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

Cardiopulmonary Exercise Testing – Indications and Interpretation

David M Systrom, MD

CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

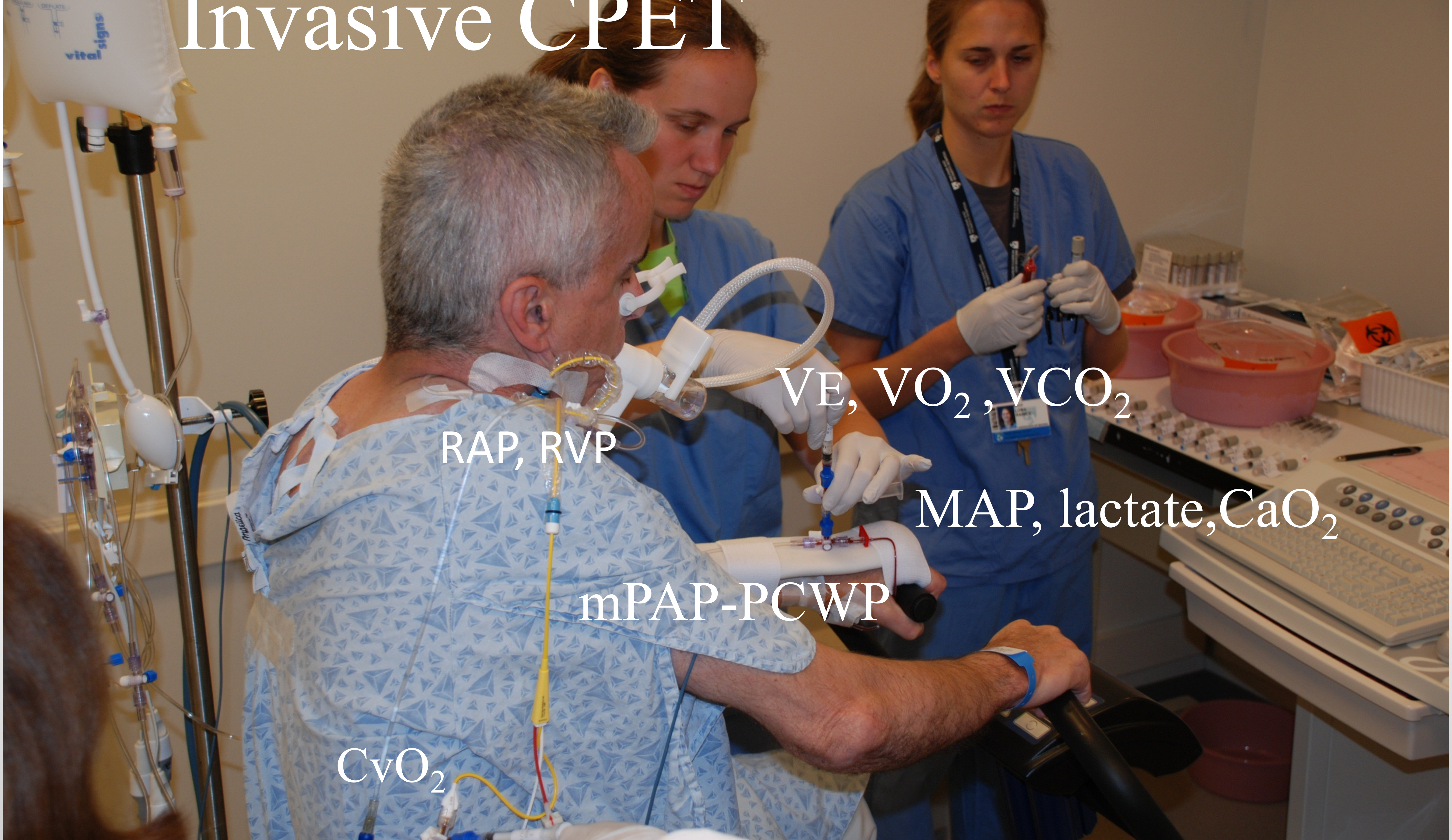
Disclosures

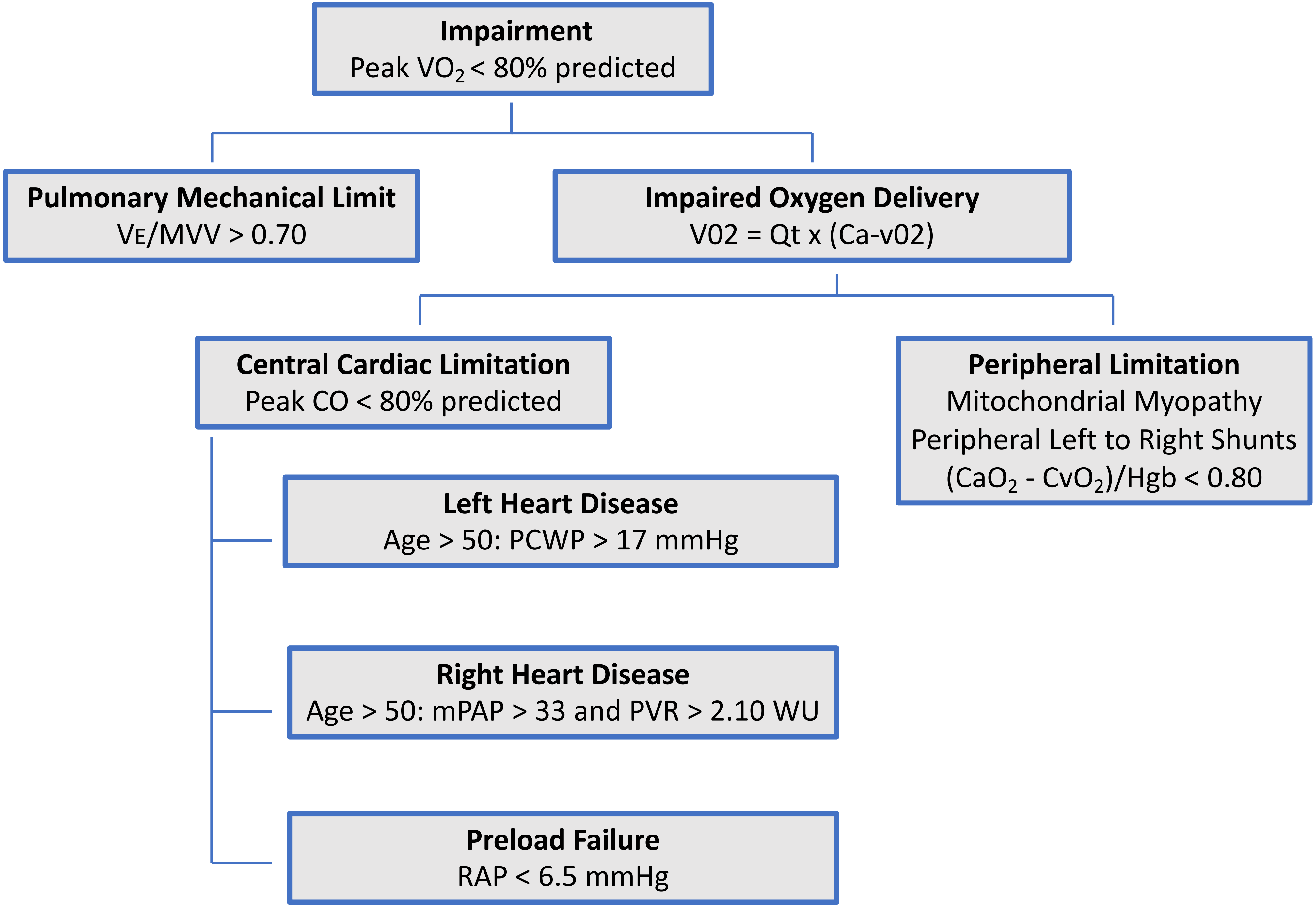
None

Harvard Fatigue Lab

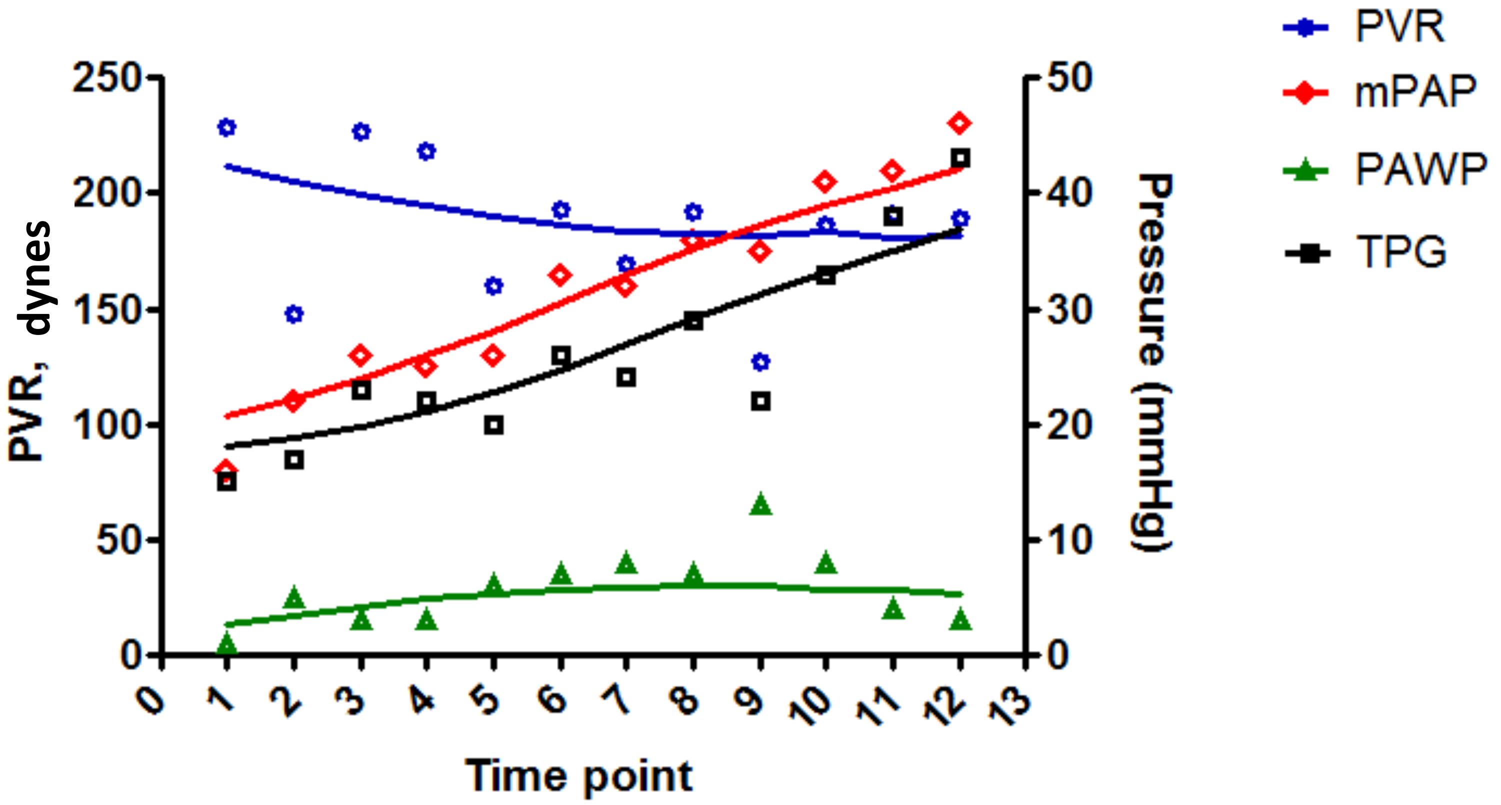
Cardiopulmonary Exercise Test

Invasive CPET

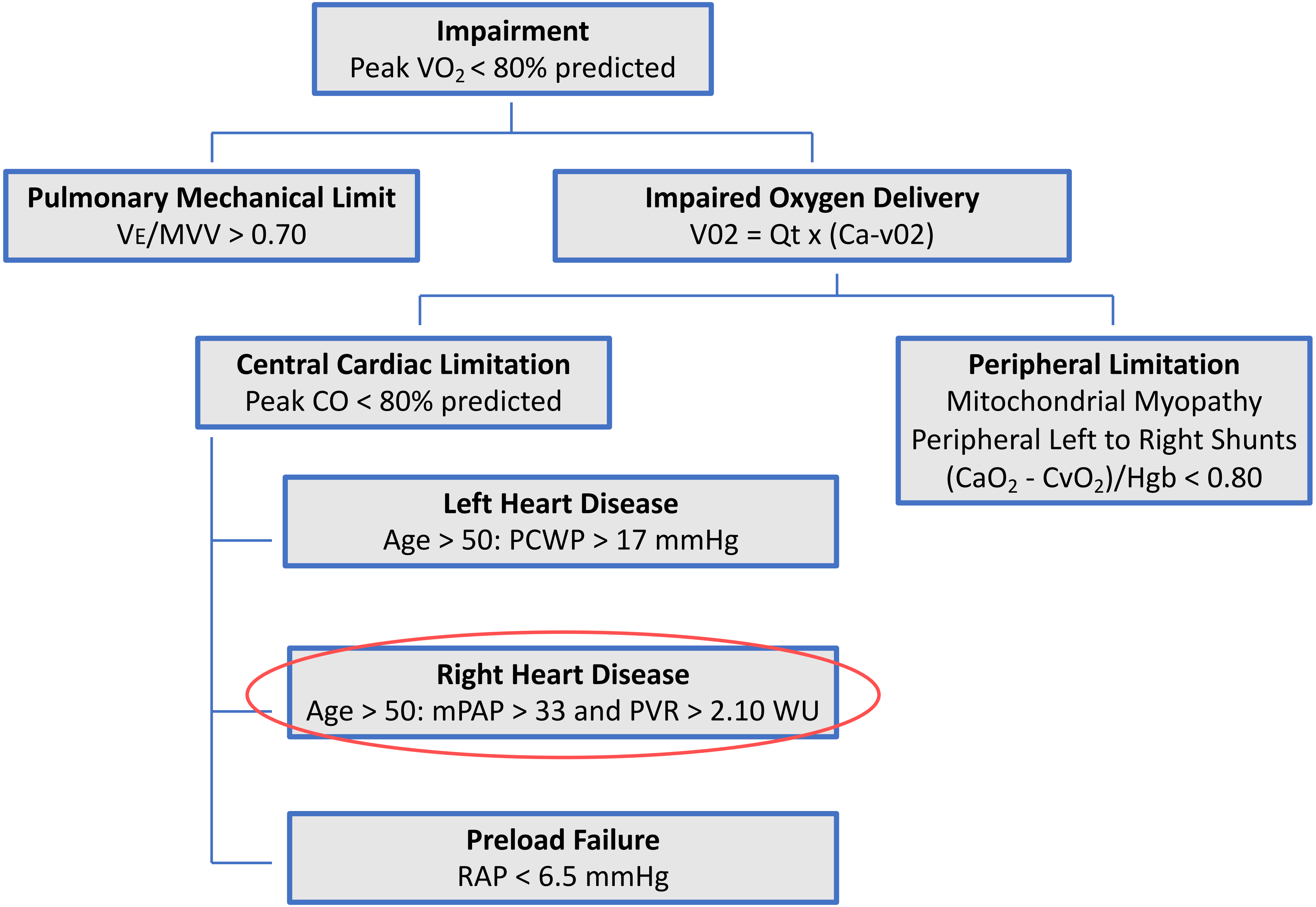



Impairment
Peak VO2 < 80% predicted
Pulmonary Mechanical Limit
VE/MVV > 0.70
Impaired Oxygen Delivery
V02 = Qt x (Ca-v02)
Central Cardiac Limitation
Peak CO < 80% predicted
Peripheral Limitation
