30	33
PAWP, mmHg	19	17
TPG, mmHg	21	22
DPG, mmHg	14	12
TPR, Woods Unit	2.1	3.2 *
PVR, Woods Unit	1.34	2.10 *
mPAP/CO slope	2.0	2.8 *

* $p < 0.05$ comparing ≤ 50 years and > 50 years

ePH definition during upright exercise:

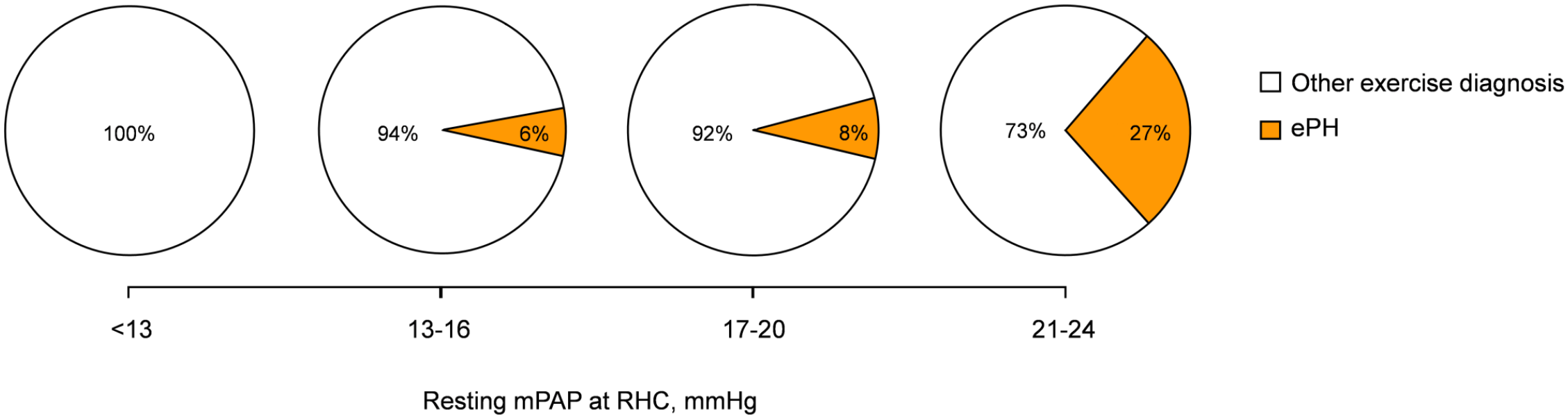
- ≤50 years old: peak mPAP >30 mmHg and peak PVR >1.34 WU
- >50 years old: peak mPAP >33 mmHg and peak PVR >2.10 WU

Oliveira RK et al. *Eur Resp J* 2016; 47:1179-88

Pulm Circ. 2017 Jul-Sep;7(3):654-665. doi: 10.1177/2045893217709025. Epub 2017 Jun 8.

Functional impact of exercise pulmonary hypertension in patients with borderline resting pulmonary arterial pressure.

