Neurovascular Dysregulation During Exercise in ME/CFS & Long COVID

David M. Systrom, M.D.

Pulmonary and Critical Care Medicine
Brigham & Women's Hospital

CDC SEC Call Presentation

Disclosures

- none

Harvard Fatigue Lab
1927-47

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

- Intractable fatigue > 6 mos
- Post exertional malaise
- Non-refreshing sleep
- Brain fog
- Orthostatic intolerance

Long COVID

- New symptoms lasting three or more months after acute COVID
- Fatigue/PEM
- Fever
- Dyspnea/Cough
- Chest pain/palpitations

Long COVID Incidence

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

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Weekly COVID-19 Mortality Overview

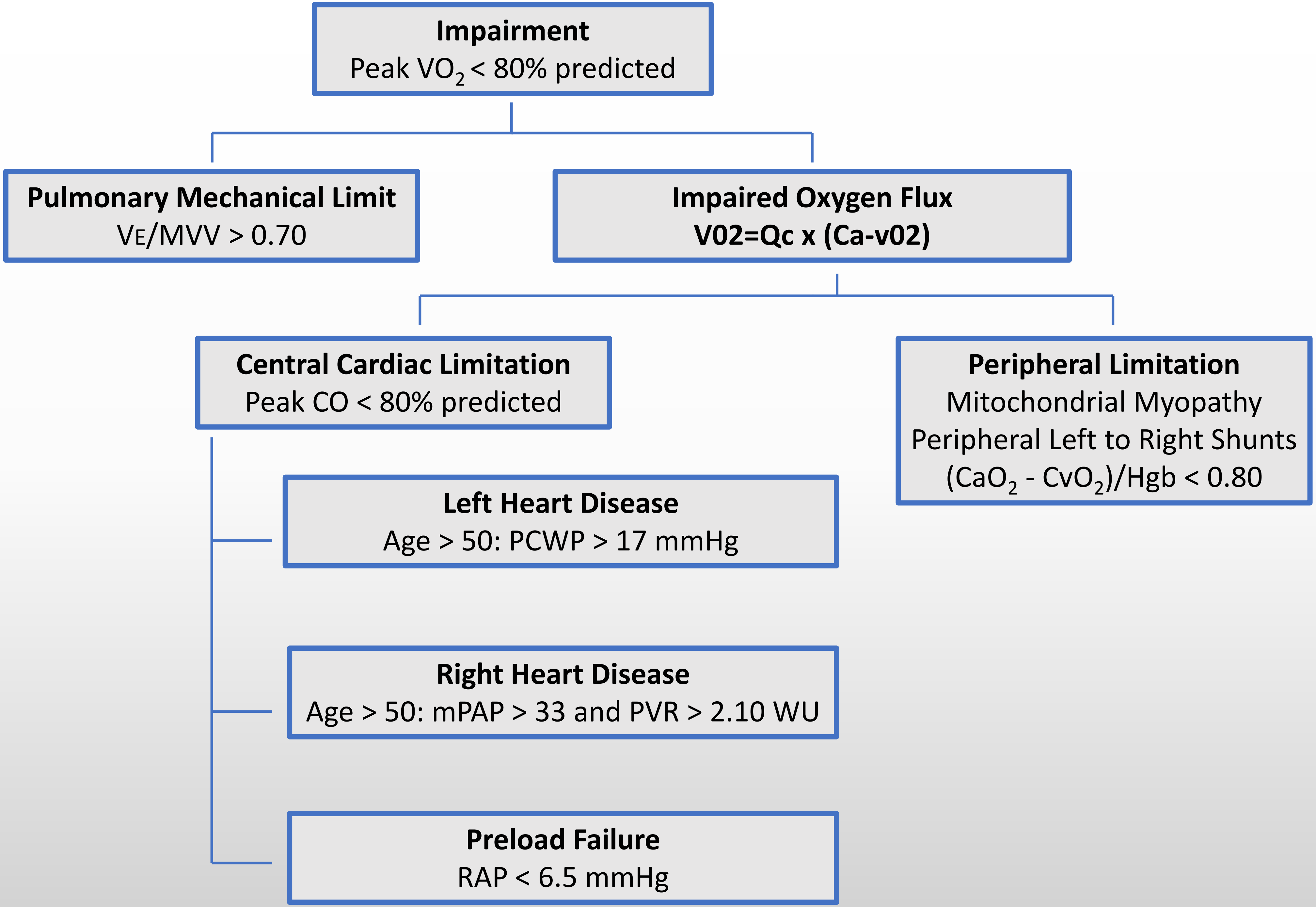
Nearly One in Five American Adults Who Have Had COVID-19 Still Have “Long COVID”

Long COVID Prevalence

- Overall =1 in 13 adults in the U.S. (7.5%)
- Ages 50-59 = 3x vs age 80 and older
- Female > male (9.4% vs. 5.5%).
- 9% of Hispanic > White (7.5%) > Black (6.8%), > Asian (3.7%)
- Higher w/ severe acute dz, but occurs in mild/asx!

Exercise Pathophysiology

- Vascular dysregulation
- Small fiber autonomic neuropathy
- Inflammation
- Skeletal muscle mitochondrial dysfunction
- Dyspnea
- Treatment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Peak VO_2 < 80% predicted
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V_E/MVV > 0.70
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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

Invasive Cardiopulmonary Exercise Test

Exercise Test video unavailable due to file size limit.

Please go to https://youtu.be/rN-JESTenjE to view video embedded in slide.

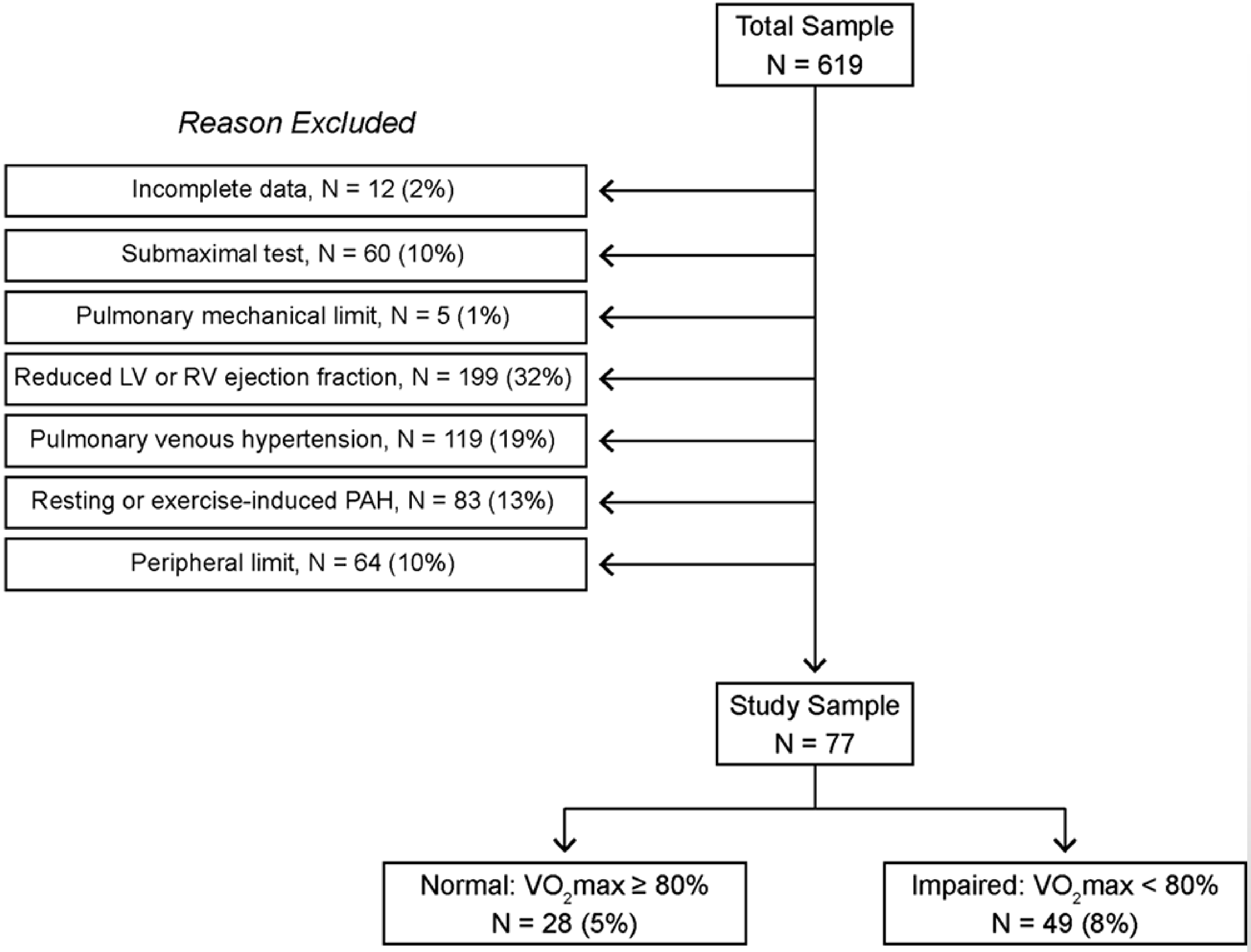
ORIGINAL RESEARCH

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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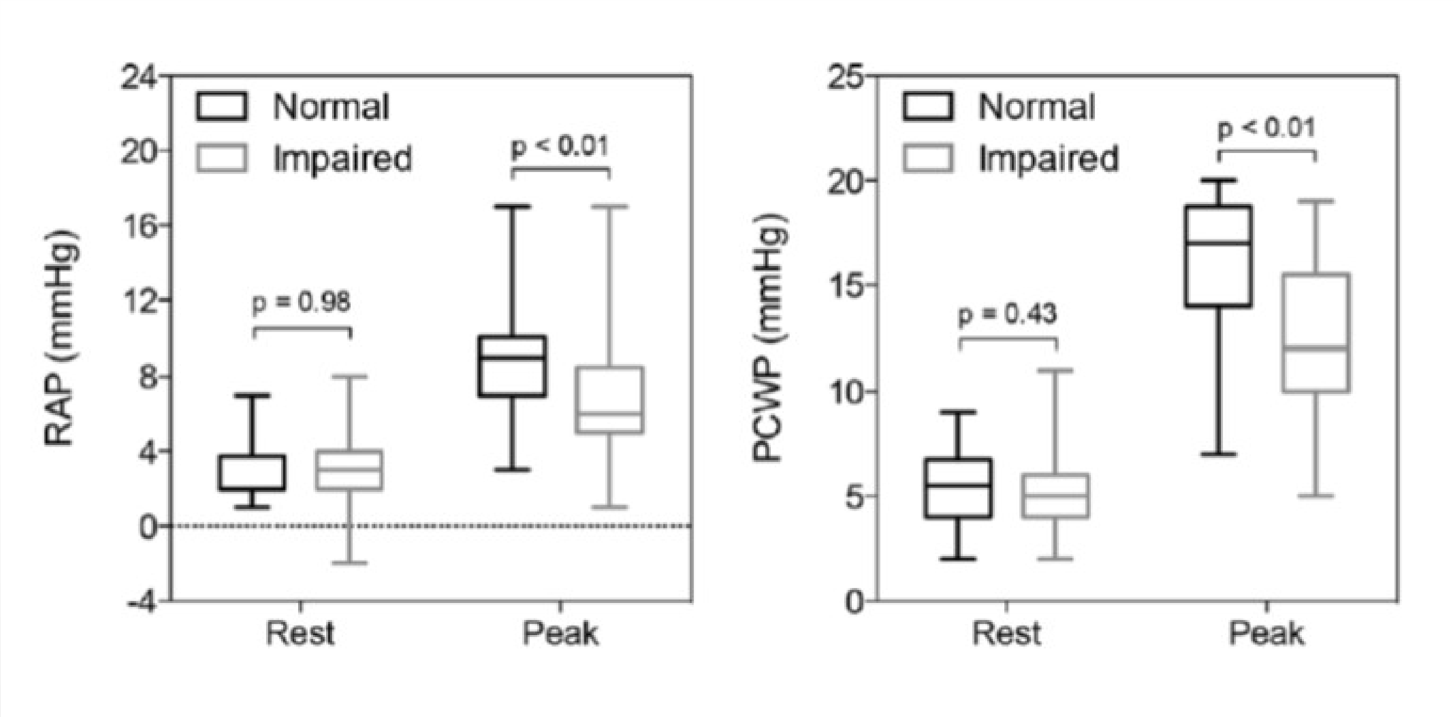