Mitochondrial Myopathy
Peripheral Left to Right Shunts
(CaO2 - CvO2)/Hgb < 0.80
Left Heart Disease
Age > 50: 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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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.

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	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 (ePH)

	≤ 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:

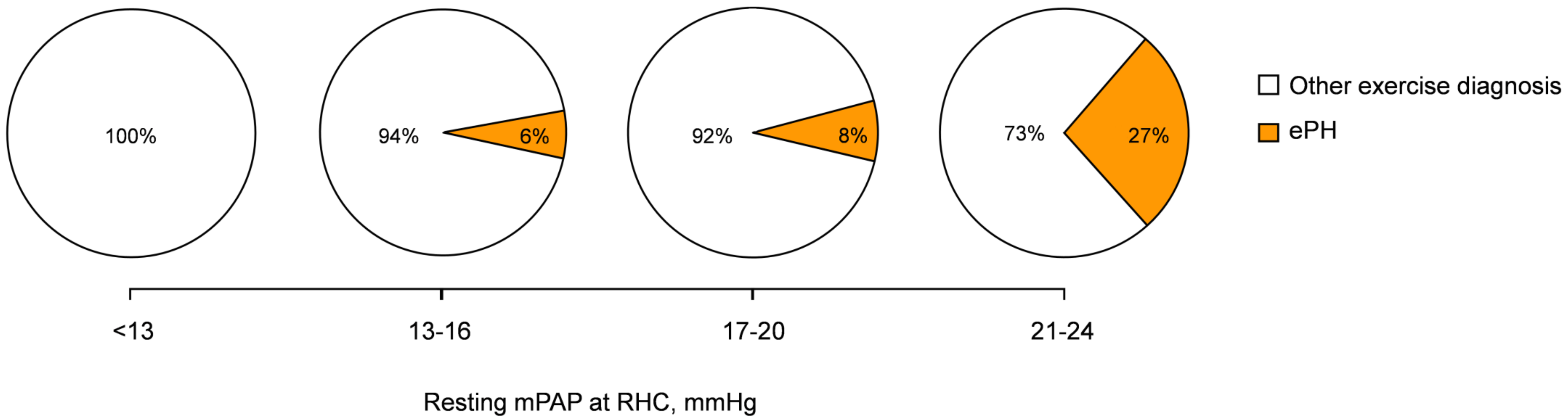
- ≤50 years old: peak mPAP >30 mmHg and peak PVR >1.34 WU
- >50 years old: peak mPAP >33 mmHg and peak PVR >2.10 WU

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].