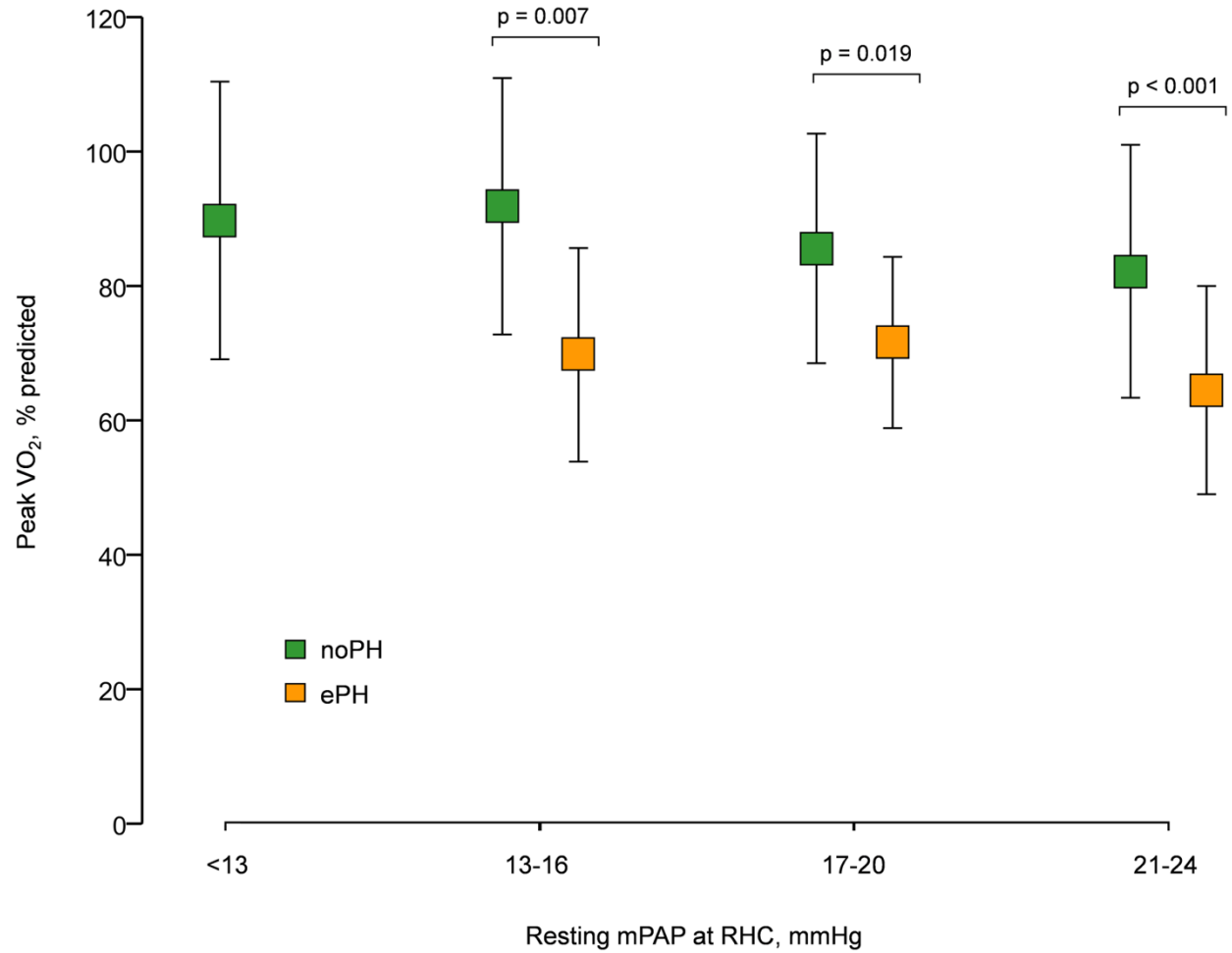
Oliveira RKF[1,2,3], Faria-Urbina M[1,2], Maron BA[4,5], Santos M[6], Waxman AB[1,2], Systrom DM[1,2].



Pulm Circ. 2017 Jul-Sep;7(3):654-665. doi: 10.1177/2045893217709025. Epub 2017 Jun 8.

Functional impact of exercise pulmonary hypertension in patients with borderline resting pulmonary arterial pressure.

Oliveira RKF[1,2,3], Faria-Urbina M[1,2], Maron BA[4,5], Santos M[6], Waxman AB[1,2], Systrom DM[1,2].



Pulmonary haemodynamics during exercise – research network" (PEX-NET)

- Investigate the prognostic relevance of pulmonary hemodynamics during exercise
- primary end-point: mortality/lung transplantation
- secondary end-points
  - hospitalization
  - development of PH at rest
  - initiation of targeted PAH medication

Exercise Pulmonary Hypertension

- Presents w/ unexplained dyspnea
- Intermediate exercise phenotype between normal and resting PAH
- ? Early disease vs stable variant
- Missed by TTE and resting RHC
- Pulmonary vasodilator responsive
- Worse outcome untreated