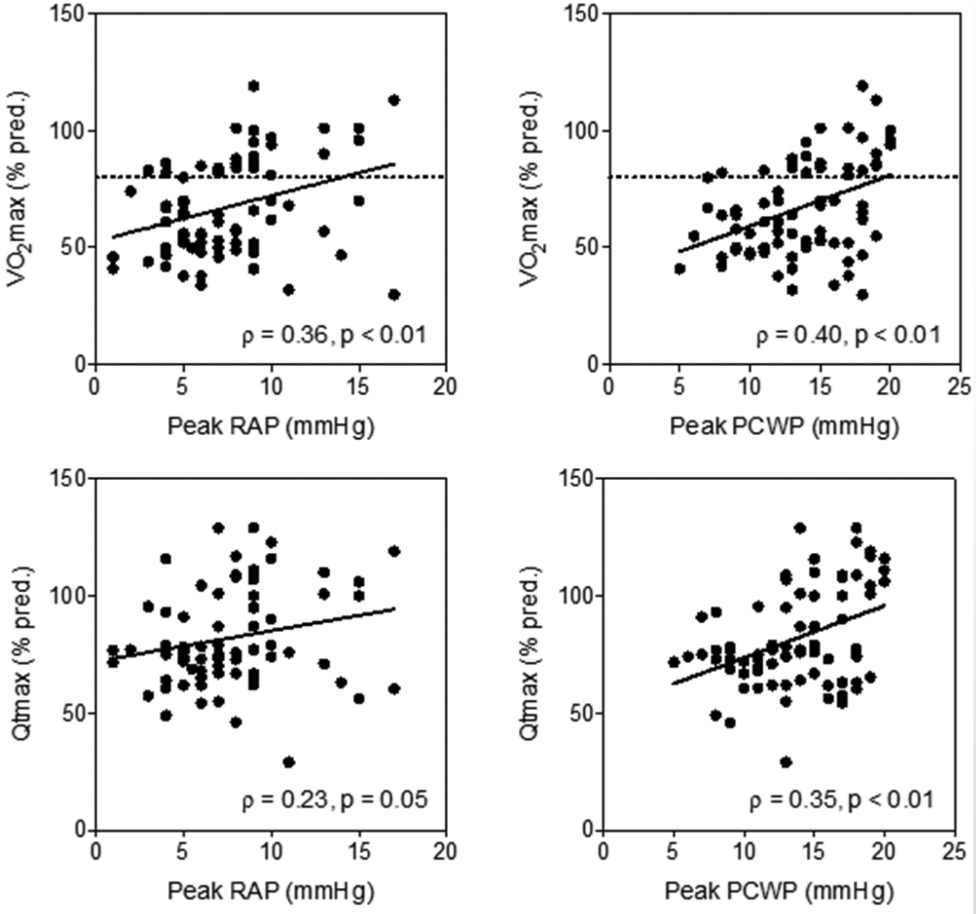

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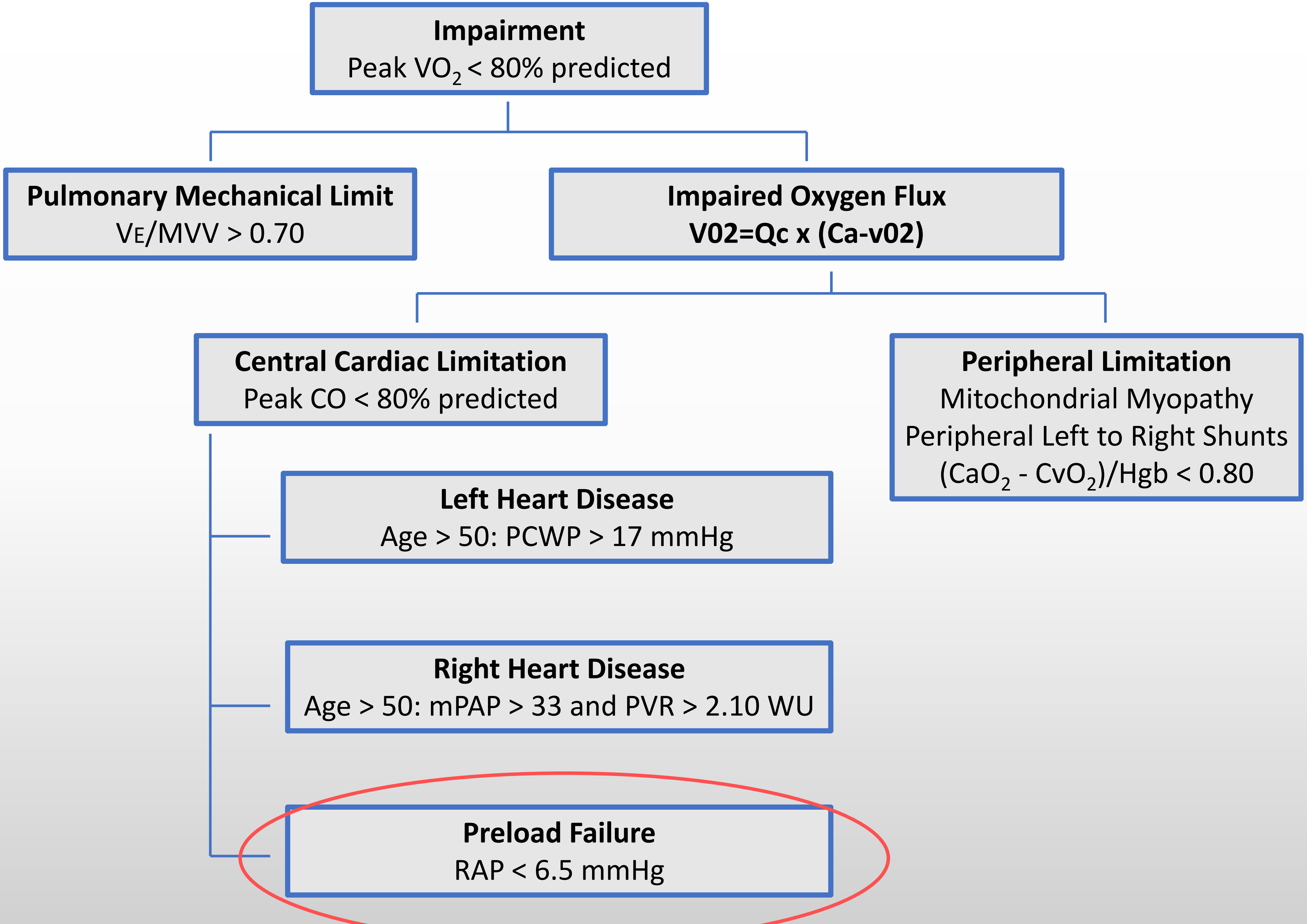
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In ME/CFS:

- Vascular dysregulation (preload failure) contributes to exertional intolerance
- Small fiber neuropathy is prevalent
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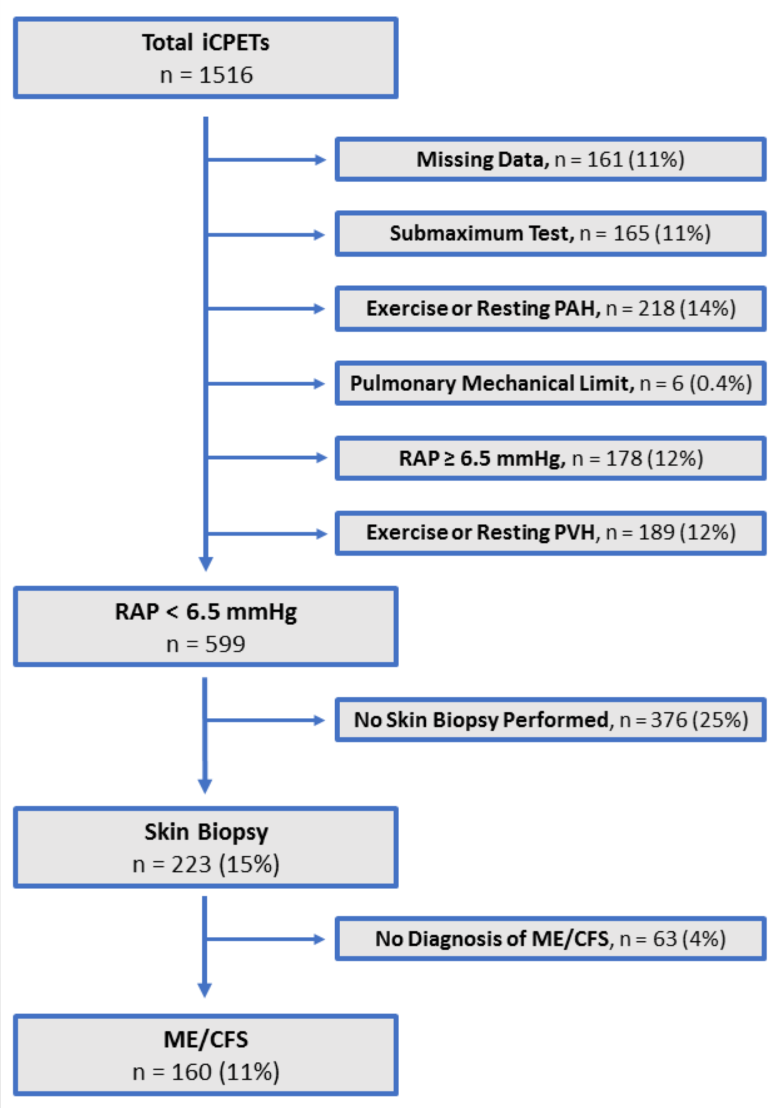
- Skeletal muscle mitochondrial dysfunction
- Dyspnea/hyperventilation
- Repurposed drugs useful