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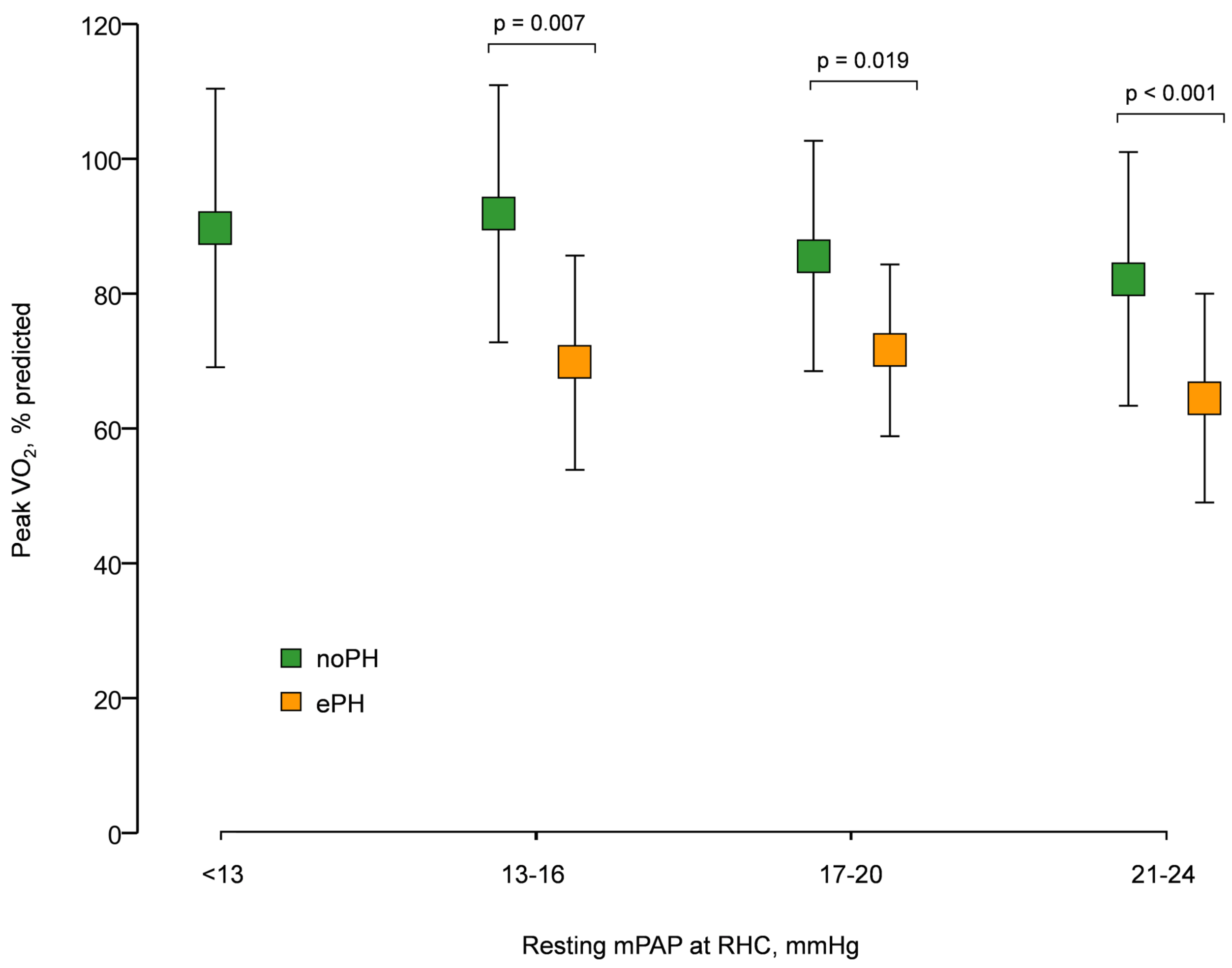
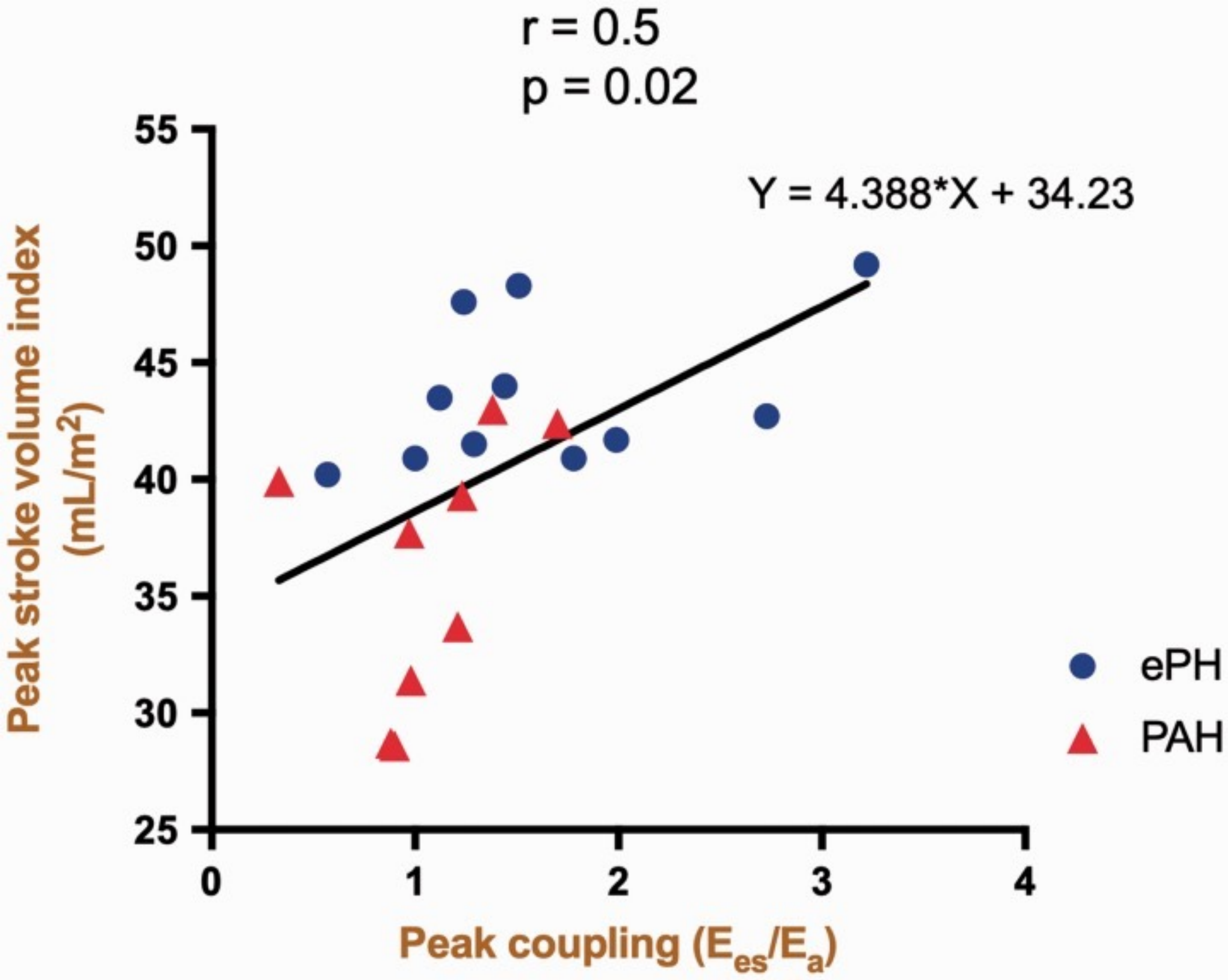
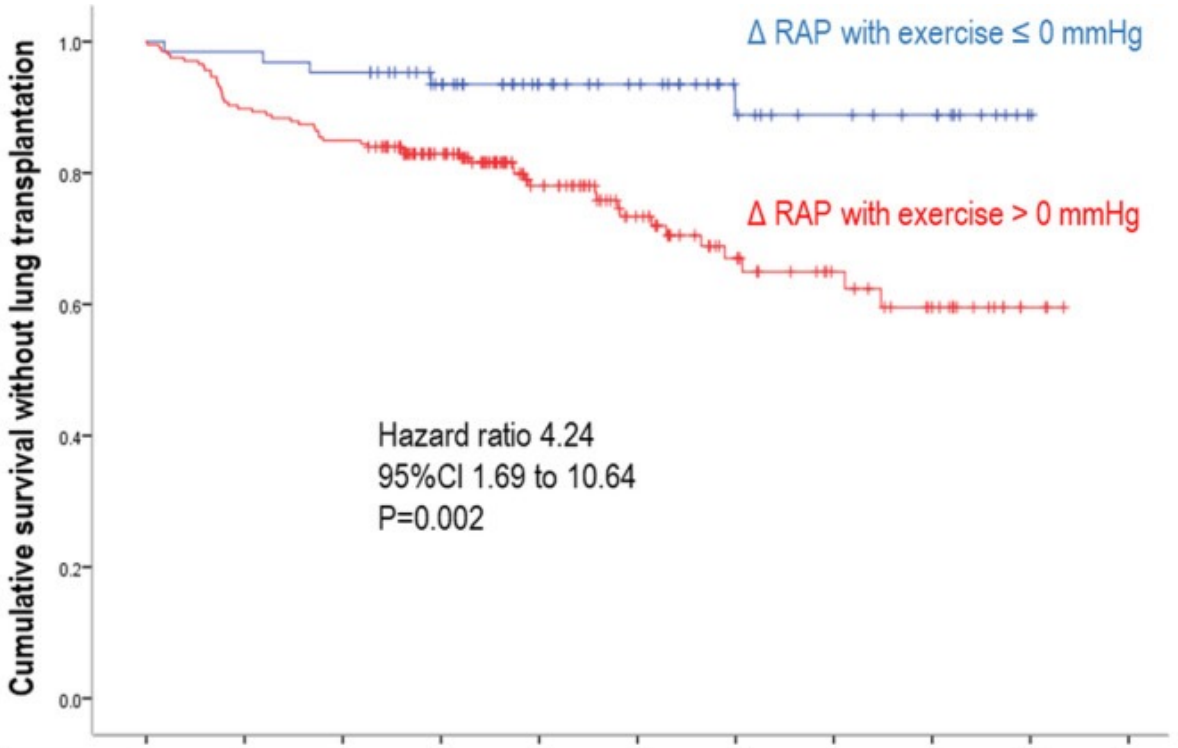


Exercise RV-PA uncoupling in PAH



Singh, I, Rahaghi, FN, Naeije, R , Oliveira, RKF, Vanderpool, RR, Waxman, AB Systrom, DM
Pulm Circ Jul-Sep 2019;9(3):2045894019862435.

Right Atrial Pressure During Exercise Predicts Survival in Patients With Pulmonary Hypertension



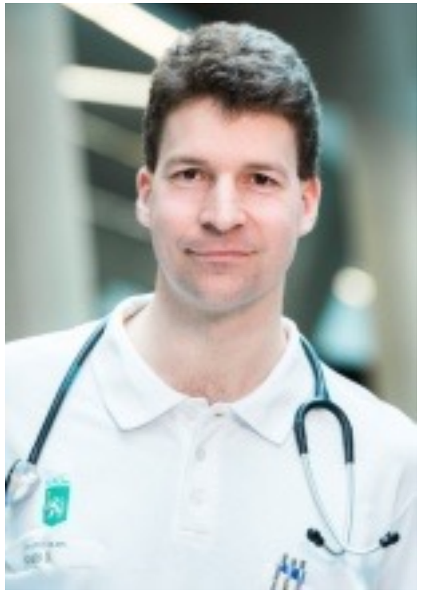
Years	1	2	3	4	5	6	7	8	9	10	11
Δ RAP with exercise ≤ 0 mmHg	64	63	61	50	36	30	22	14	11	1	0
Δ RAP with exercise> 0 mmHg	206	185	175	138	84	56	36	25	16	3	0

Silvia Ulrich, MD

Lichtblau, J et al., Am Heart Assoc 2020 Nov 17;9. doi: 10.1161/JAHA.120.018123. Epub 2020 Nov 4.

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

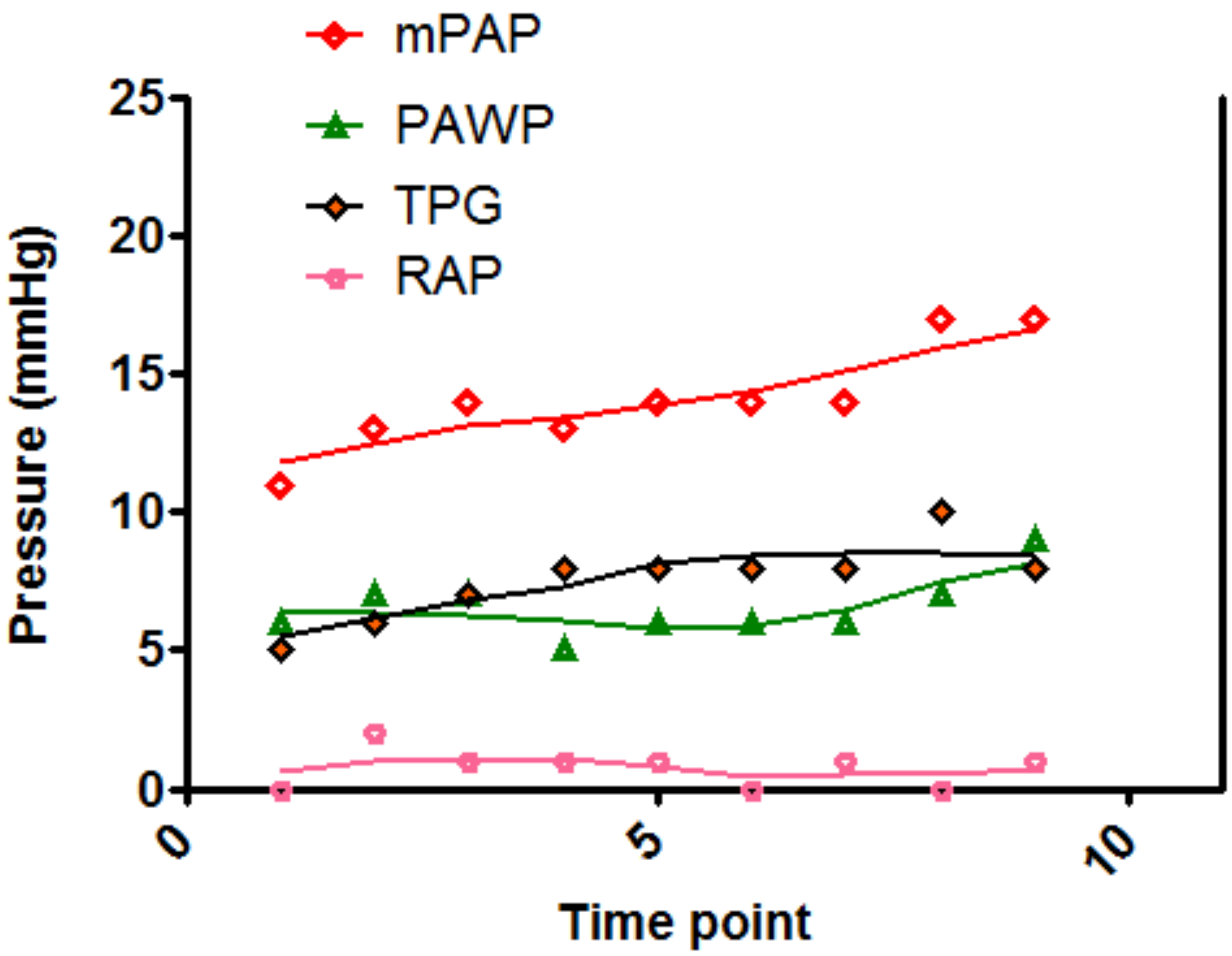
Case CG

- 42 yo F
- Well until acute COVID 3/21: 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