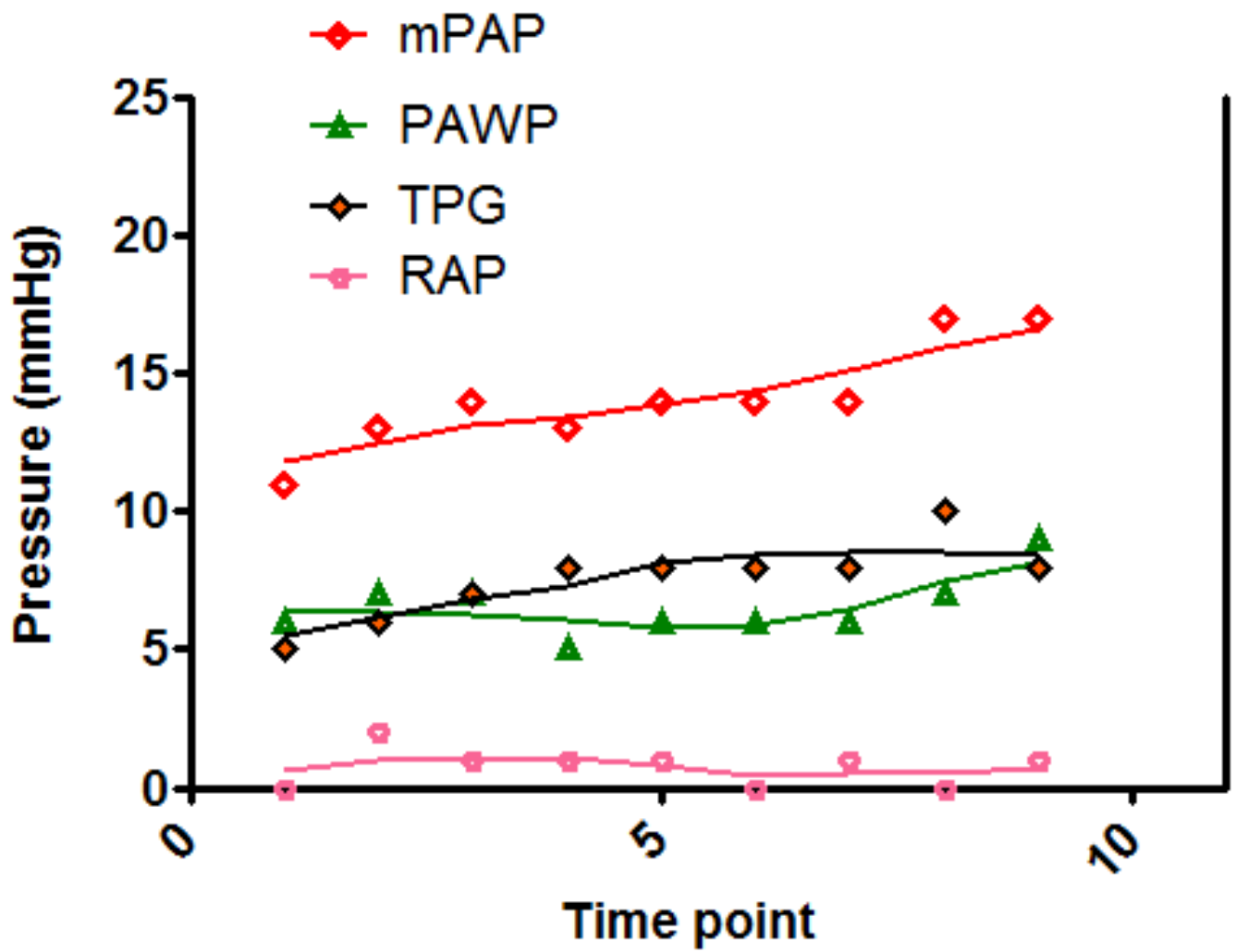
Case CG

- 42 yo F
- Well until acute COVID: cough and fever> 2 week hospitalization, ICU, no intubation
- At D/C and one yr post: fatigue, post exertional malaise, non refreshing sleep, brain fog, orthostatic intolerance, 1 FOS DOE
- Exam, routine labs, TTE, CT chest: all normal

CG: Mildly depressed V02 peak
Normal pulmonary blood flow

- ----------
- Predicted Measured % Pred
- ----------
- Peak VO2 (mL/min) 1595 1173 74%
- Cardiac Output (L/min) 11.4 10.6 93%