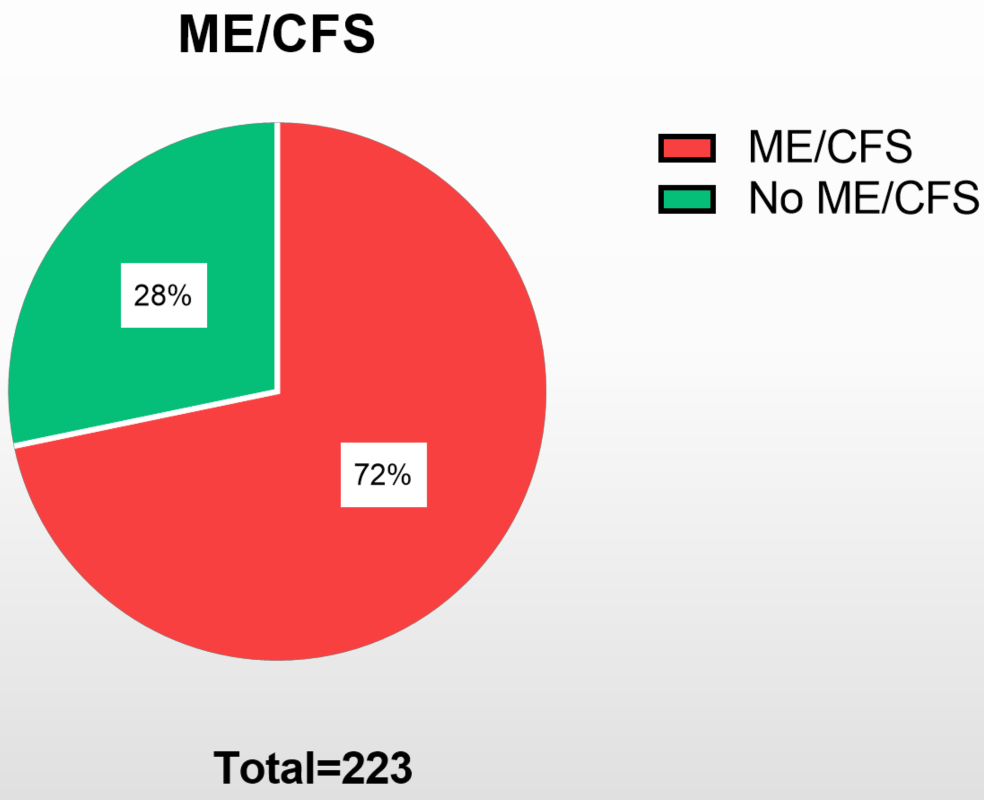
Insights From Invasive Cardiopulmonary Exercise Testing of Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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.

Prevalence of ME/CFS in Preload Failure

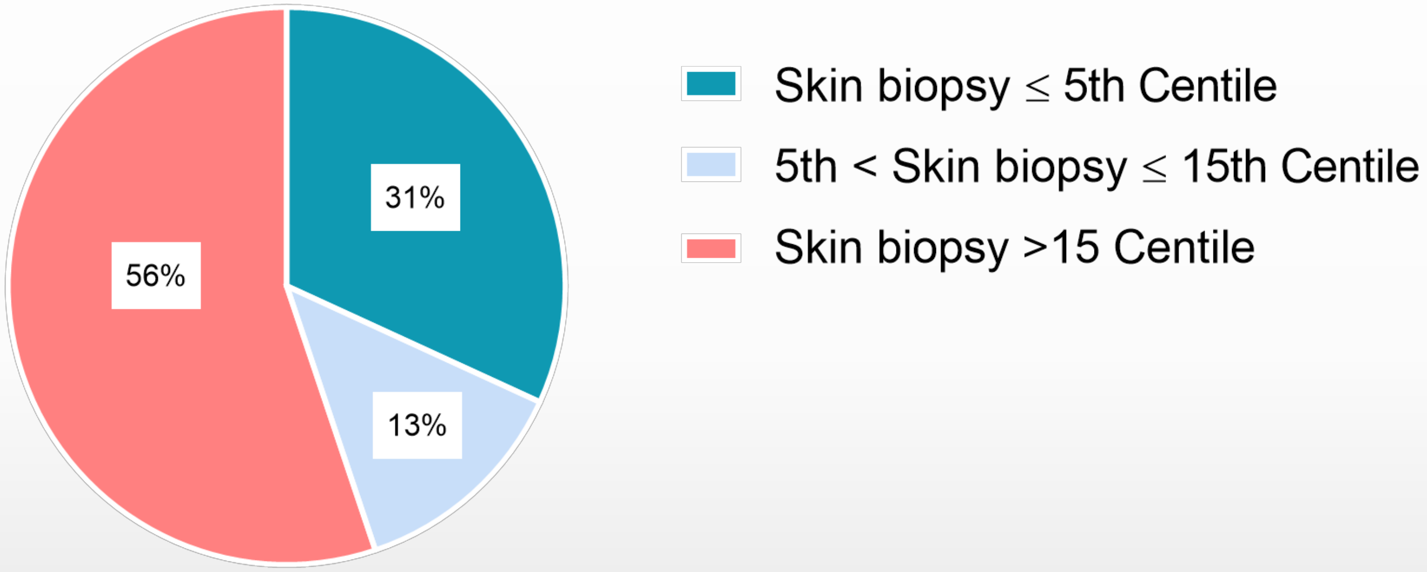




Prevalence of Small Fiber Neuropathy in Preload Failure

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%)
≤ 5^{th} centile	50 (31%)
5^{th} < centile ≤ 15^{th} centile	20 (13%)
POTS	52 (33%)
Fibromyalgia	35 (22%)
MCAS	11 (22%)
Preceding Infection	39 (24%)

Skin biopsy in ME/CFS



Total=160

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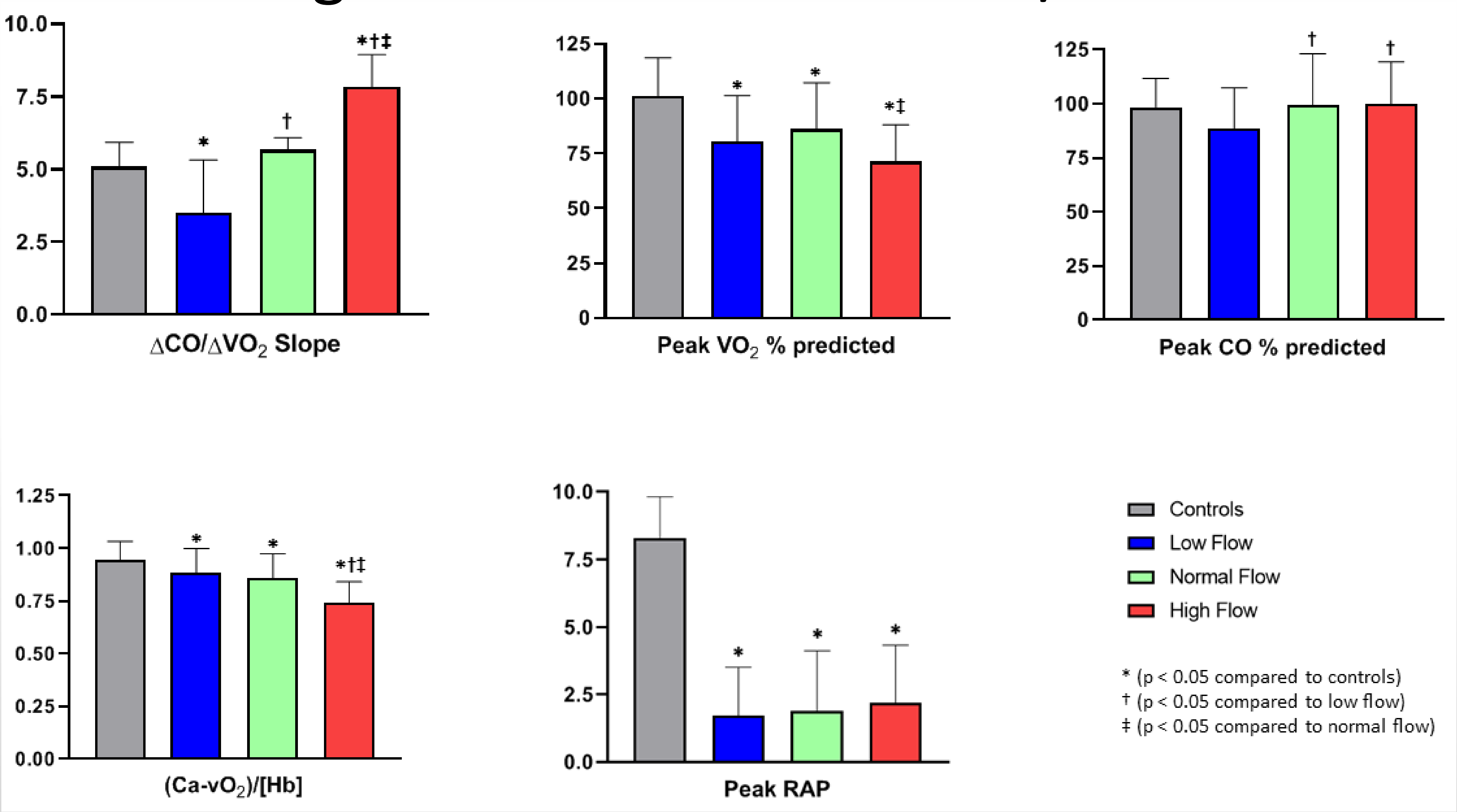
High flow v. low flow in ME/CFS