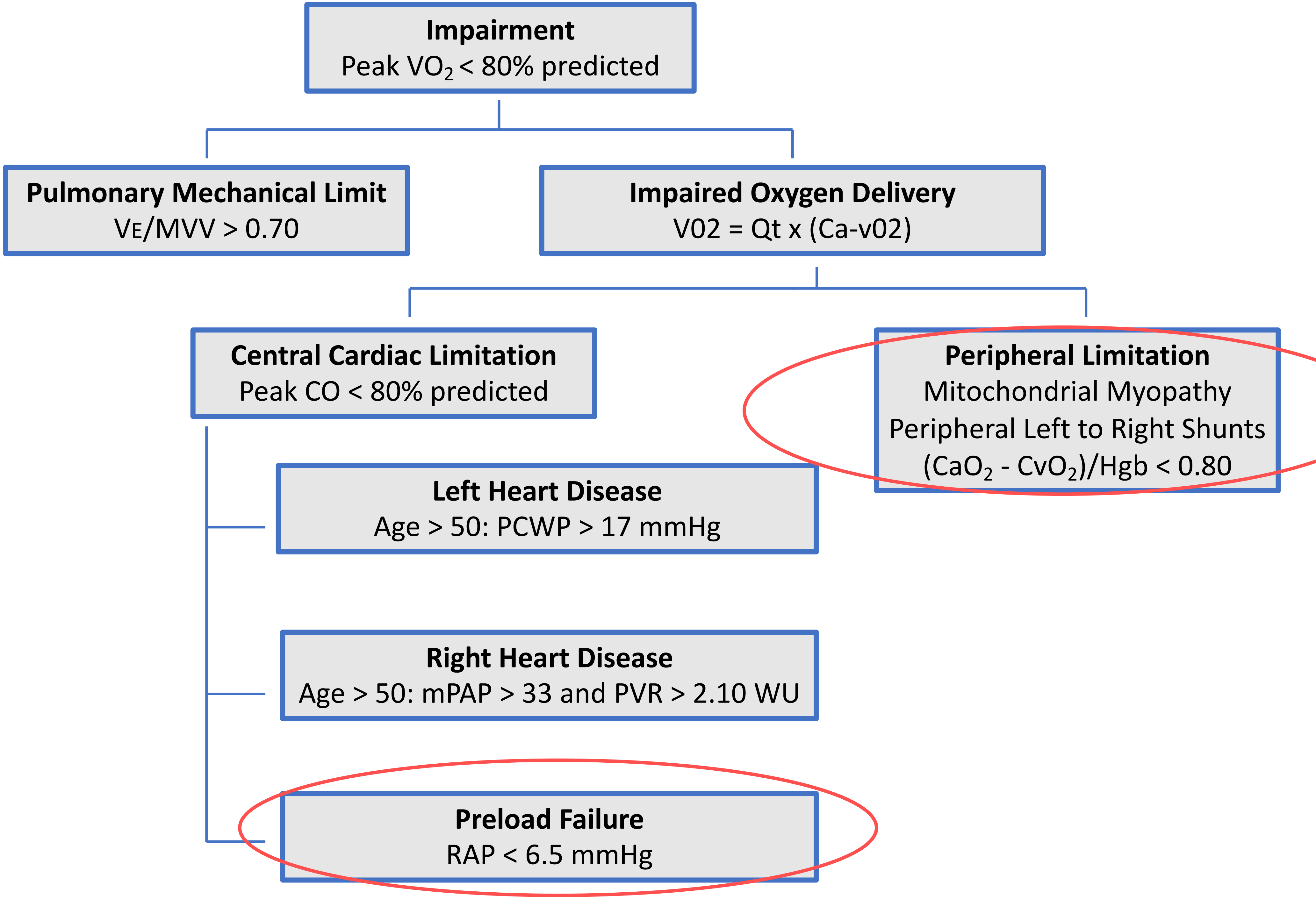
- Time Watts VO2 Qt SvO2 HR SV BP
- ---
- REST 0 228 4.15 66.4 61 68.0 96/67
- ---
- ---
- PEAK 115 1173 10.57 **37.7** 131 80.7 111/69

CG: Skin Bx for SFN

9/20/2021
Reported: 10/4/2021 13:15
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.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Preload Failure
RAP < 6.5 mmHg