CG: iCPET>Preload failure



CG: Impaired Systemic 0_2 extraction

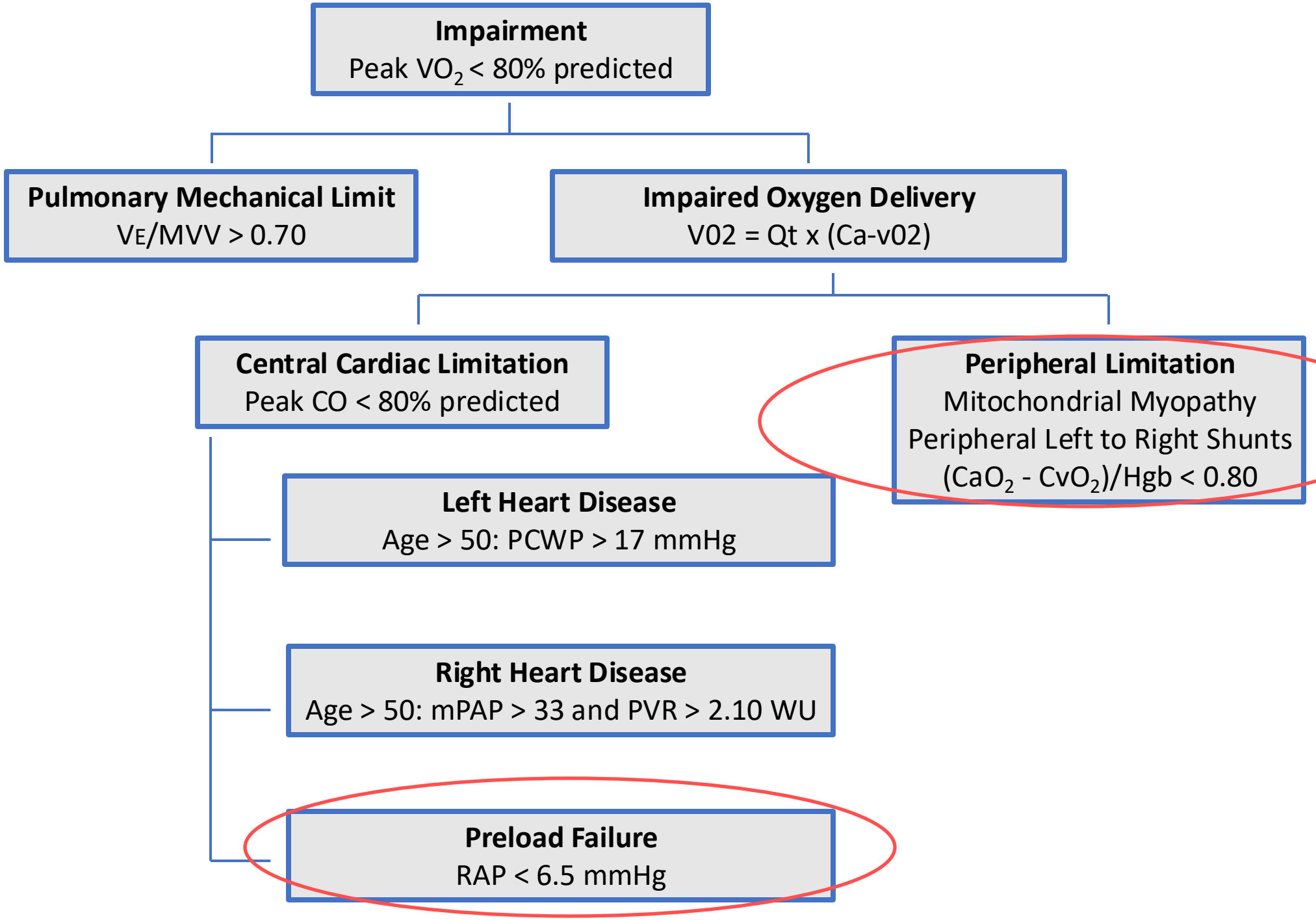
- Time Watts VO2 Qt SvO2 HR SV BP
- ----------
- REST 0 228 4.15 66.4 61 68.0 96/67
- ----------
- ----------
- PEAK 115 1173 10.57 **37.7** 131 80.7 111/69

CG: Skin Bx for SFN

Results To:
David M Systrom MD

FINAL PATHOLOGIC DIAGNOSIS:
SKIN (STANDARD LOWER-LEG SITE), PUNCH BIOPSY:

Morphometric quantitation of epidermal nerve endings yielded epidermal neurite
density (END) of 117 neurites/mm2 skin surface area, at **less than the 1st**
centile. ENDs d 5th centile of predicted are interpreted as pathologically
confirming small-fiber axonopathy in clinically suspected patients.


Impairment
Peak VO_2 < 80% predicted
Pulmonary Mechanical Limit
V_E/MVV > 0.70
Impaired Oxygen Delivery
V02 = Qt x (Ca-v02)
Central Cardiac Limitation
Peak CO < 80% predicted
Peripheral Limitation
Mitochondrial Myopathy
Peripheral Left to Right Shunts
$(CaO_2 - CvO_2)$/Hgb < 0.80
Left Heart Disease
Age > 50: PCWP > 17 mmHg
Right Heart Disease
Age > 50: mPAP > 33 and PVR > 2.10 WU
Preload Failure
RAP < 6.5 mmHg