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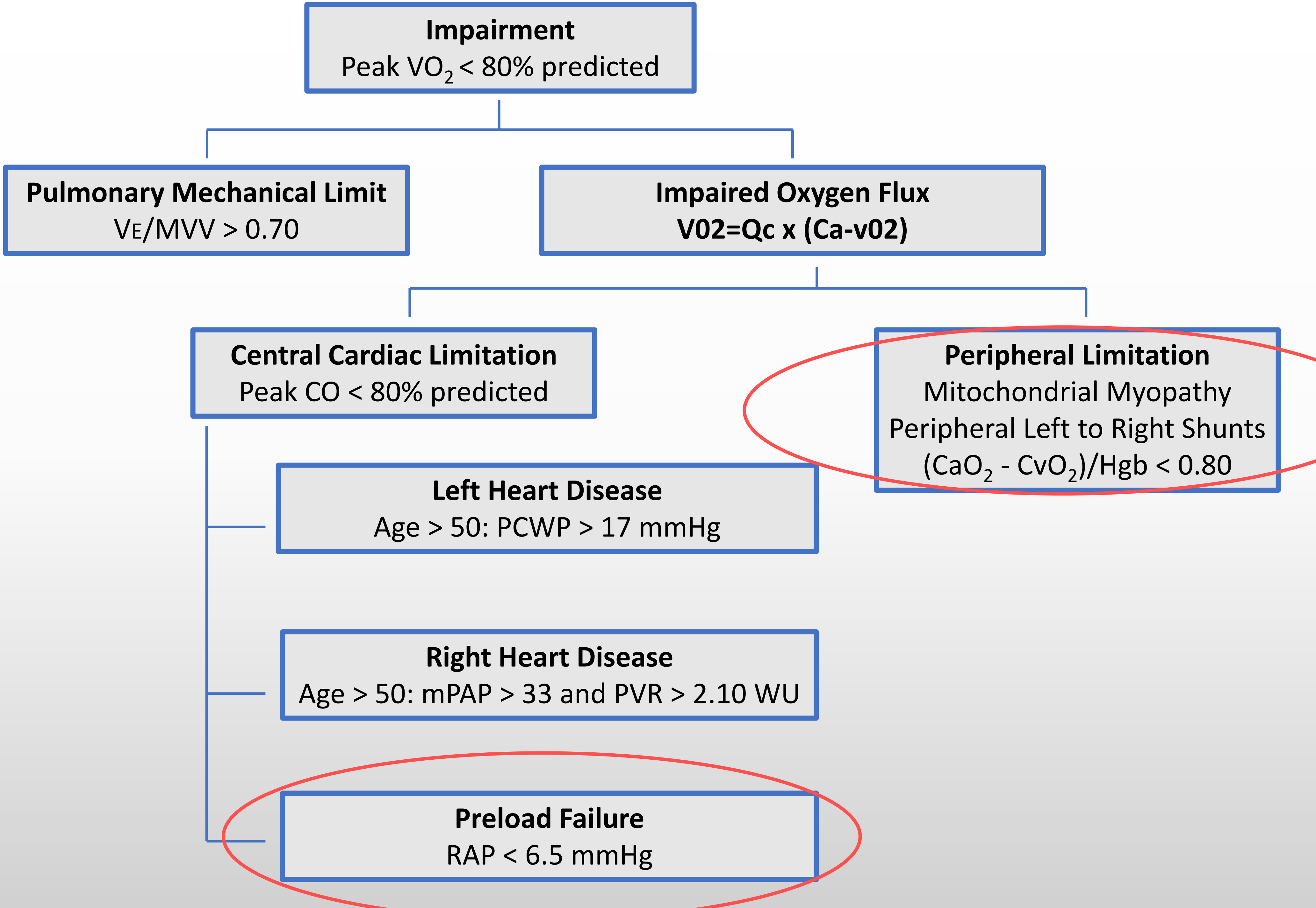
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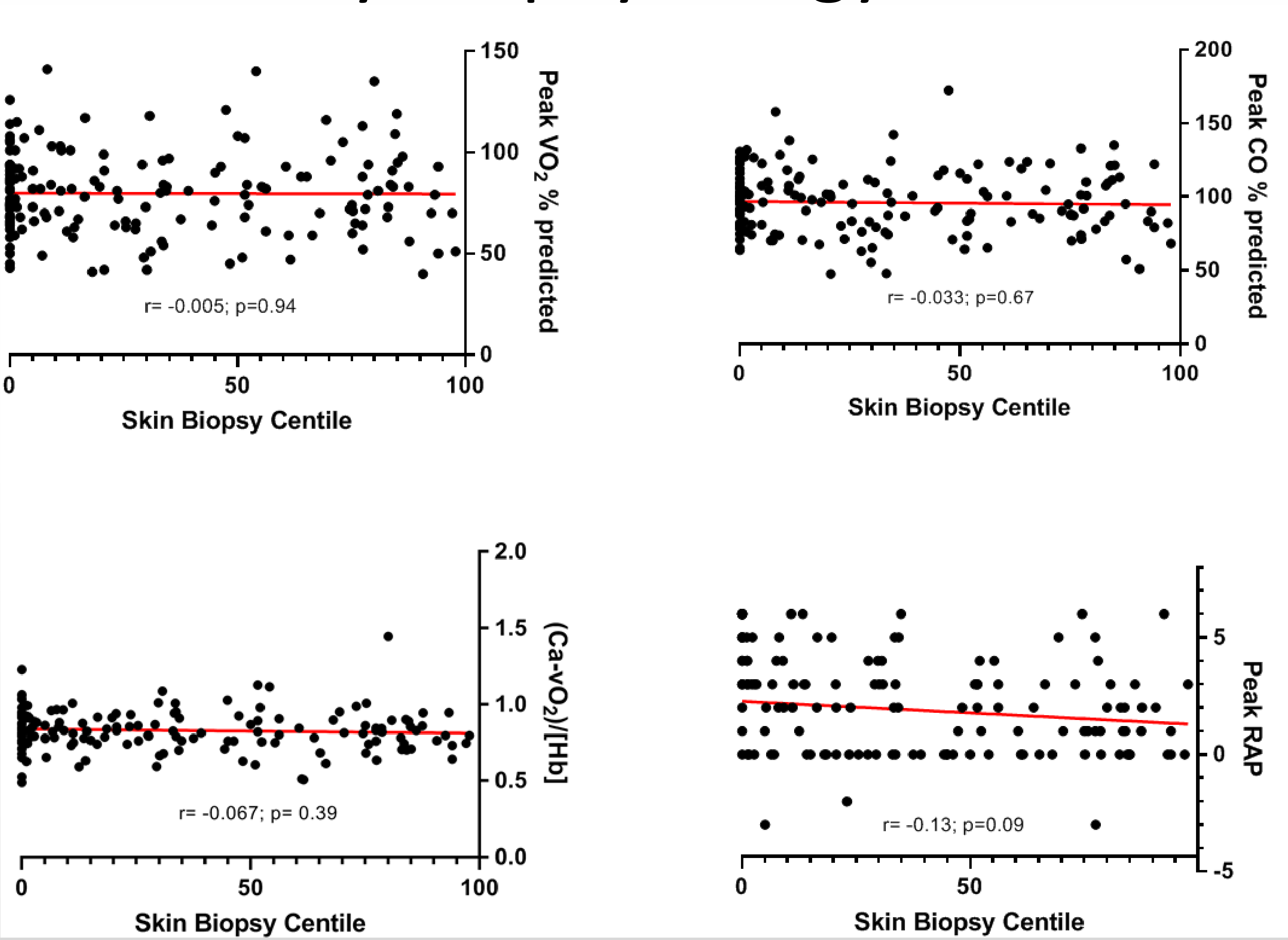
Anatomy ≠ physiology



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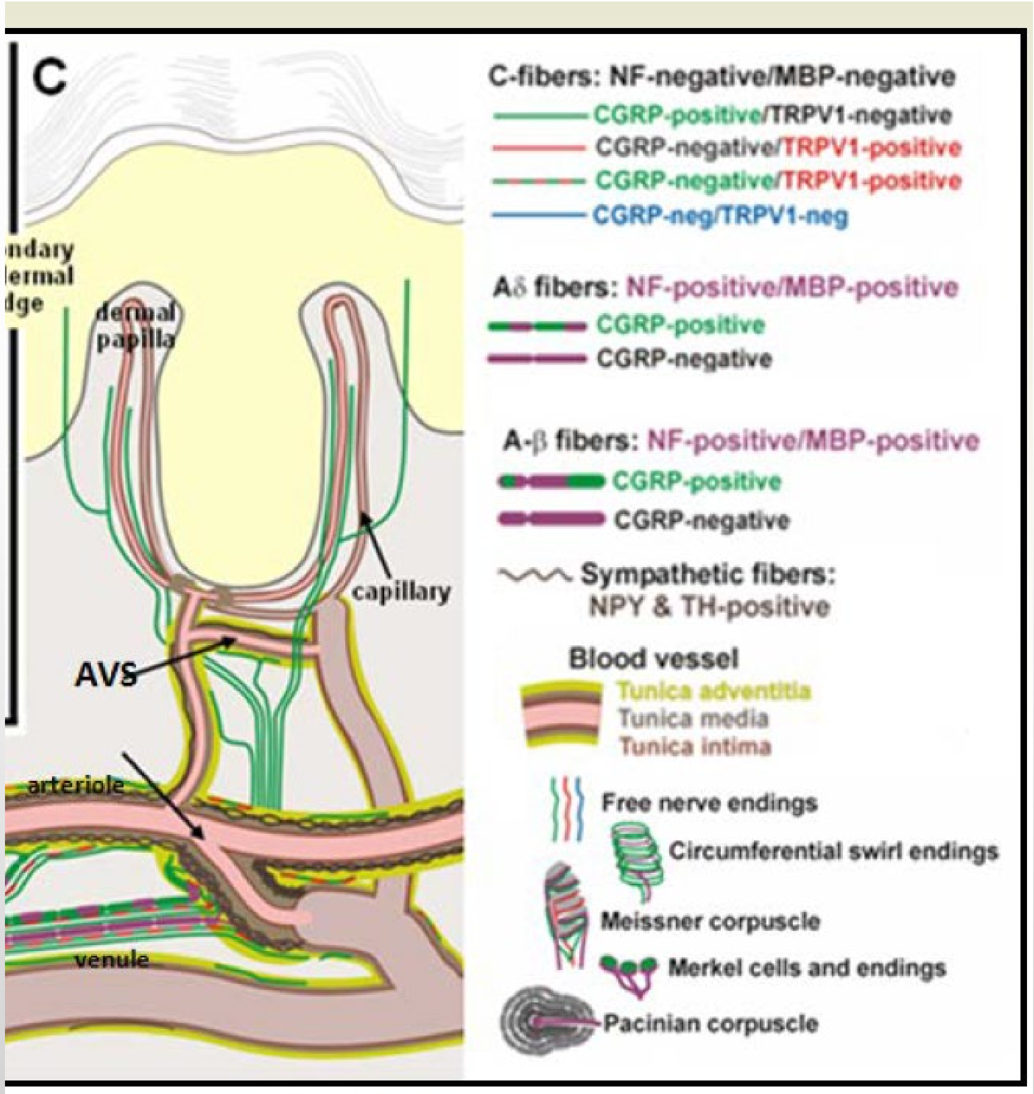
Left to right shunting in ME/CFS??



In ME/CFS:

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- Small fiber neuropathy is prevalent
- Acute exercise activates the inflammasome
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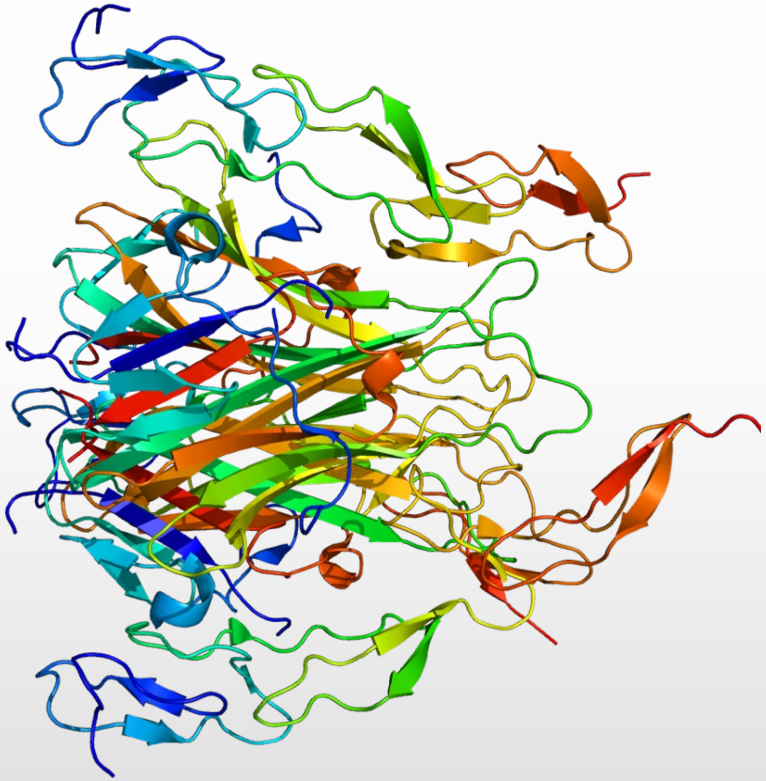
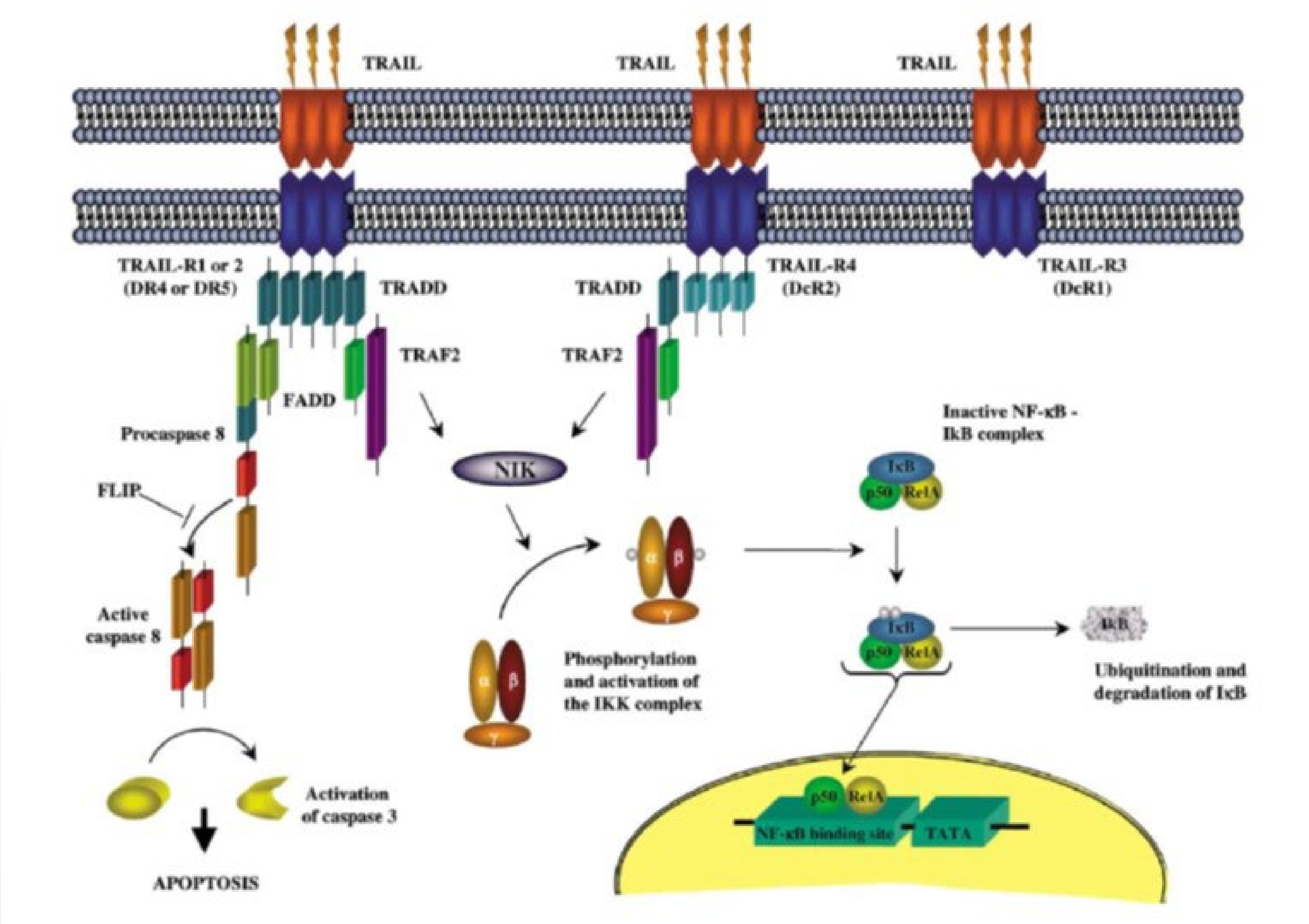
Why small fiber neuropathy in ME/CFS?

- Autoimmunity
- Inflammation

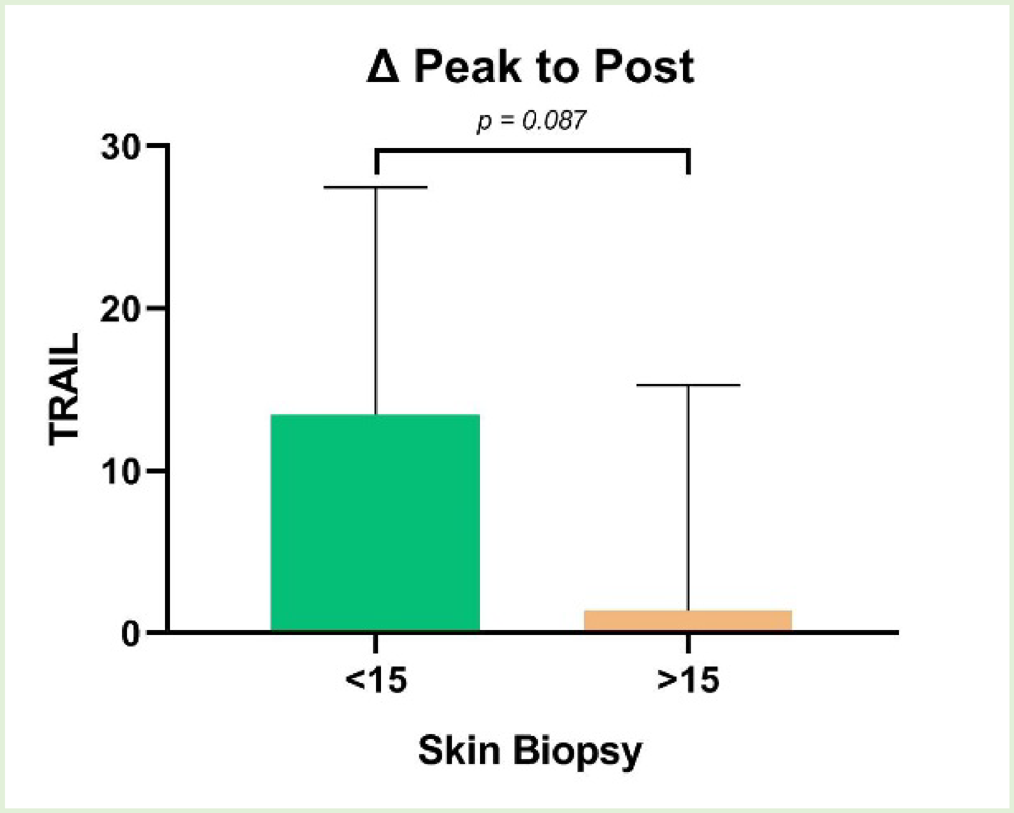
TNF-related apoptosis-inducing ligand (TRAIL)