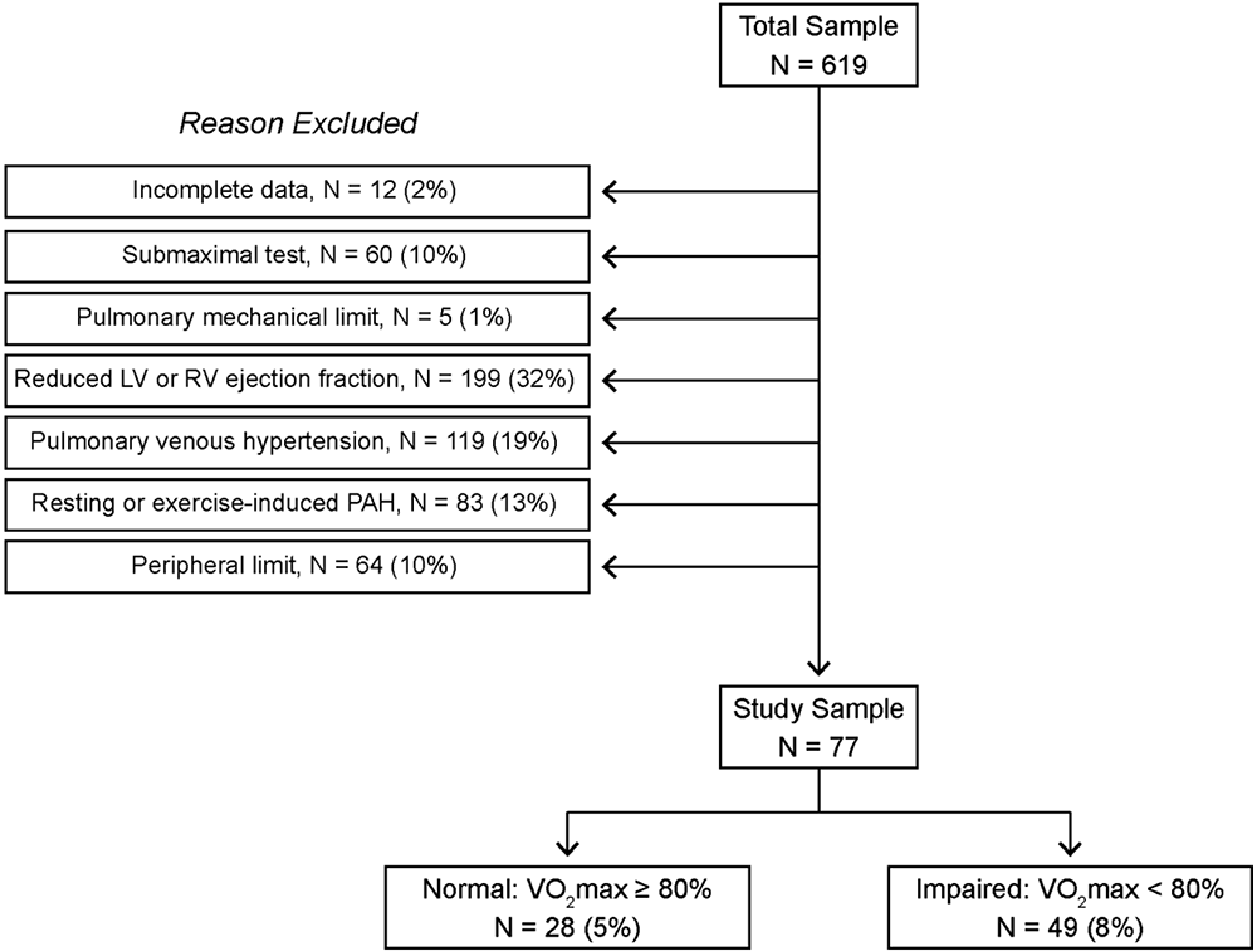
ORIGINAL RESEARCH

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



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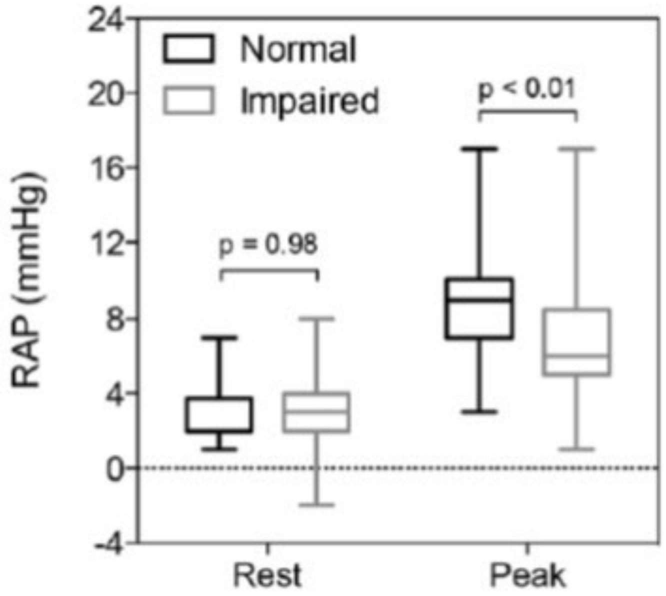
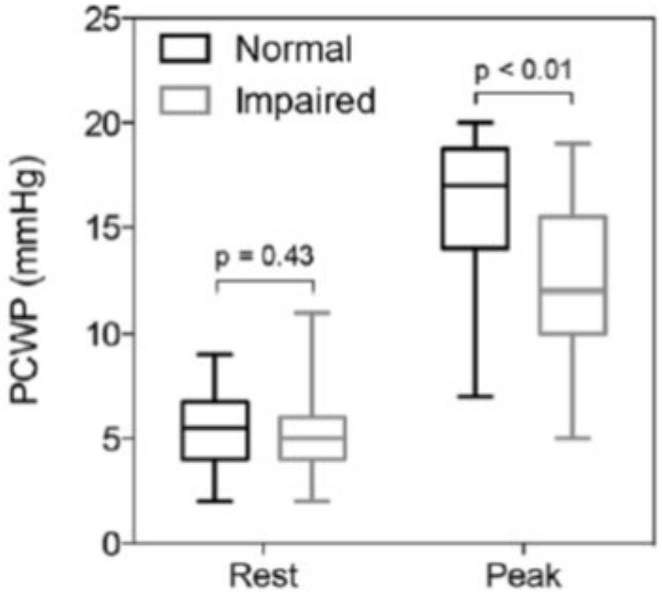
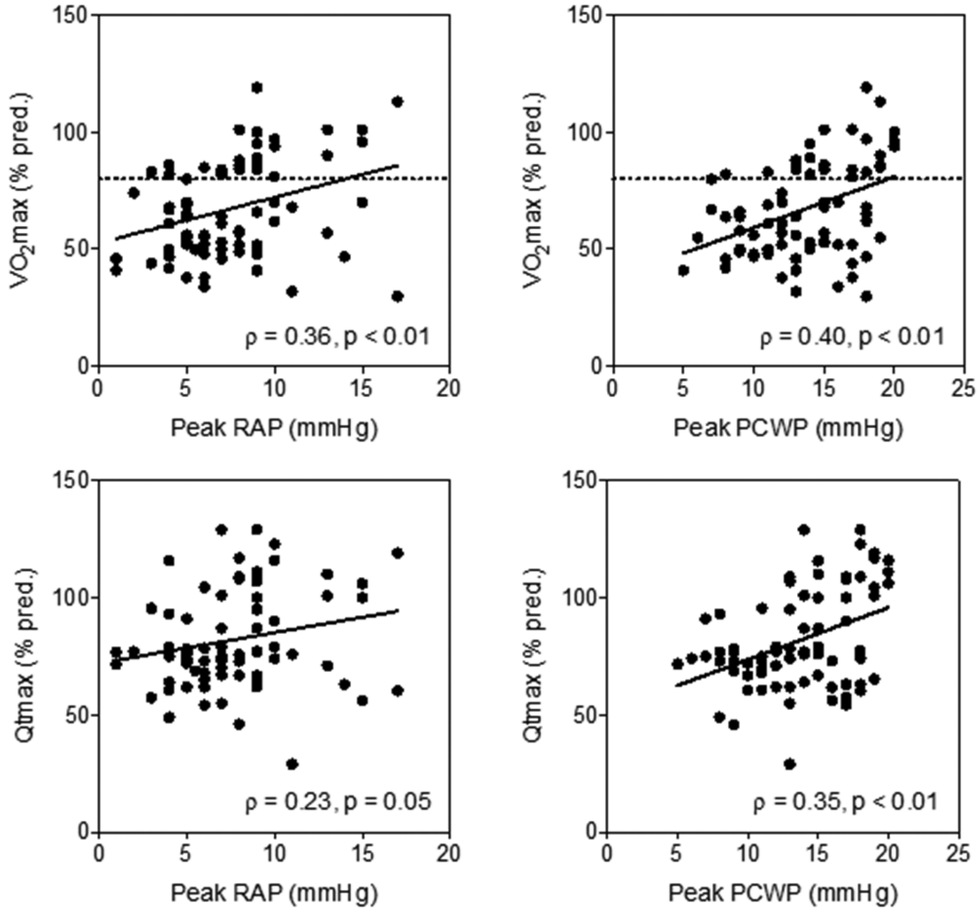
Preload Failure







Pulmonary Circulation. March 2016:55-62.
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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.

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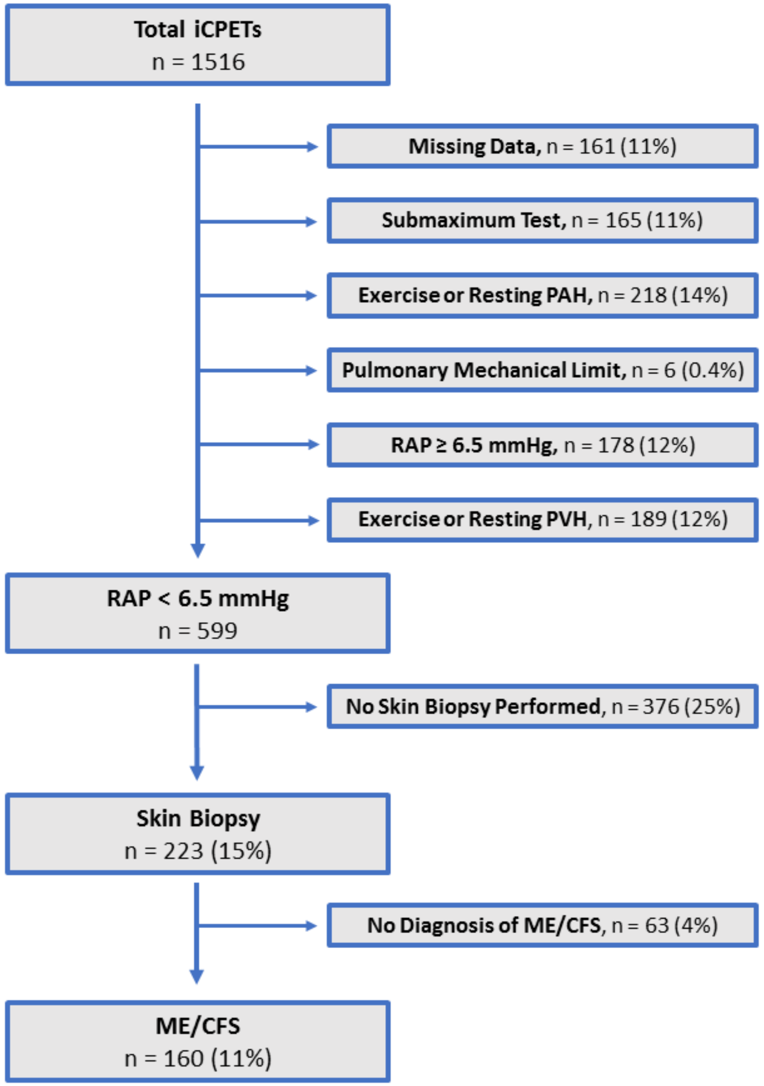