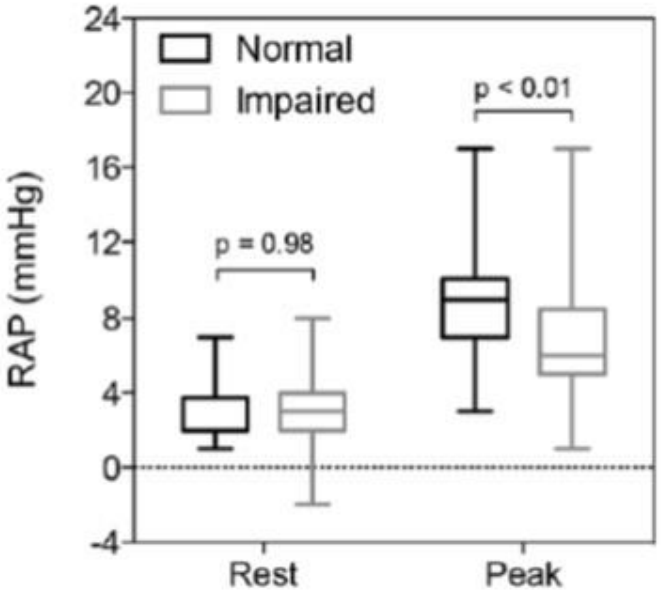
Unexplained exertional dyspnea caused by low ventricular filling pressures: results from clinical invasive cardiopulmonary exercise testing

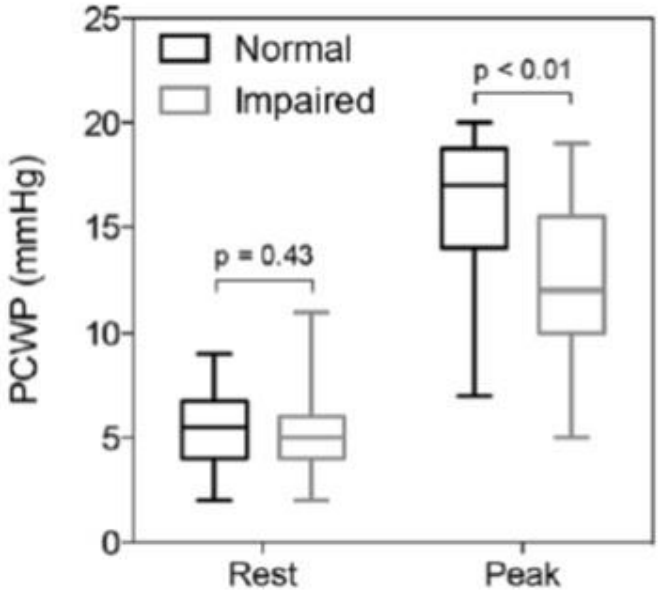
William M. Oldham,[1,2,3] Gregory D. Lewis,[3,4] Alexander R. Opotowsky,[2,3,5] Aaron B. Waxman,[1,2,3] David M. Systrom[1,2,3]

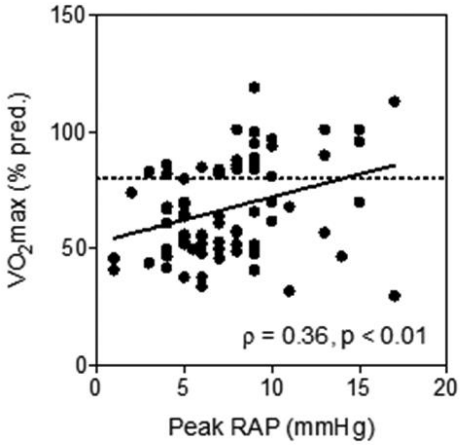
[1]Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; [2]Heart and Vascular Center, Brigham and Women's Hospital, Boston, Massachusetts, USA; [3]Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA; [4]Pulmonary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

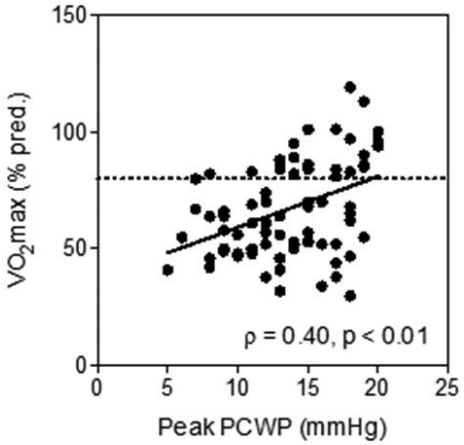
Pulmonary Circulation. March 2016:55-62.
doi:10.1086/685054