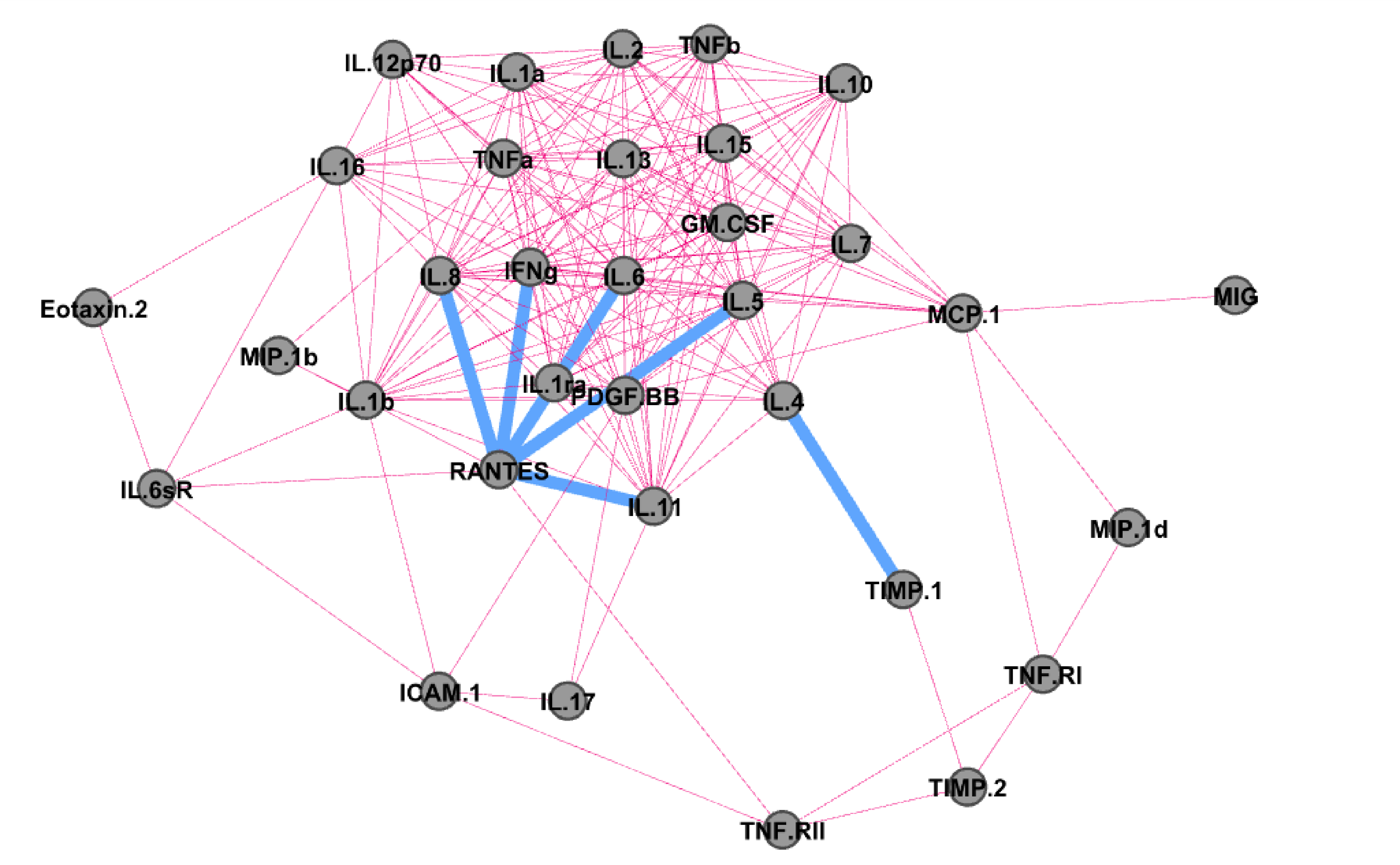
TRAIL & the Inflammasome



Exercise Changes in Plasma TRAIL with SFN



ME/CFS vs Nl Post-Peak Cytokine Multiplex



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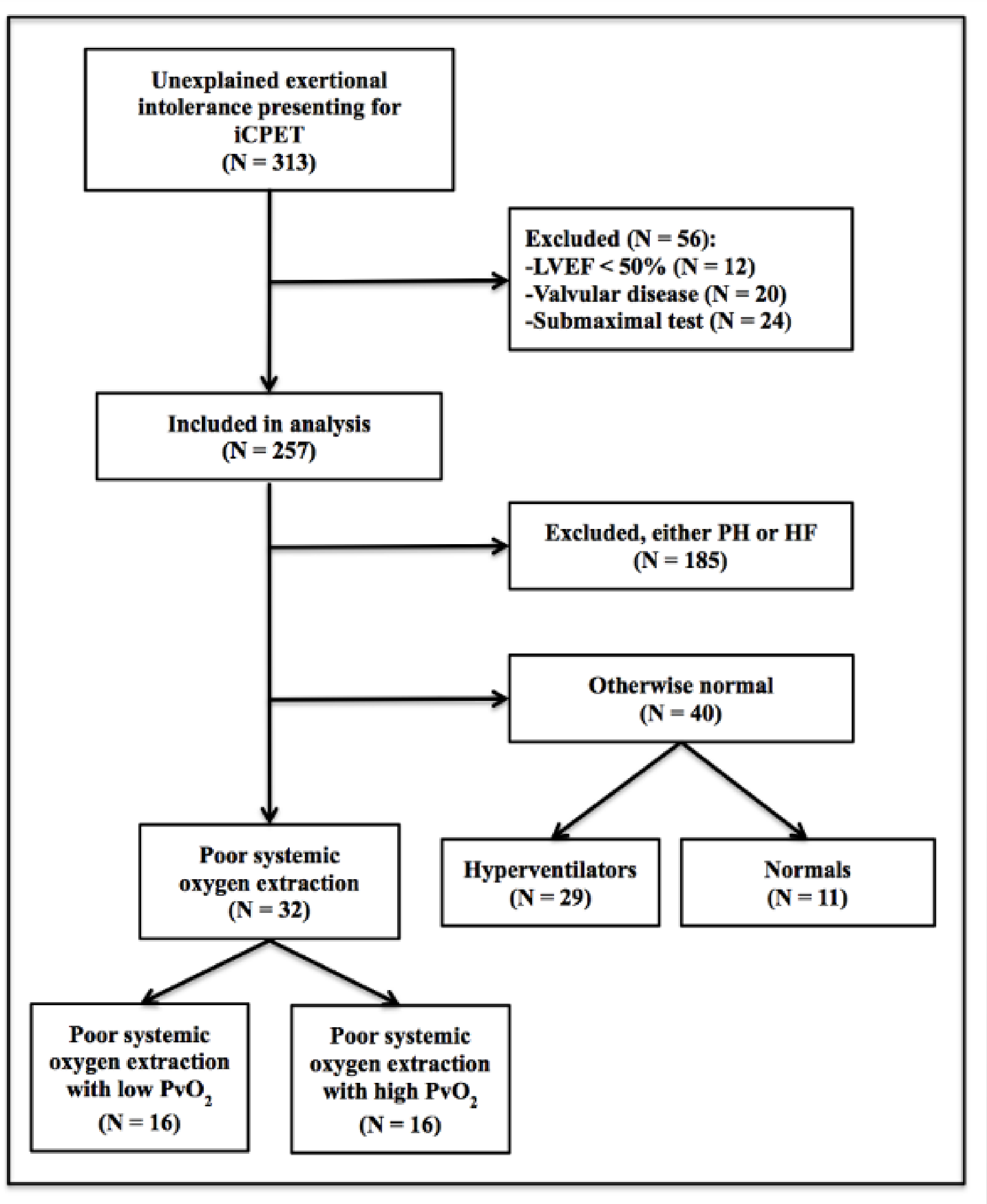
Unexplained Exertional Intolerance Associated with Impaired Systemic Oxygen Extraction



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.

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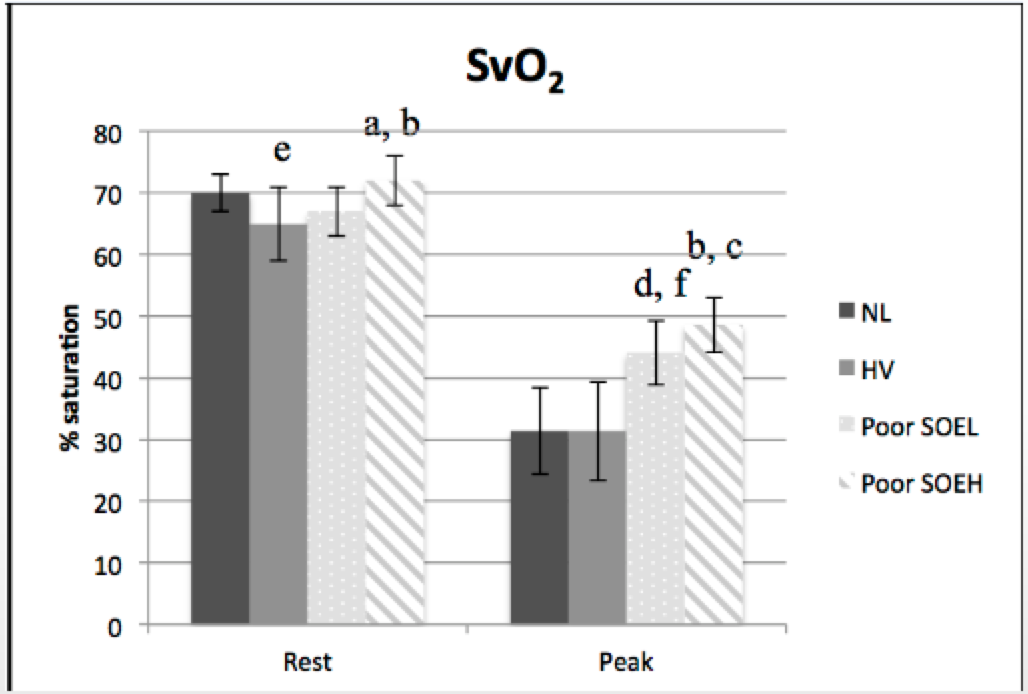

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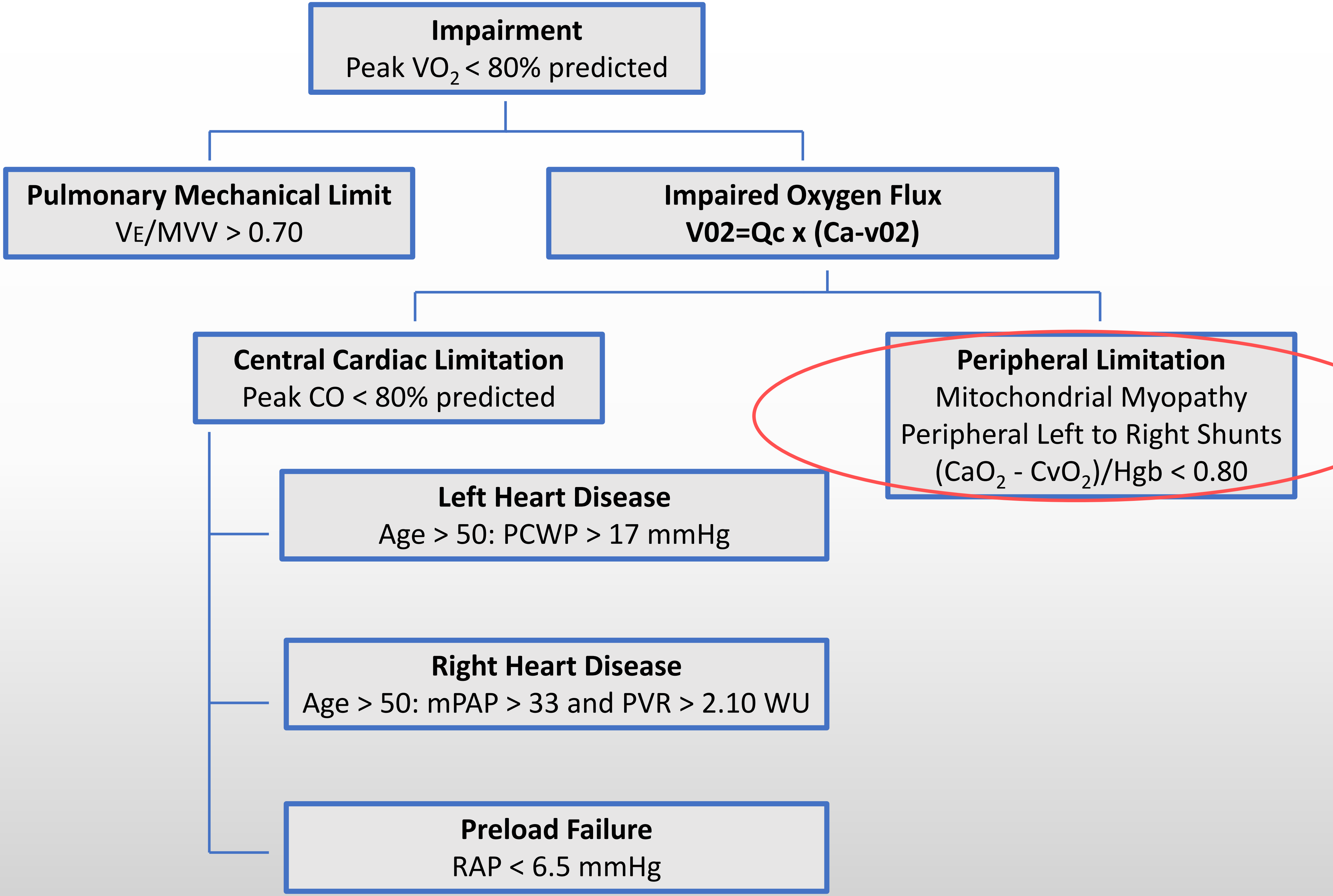
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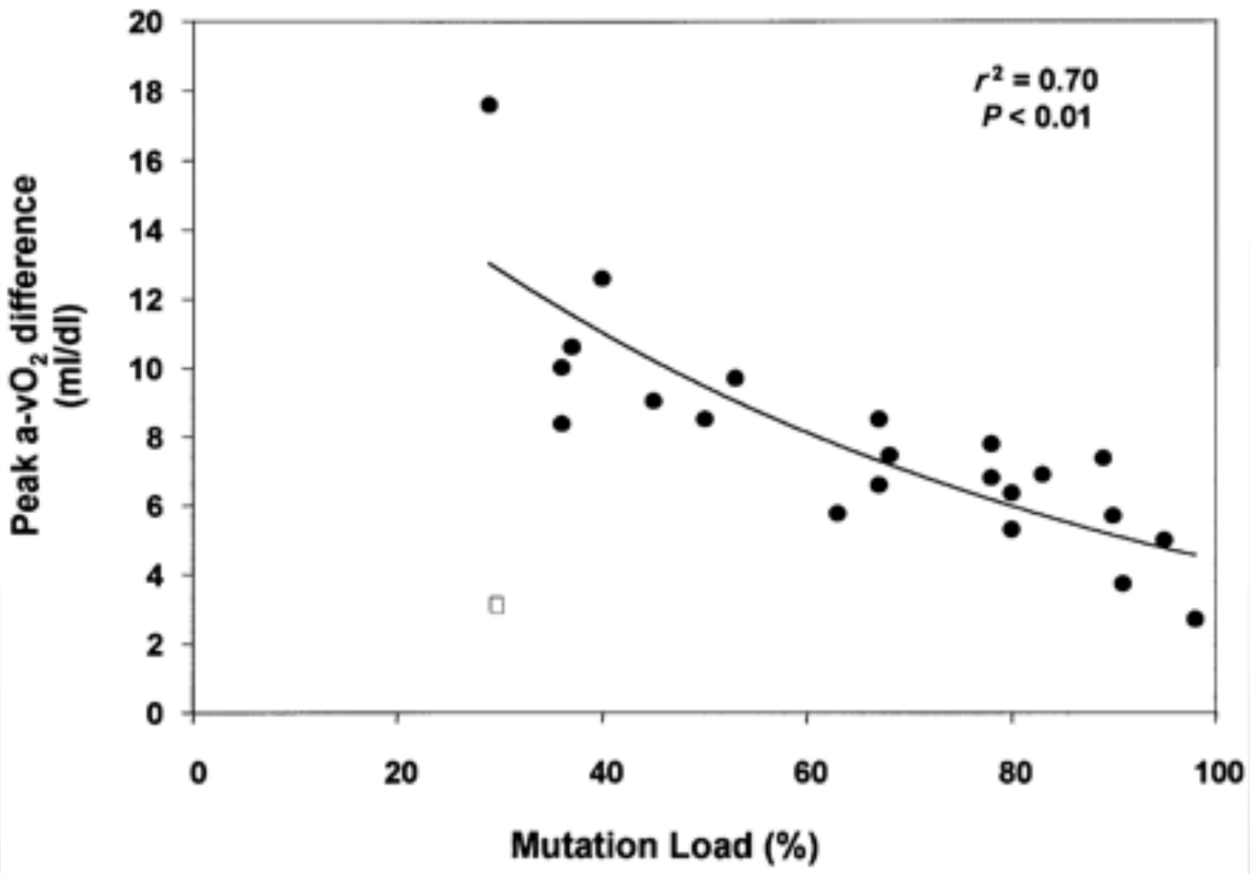
Systemic O_2 Extraction is Impaired in Mt Myopathy