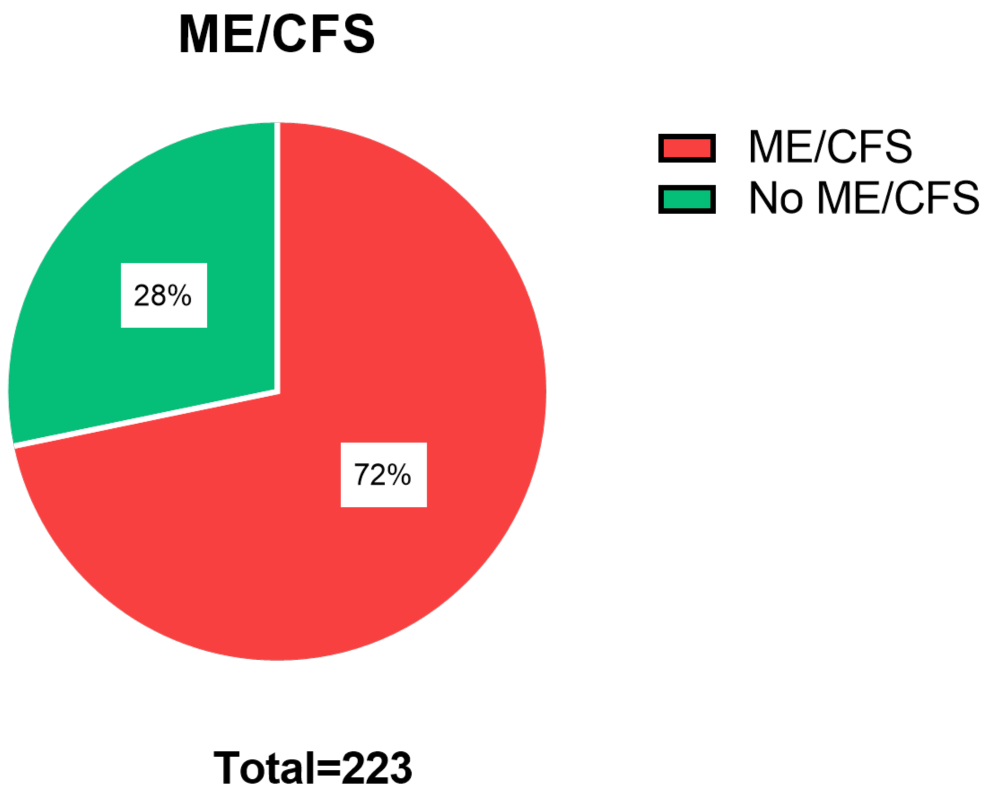

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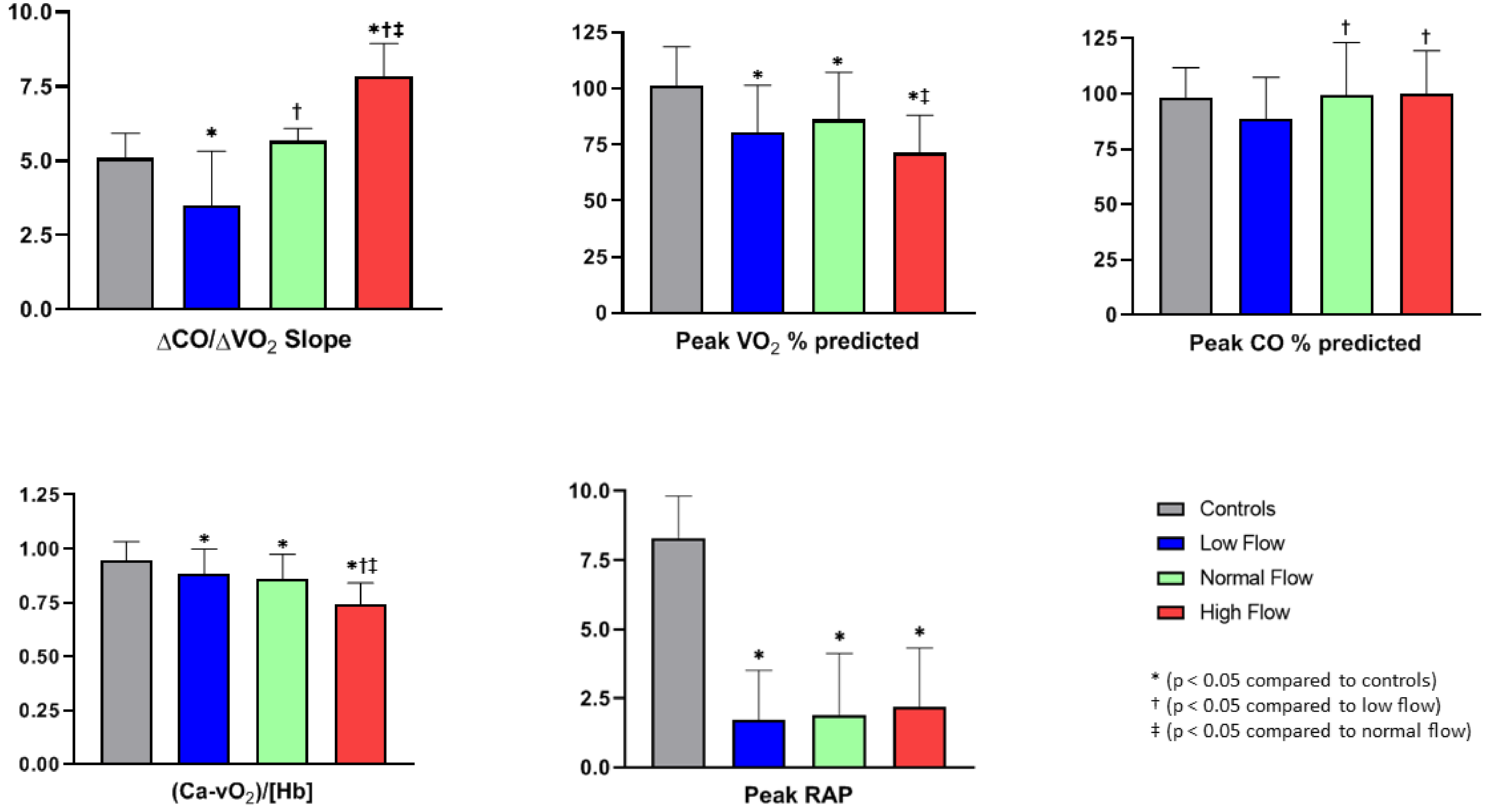
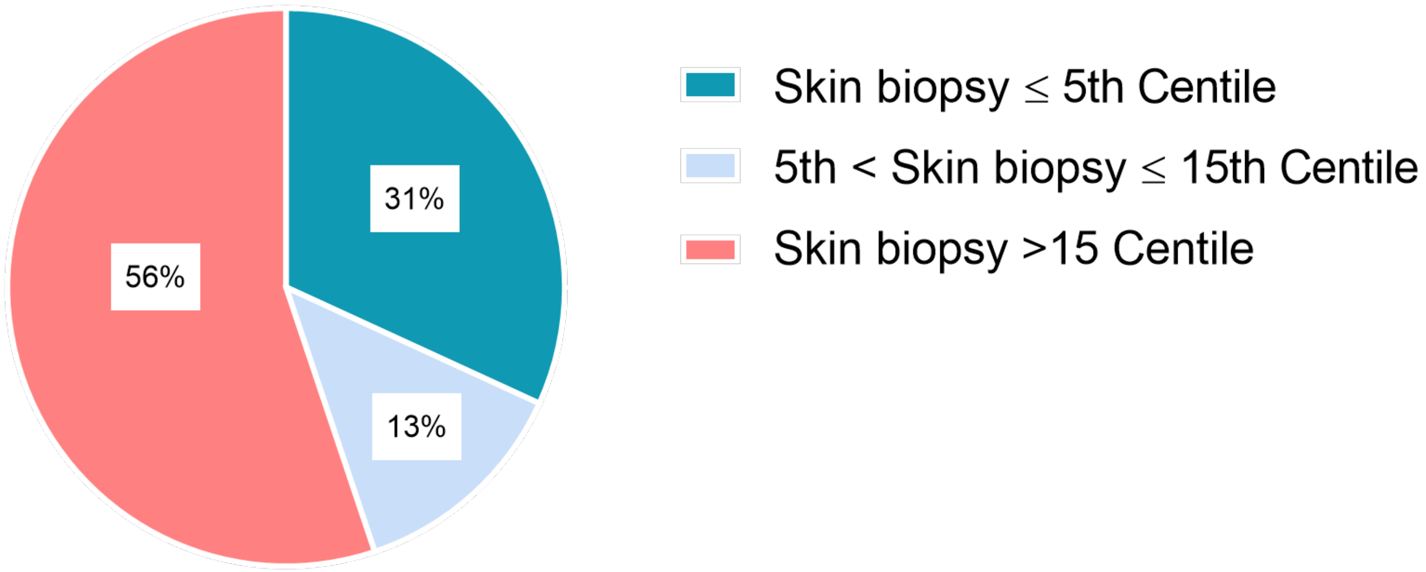
High flow v. low flow in ME/CFS



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

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%)

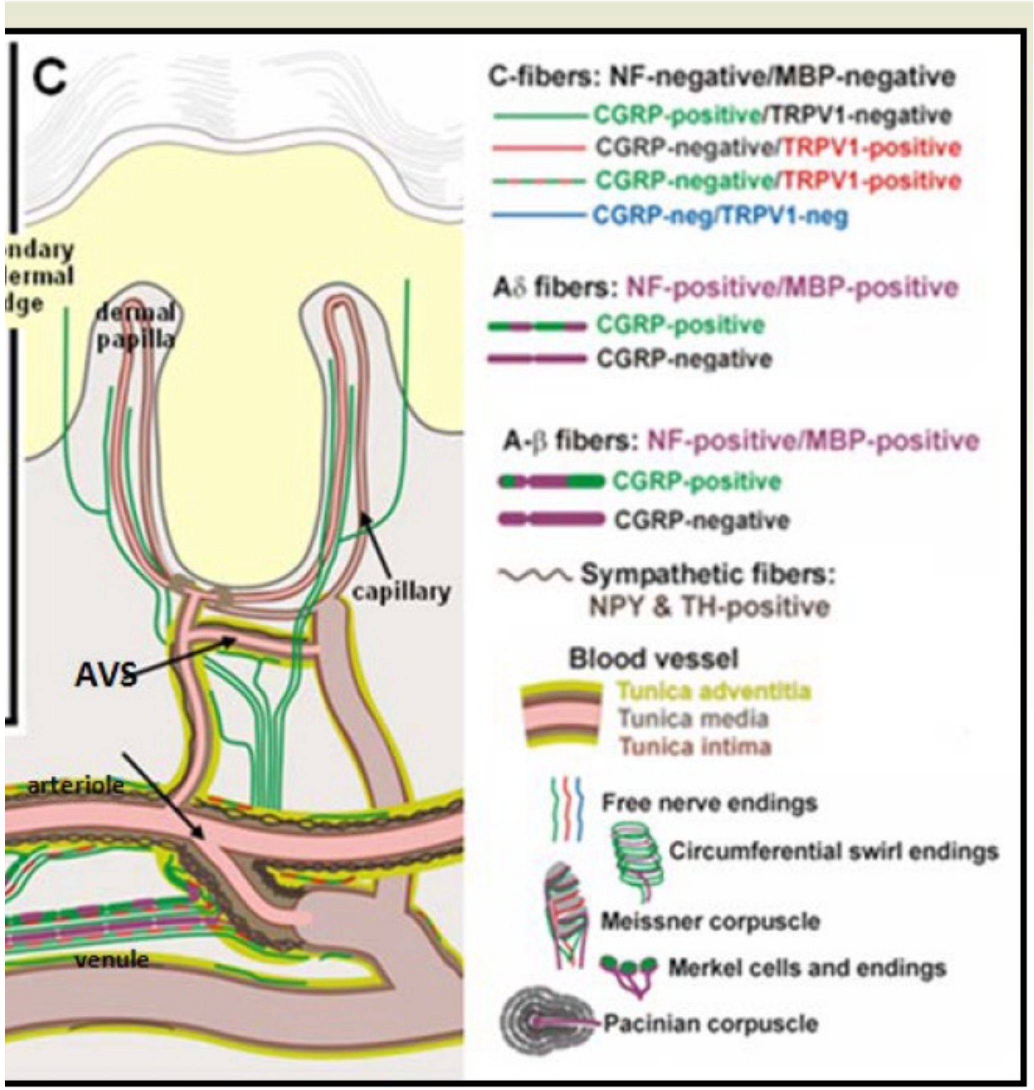
Skin biopsy in ME/CFS



Total=160

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

Left to right shunting in ME/CFS??



› 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, Mt myopathy, SFN
- 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, IVIg

Pt MP

28-year-old woman with increasing DOE/fatigue x 5 mos.

A year prior she noted DOE climbing 6-7 stairs, now on level ground w/ B leg fatigue, PEM

Past medical history:
Childhood asthma
2003 mild aortic stenosis and insufficiency
1999 Raynaud's Disease
1999 Migraine headaches
S/p negative Tilt Table

ROS: No myalgias, arthralgias, cough, wheezing.