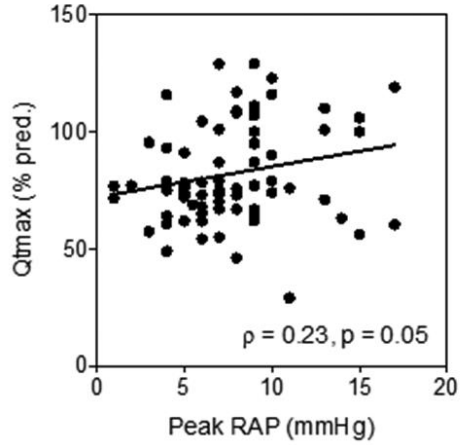
Preload Failure

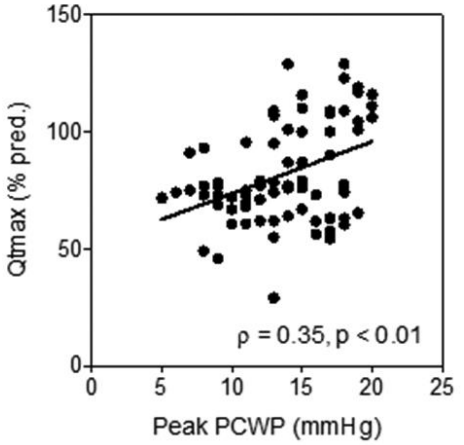












Pulmonary Circulation. March 2016:55-62.
doi:10.1086/685054

Clinical Definitions
ME/CFS (Myalgic encephalomyelitis/chronic fatigue syndrome)

- Intractable fatigue > six months
- Post-exertional malaise
- Non-refreshing sleep
- Brain fog
- Orthostatic intolerance

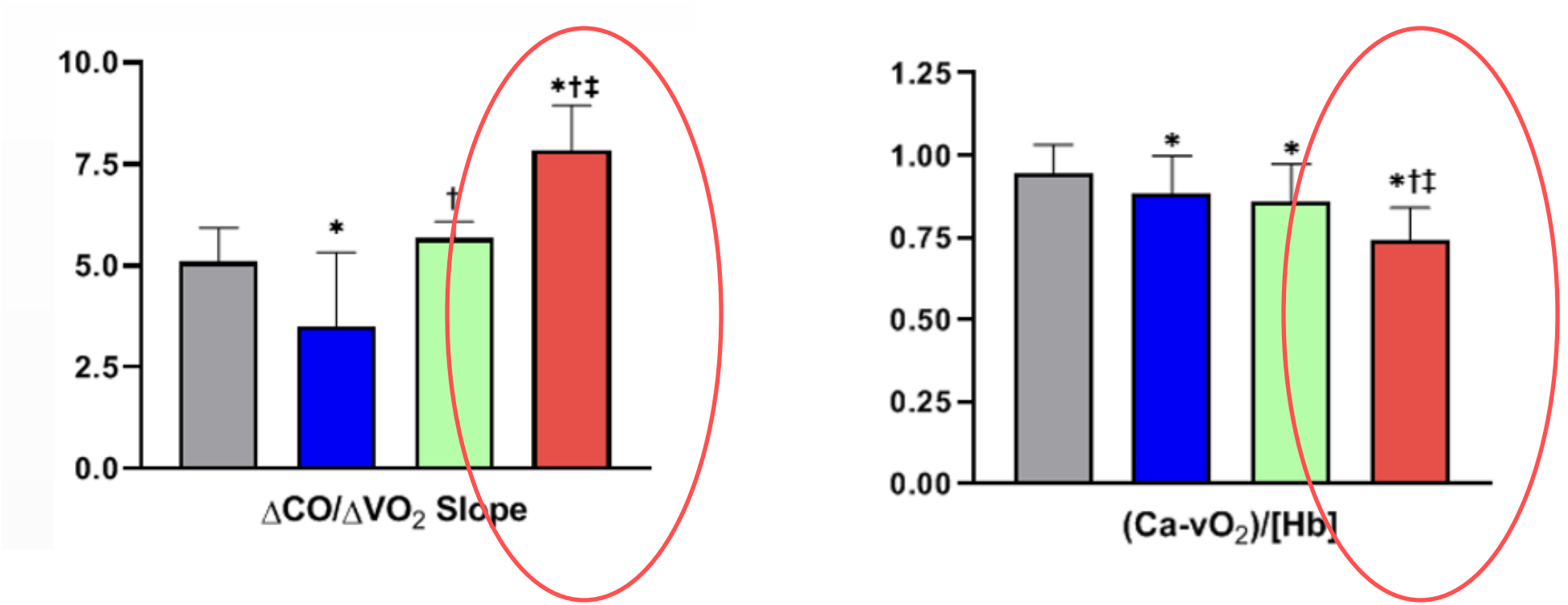
Insights From Invasive Cardiopulmonary Exercise Testing of Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Phillip Joseph, MD; Carlo Arevalo, MD; Rudolf K. F. Oliveira, MD, PhD; Mariana Faria-Urbina, MD; Donna Felsenstein, MD; Anne Louise Oaklander, MD, PhD; and David M. Systrom, MD

Chest. 2021 Aug;160(2):642-651. doi: 10.1016/j.chest.2021.01.082. Epub 2021 Feb 10. PMID: 33577778.