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

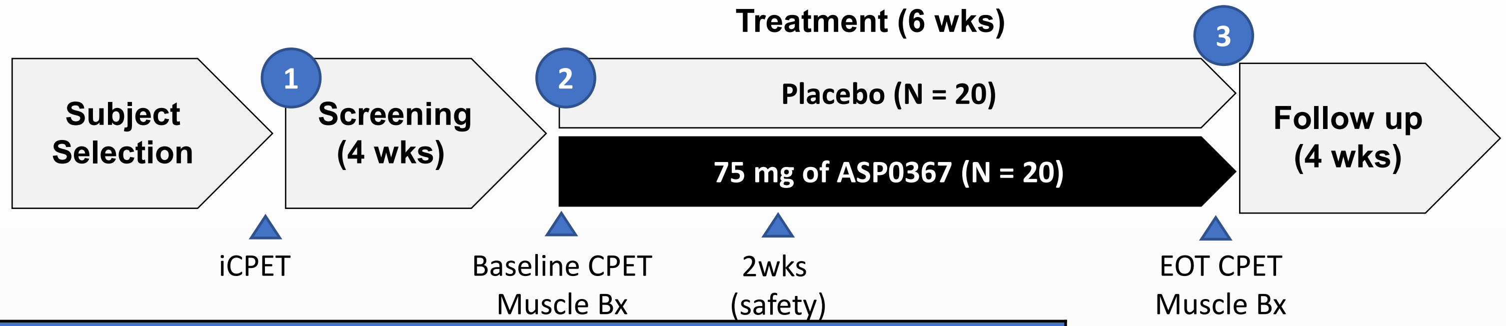
Brain. 2003;126(2):413-423. doi:10.1093/brain/awg028

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

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> 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]

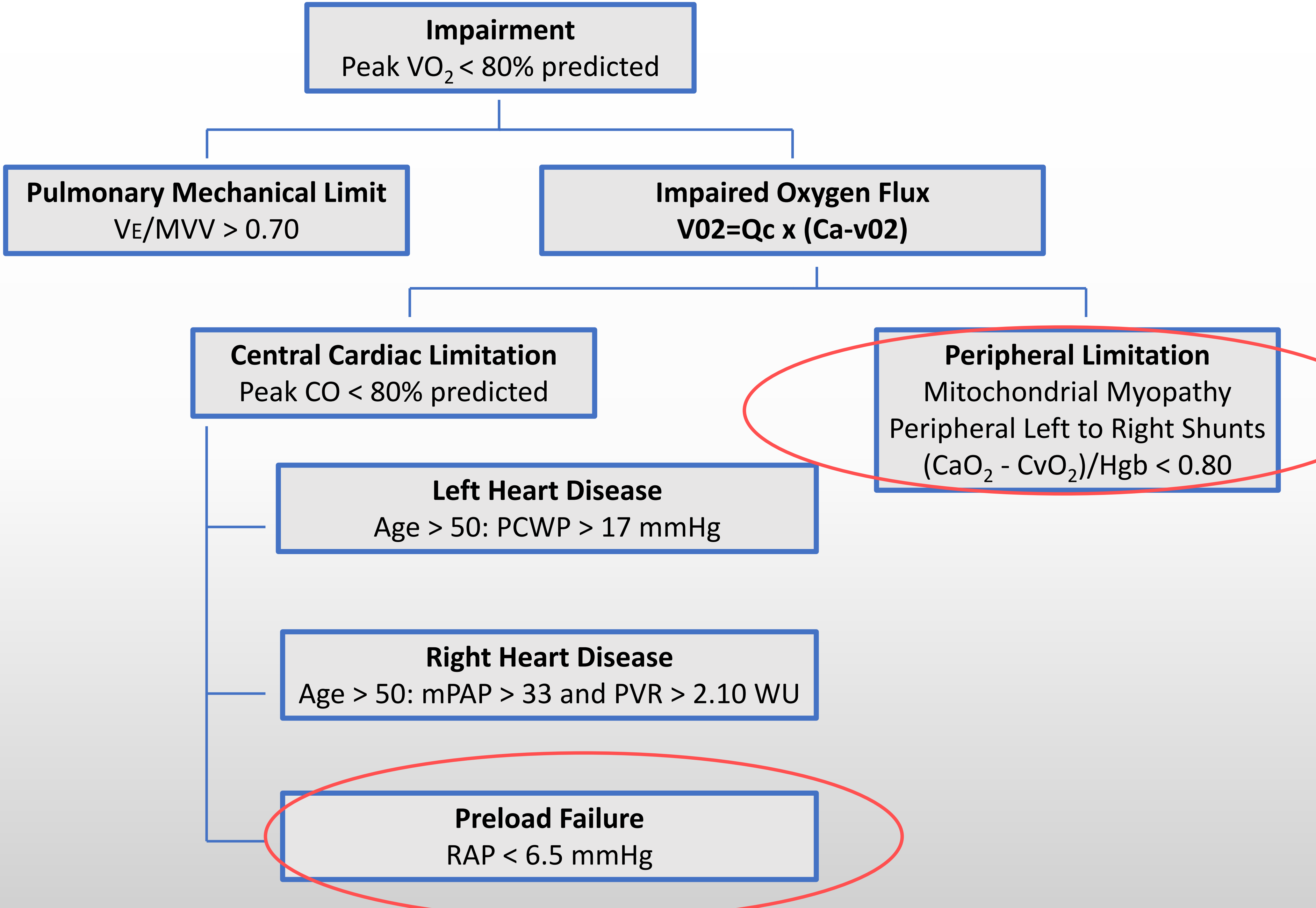
Affiliations + expand

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.



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VE/VCO_2 slope	35 ± 5	27 ± 5	.01

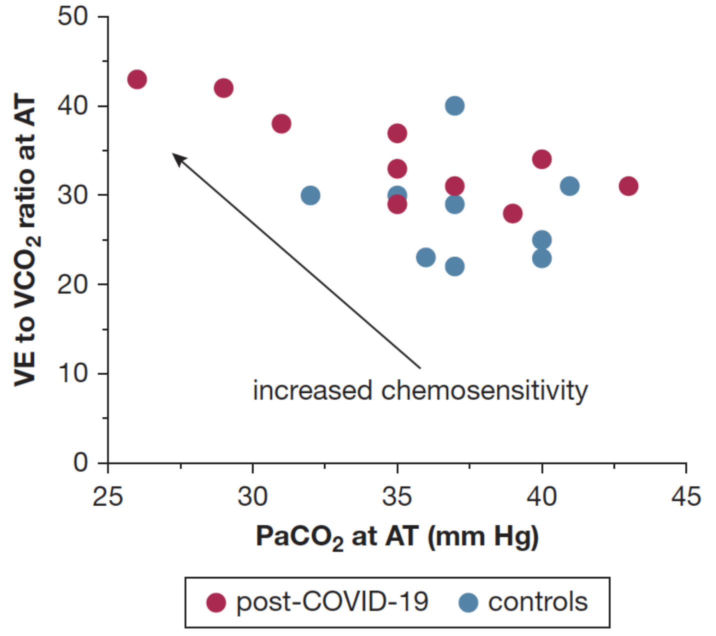

Figure 2 – *Graph showing abnormal ventilatory efficiency in patients who have recovered from COVID-19 at the AT. AT = anaerobic threshold; VE/VCO_2 = ventilatory efficiency.*

VE/VC02=1/PaC02 x (1-VD/VT)

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.

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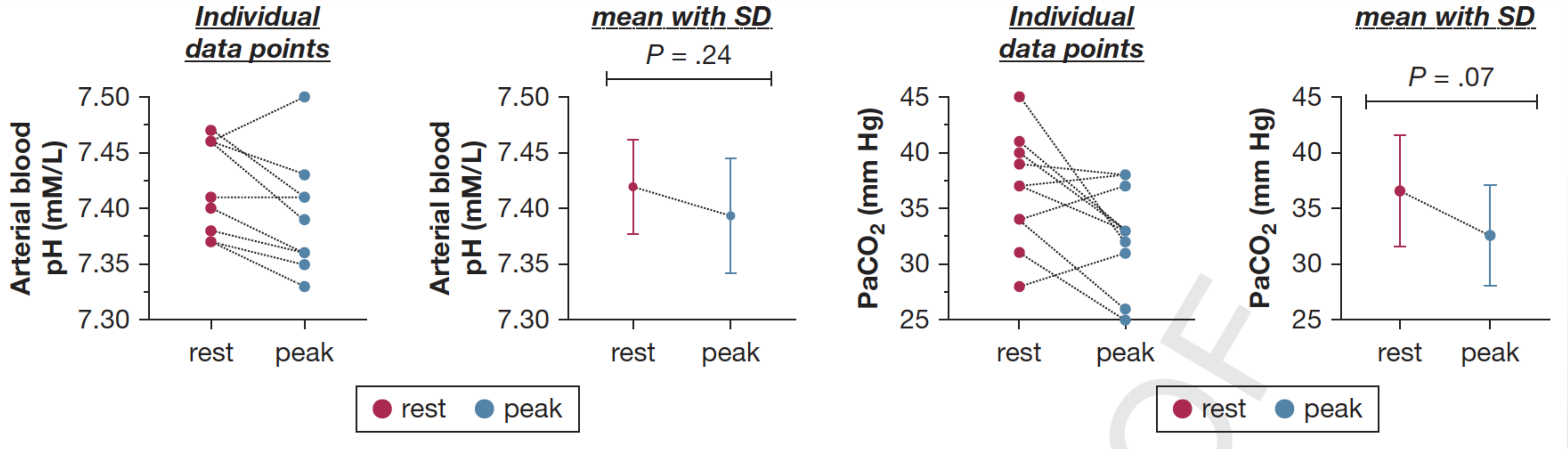