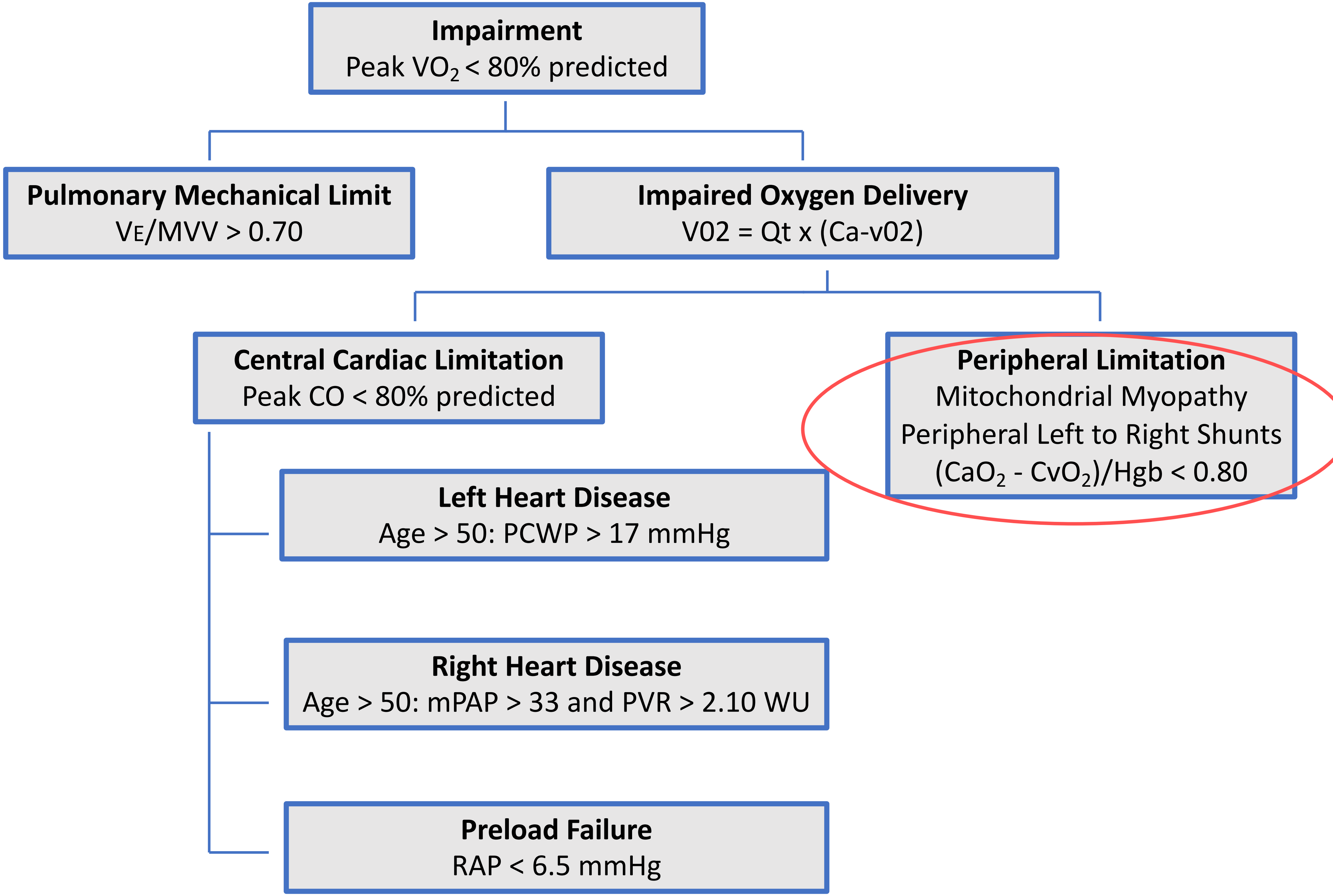
Pt MP

	Predicted	Measured	
VO2max (mL/min)	1820	1198	66%
Cardiac Output max (L/min)	13	13.5	104%

Case MP

= ADVANCED CARDIOPULMONARY GASES =

Time	CaO_2	CvO_2	$Ca\text{-}vO_2$	PaO_2	$PaCO_2$	pH	Lactate
REST	18.7	11.8	6.9	106	43	7.39	0.5
FW1	18.2	9.0	9.2	95	41	7.38	0.9
1	17.2	9.4	7.8	110	36	7.41	0.9
2	17.8	9.7	8.1	105	40	7.41	0.9
3	18.5	9.6	8.9	110	39	7.40	1.1
4	17.9	9.4	8.5	104	39	7.39	2.1
5	17.4	9.2	8.2	116	38	7.38	3.5
PEAK	18.0	9.1	8.9	125	36	7.37	5.5



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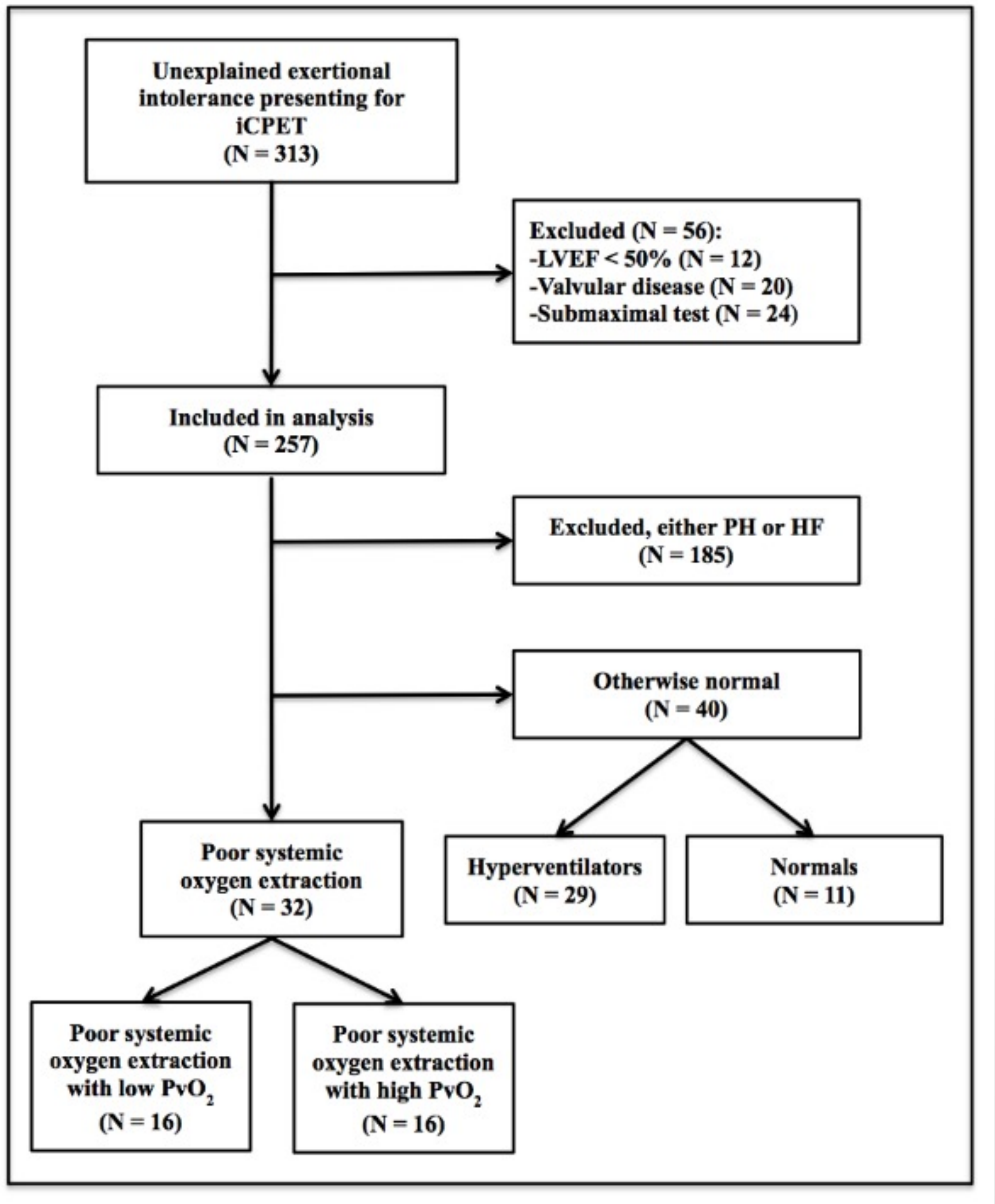
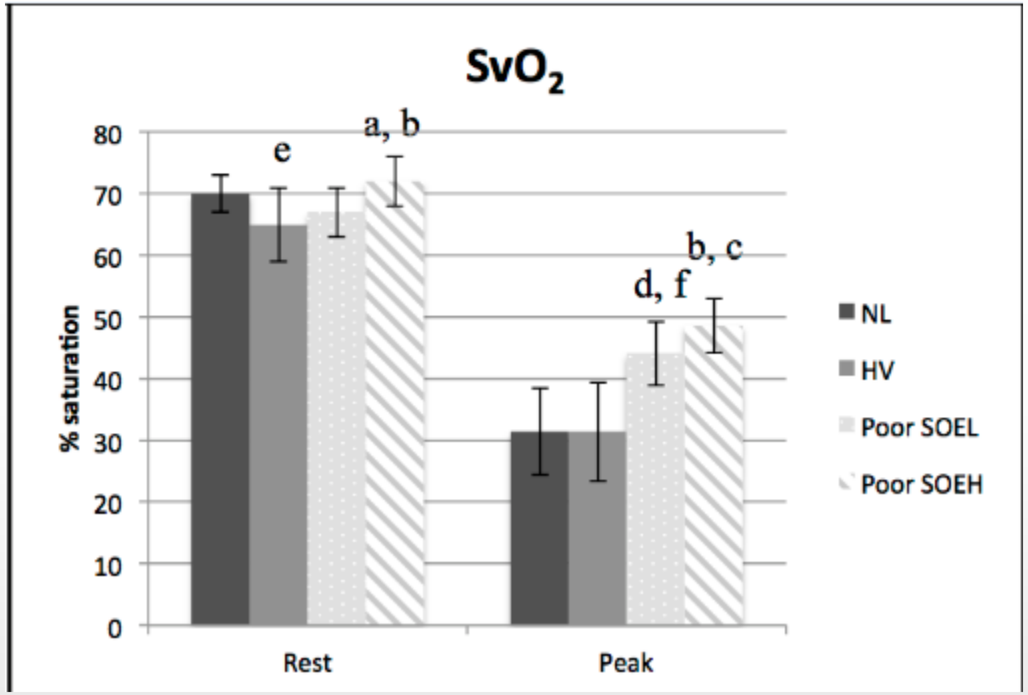
Unexplained Exertional Intolerance Associated with Impaired Systemic Oxygen Extraction