High flow = poor systemic 02 extraction

V02=Qc x (Ca-v02)

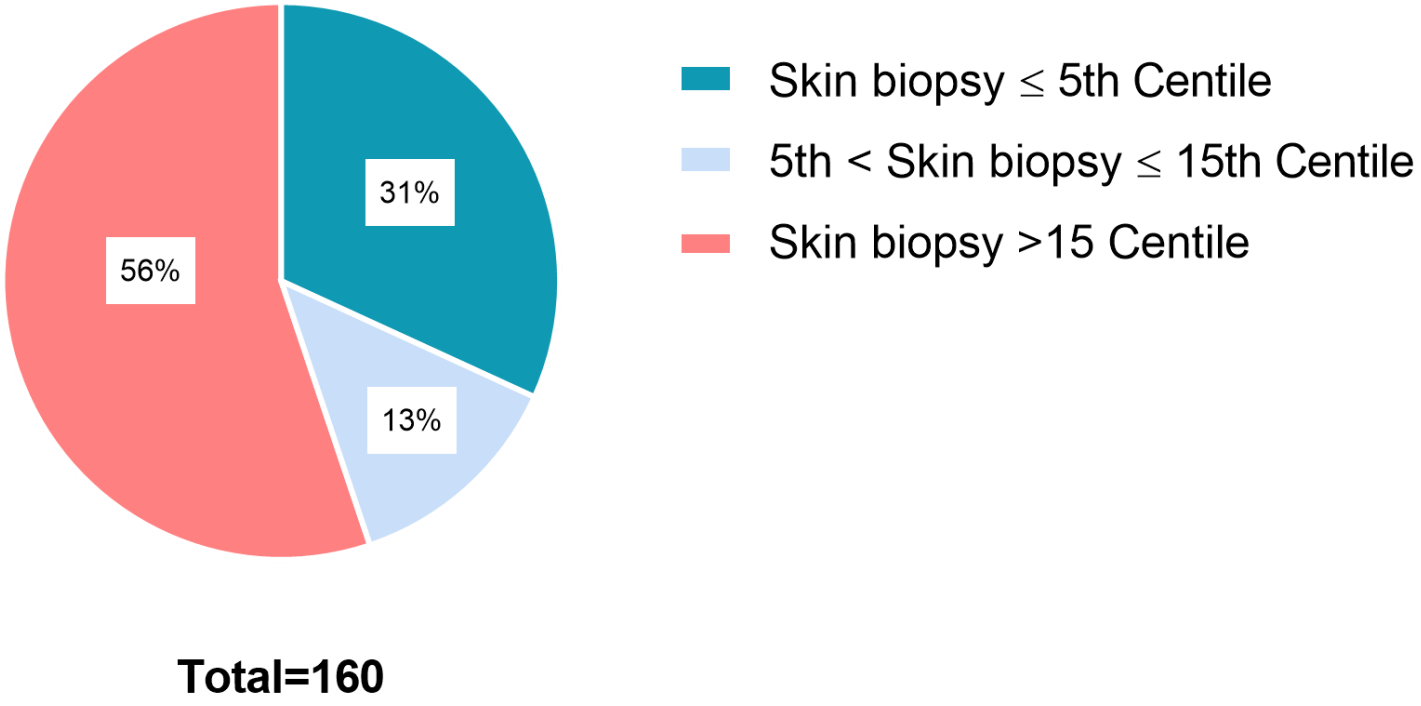


Chest. 2021 Aug;160(2):642-651. doi: 10.1016/j.chest.2021.01.082. Epub 2021 Feb 10. PMID: 33577778.