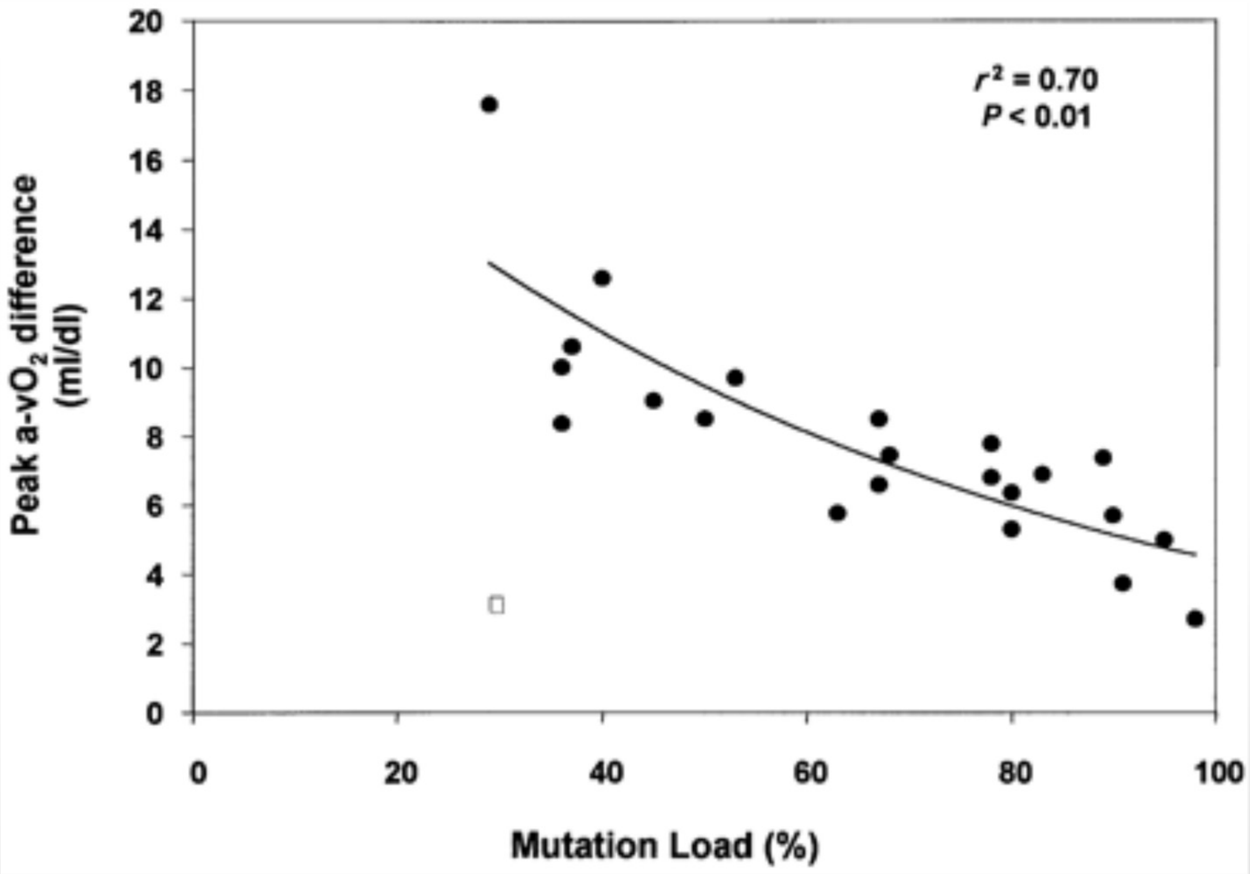
Melamed KH, Santos M, Oliveira RKF, Urbina MF, Felsenstein D, Opotowsky AR, Waxman AB, Systrom DM. Eur J Appl Physiol. 2019 Oct;119(10):2375-2389. doi: 10.1007/s00421-019-04222-6. Epub 2019 Sep 6. PMID: 31493035.

Unexplained Exertional Intolerance Associated with Impaired Systemic Oxygen Extraction



Melamed KH, Santos M, Oliveira RKF, Urbina MF, Felsenstein D, Opotowsky AR, Waxman AB, Systrom DM. Eur J Appl Physiol. 2019 Oct;119(10):2375-2389. doi: 10.1007/s00421-019-04222-6. Epub 2019 Sep 6. PMID: 31493035.

Systemic O_2 Extraction is Impaired in Mt Myopathy



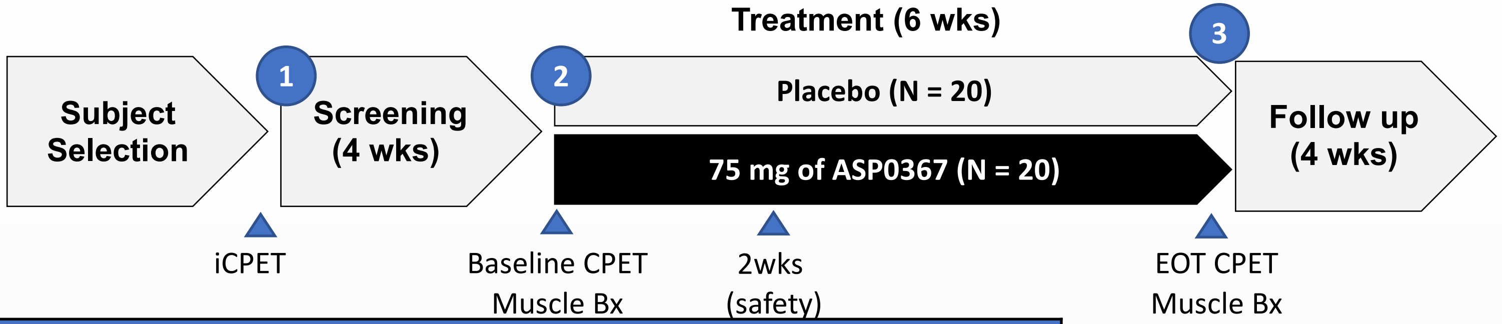
The spectrum of exercise tolerance in mitochondrial myopathies: a study of 40 patients

Brain. 2003;126(2):413-423. doi:10.1093/brain/awg028
Brain |

Skeletal Muscle Mitochondrial Dysfunction in ME/CFS?

Ca-vO2/Hgb	Vo2 Max % pred	BAYLOR RESULTS
0.7625	72	CS defect; Cx I/III defect seen before and after CS correction
0.60240964	73	CS defect; All Cx defect before CS correction but only Cx IV defect persisted afterwards
0.67857143	79	CS defect; no deficiency seen in Cx before or after CS correction
0.75483871	74	CS defect; All Cx defect before CS correction but only Cx IV defect persisted afterwards
0.67123288	73	CS defect; no deficiency seen in Cx before or after CS correction
0.69090909	56	CS defect; no deficiency seen in Cx before or after CS correction
0.83206107	72	CS defect; no deficiency seen in Cx before or after CS correction
0.8258427	80	CS defect; CX I defect before CS correction that did not persisted afterwards
0.61481481	64	No CS or CX defect (No deficiencies in mtETC enzymes activities)
0.56944444	64	CS defect; no deficiency seen in Cx before or after CS correction
0.6641791	58	CS defect; no deficiency seen in Cx before and after CS correction

ME/CFS Mito Dysfxn: Phase 1b Study Design



Phase 1b study	
Objectives	To evaluate the efficacy of ASP0367 on VO2max and SOmax per iCPET
Design	Placebo-controlled, Subject- and Investigator-blinded
Subjects	Patients (>18yrs) with unexplained exertional intolerance due to poor systemic oxygen extraction, defined as peak exercise (Ca-vO2)/[Hb] ≤ 0.85 and VO2max < 80% predicted in the absence of a cardiac or pulmonary mechanical limit[4]
Duration	6 weeks treatment
Key assessments of efficacy/safety parameters	Primary efficacy – VO2max % pred Secondary efficacy – SOEmax, CO/V02 slope, muscle bx Safety

1. iCPET to enrich ME/CFS pts with low SOE (Ca-v02/[Hb]<0.85). Patients should NOT have cardiopulmonary dysfunction.

Fz Muscle Bx (Baylor) and buccal ETC (all) will be collected at D0 and 6 weeks

2. Duration: 6 weeks….prior studies:
- 5-wk exercise increased 6MWT in CFS[1]
- 14-wks exercise improved VO2max and SOE in MM[2]
- 52-wks pyridostigmine increased VO2max and SOE in CFS[3]

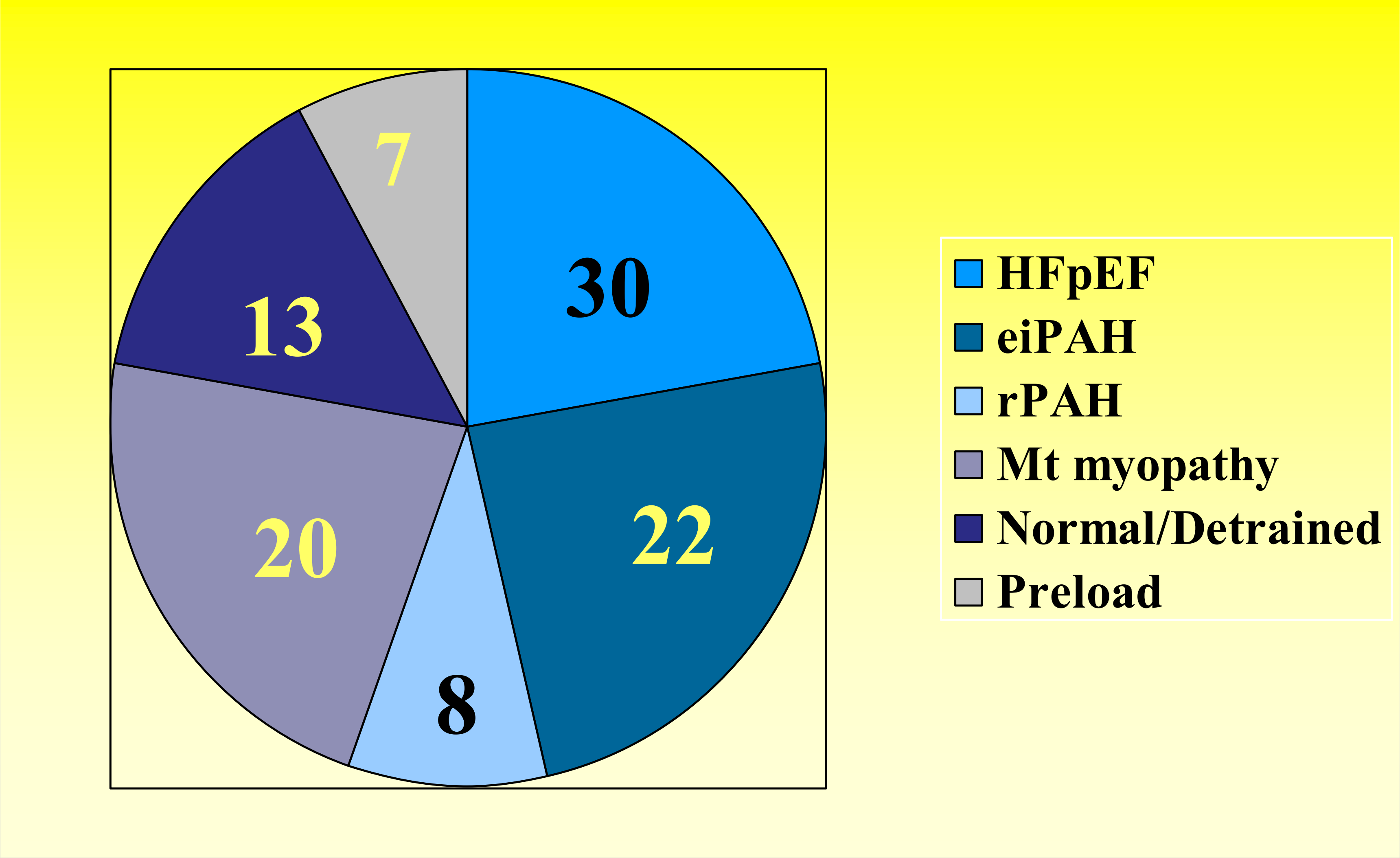
3. 1:1 randomization

1. Suzanne Broadbent et al., 2018; 2. Tanja Taivassalo et al., 2001; 3. Dr.Systrom's presentation@NIH conference; 4. Kathryn H. Melamed et al., 2019

Mitochondrial Myopathy

- Present in adulthood w/ dyspnea > fatigue
- Associated w/ viral syndromes, statins, fluroquinolones
- w/u iCPET> frozen muscle bx
- Rx is Vitamin cocktail, including CoEnzyme Q10

iCPET Diagnoses



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, preload failure and/or suggest a Mt myopathy

References

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