Small Fiber Neuropathy

Table 1: Baseline Characteristics	
Subjects	
Number	160
Age (year)	47 ± 16
Female (%)	125 (78%)
White Race (%)	149 (93%)
Weight (kg)	73 ± 17
Height (cm)	167 ± 9
BMI (kg.m-2)	25.6 ± 5.3
Hb (g/dL)	14.1 ± 1.4
Comorbidities (%)	
Hypertension	33 (21%)
Obesity	33 (21%)
Dyslipidemia	28 (18%)
CV family history	10 (6%)
Diabetes mellitus	6 (4%)
Coronary artery disease	3 (2%)
Prior myocardial infarction	5 (3%)
Medications (%)	
Statins	26 (16%)
Beta blockers	25 (16%)
Aspirin	25 (16%)
Calcium channel blockers	14 (9%)
Diuretics	14 (9%)
ACE inhibitors	11 (7%)
Associated Conditions (%)	
Small Fiber Polyneuropathy	70 (44%)
≤ 5th centile	50 (31%)
5th < centile ≤ 15th centile	20 (13%)
POTS	52 (33%)
Fibromyalgia	35 (22%)
MCAS	11 (22%)
Preceding Infection	39 (24%)

Skin biopsy in ME/CFS



Total=160

Chest. 2021 Aug;160(2):642-651. doi: 10.1016/j.chest.2021.01.082. Epub 2021 Feb 10. PMID: 33577778.

› Chest. 2021 Aug 11;S0012-3692(21)03635-7. doi: 10.1016/j.chest.2021.08.010.
Online ahead of print.

Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing

Inderjit Singh [1], Phillip Joseph [2], Paul M Heerdt [3], Marjorie Cullinan [4], Denyse D Lutchmansingh [2], Mridu Gulati [2], Jennifer D Possick [2], David M Systrom [5], Aaron B Waxman [5]

Affiliations + expand

PMID: 34389297 PMCID: PMC8354807 DOI: 10.1016/j.chest.2021.08.010

Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing

Variable	Patients Recovered from COVID-19 (n = 10)	Control Participants (n = 10)	*P* Value
Maximum CPET data			
Peak VO_2, % predicted	70 ± 11	131 ± 45	.001
Cardiac output, % predicted	115 ± 44	123 ± 34	.64
Peak EO_2	0.49 ± 0.1	0.78 ± 0.1	< .0001
RA pressure, mm Hg	3 ± 4	6 ± 3	.08

Singh I, Joseph P, Heerdt PM, Cullinan M, Lutchmansingh DD, Gulati M, Possick JD, Systrom DM, Waxman AB. Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing. Chest. 2021 Aug 11:S0012-3692(21)03635-7. doi: 10.1016/j.chest.2021.08.010. Epub ahead of print. PMID: 34389297; PMCID: PMC8354807.

Case CG
Follow-up

- started pyridostigmine 30 mg po BID, graded exercise
- fatigue, OI and DOE “85% better”

Preload Failure/L to R shunting

- Young women, SOB, fatigue, lightheadedness
- Exacerbations after stress: viral, COVID
- Overlap w/ POTS/OH, SFN , Mt myopathy
- Tilt Table may help, cort stim, consider structurally impaired venous return, e.g., chronic DVT
- Rx salt and H_20 load, compression stockings, graded exercise, fludrocortisone, midodrine, pyridostigmine, LDN, IVIg

Take-Home Messages

a. CPET is indicated for un- or underexplained exertional intolerance after a thorough hx, exam, routine labs, full PFT's, TTE and chest radiography when appropriate
b. niCPET can screen for degree of impairment, differentiate heart v. lung dz
c. iCPET can rule in or out exercise PH, HFpEF, dysautonomia and/or suggest a Mt myopathy

References

- Maron BA, Cockrill BA, Waxman AB, Systrom DM. The invasive cardiopulmonary exercise test. Circulation. 2013;127:1157-1164
- Oldham WM, Lewis GD, Opotowsky AR, Waxman AB, Systrom DM. Unexplained exertional dyspnea caused by low ventricular filling pressures: results from clinical invasive cardiopulmonary exercise testing. Pulm Circ 2016; 6:1, 55-62
- Joseph, P, et al. Chest. 2021 Aug;160(2):642-651. doi: 10.1016/j.chest.2021.01.082. Epub 2021 Feb 10. PMID: 33577778.
- Singh I, Joseph P, Heerdt PM, Cullinan M, Lutchmansingh DD, Gulati M, Possick JD, Systrom DM, Waxman AB. Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing. Chest. 2021 Aug 11:S0012-3692(21)03635-7. doi: 10.1016/j.chest.2021.08.010.
- Joseph P , et al. Exercise Pathophysiology in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Post-Acute Sequelae of SARS-CoV-2: More in Common Than Not?. Chest 2023; 164(3):717-726. doi: https://doi.org/10.1016/j.chest.2023.03.049