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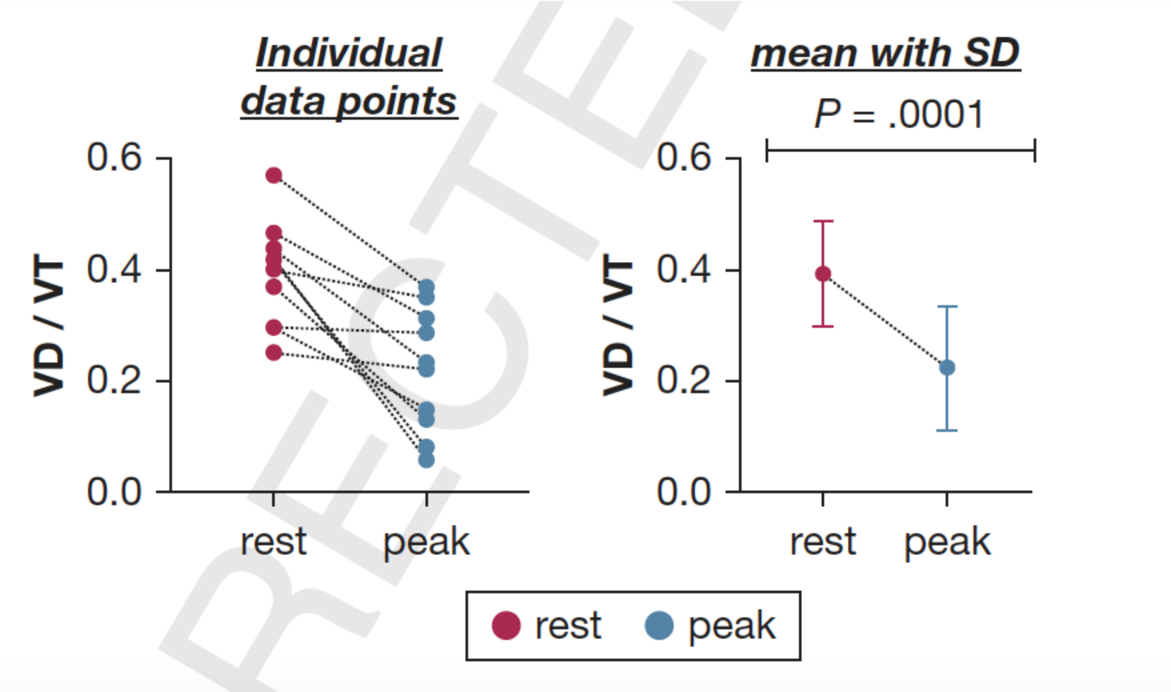

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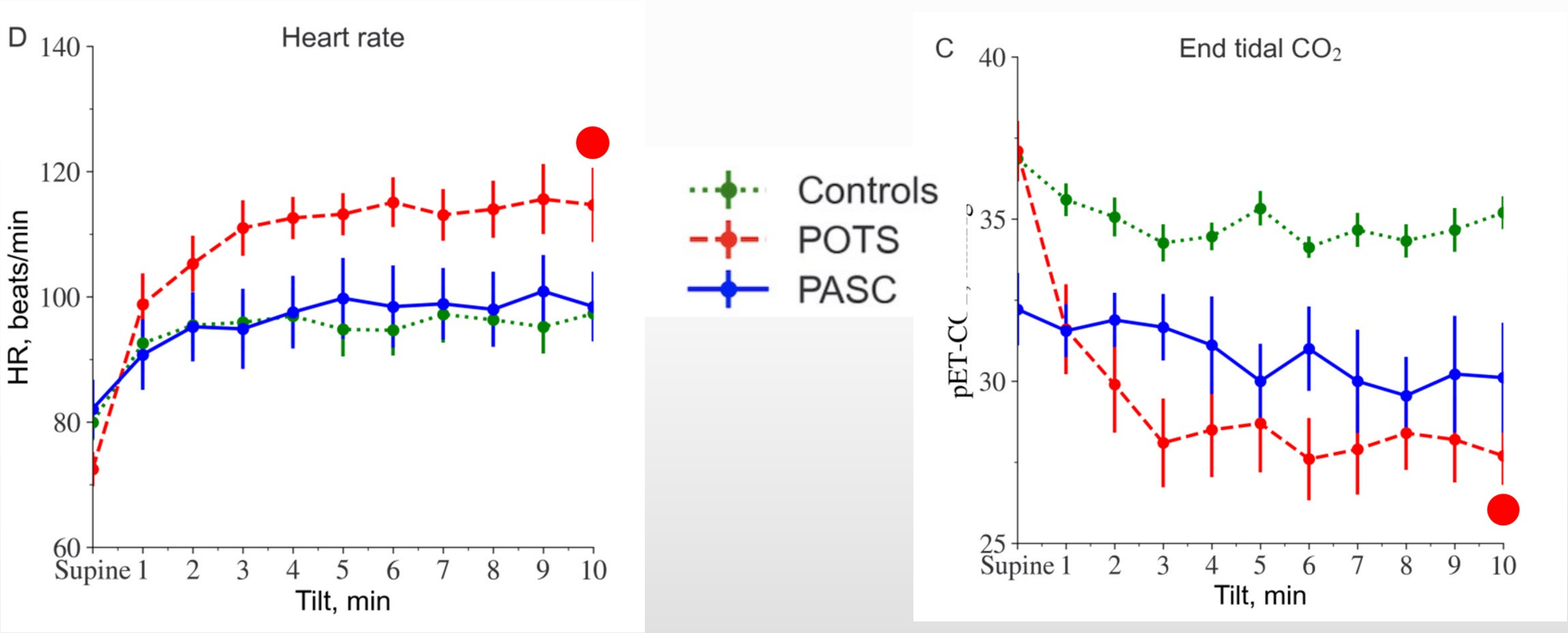
Multisystem Involvement in Post-acute Sequelae of COVID-19 (PASC)
Subtitle: PASC

Peter Novak, MD, PhD[1,5] Shibani S. Mukerji, MD, PhD[2,5], Haitham S. Alabsi, MD[2,5], David Systrom, MD[3,5], Sadie P. Marciano, PA-C[1], Donna Felsenstein, MD,[4,5], William J. Mullally MD[1,5+], David M. Pilgrim, MD[1,5+]



Novak P, Mukerji SS, Alabsi HS, Systrom D, Marciano SP, Felsenstein D, Mullally WJ, Pilgrim DM.
Multisystem Involvement in Post-acute Sequelae of COVID-19 (PASC).
Ann Neurol. 2021 Dec 24. doi: 10.1002/ana.26286. Epub ahead of print. PMID: 34952975.

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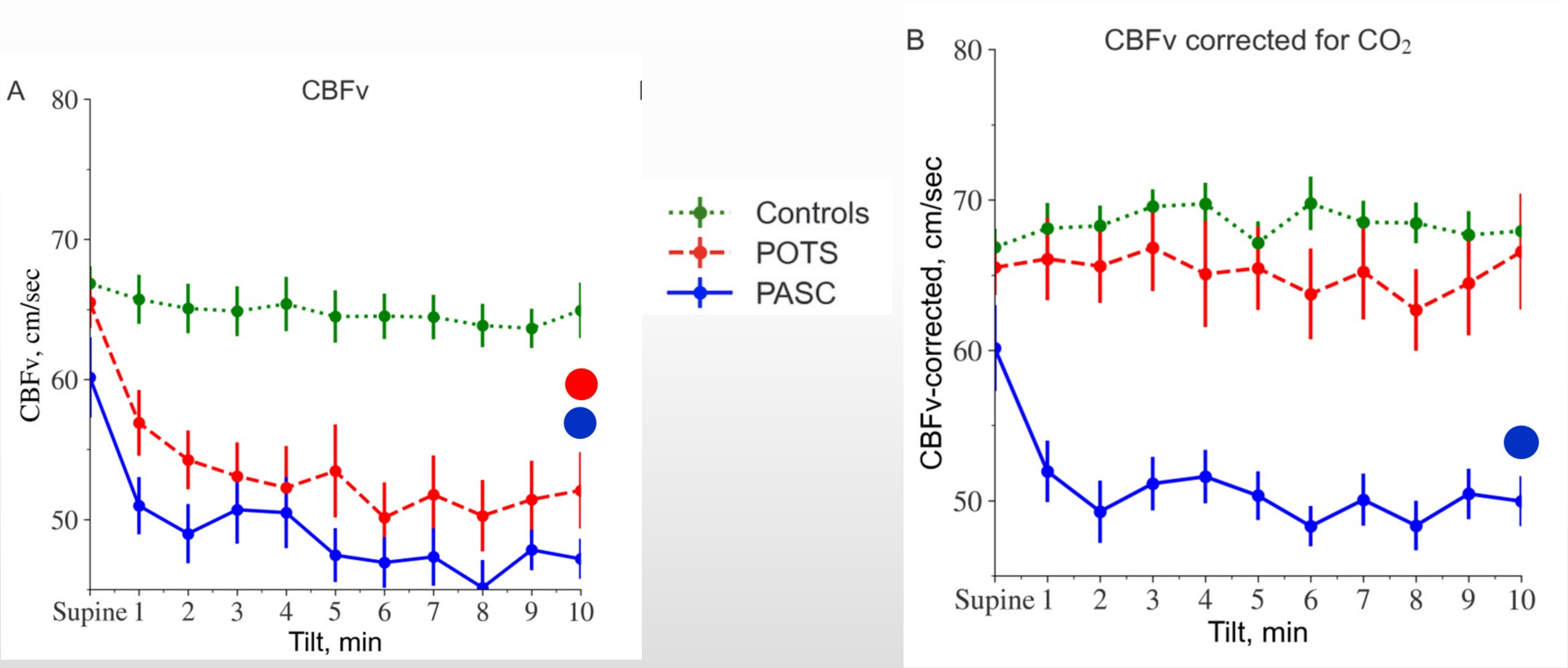

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Ann Neurol. 2021 Dec 24. doi: 10.1002/ana.26286. Epub ahead of print. PMID: 34952975.

Review > Ann Am Thorac Soc. 2021 Apr;18(4):573-581.
doi: 10.1513/AnnalsATS.202005-581CME.

Dyspnea in Chronic Low Ventricular Preload States

Rubabin Tooba [1], Kenneth A Mayuga [2], Robert Wilson [3], Adriano R Tonelli [4] [5]

Affiliations — collapse

Affiliations

1. Medicine Institute.
2. Cardiac Electrophysiology, Heart and Vascular Institute.
3. Department of Neurology, Neurological Institute.
4. Department of Pulmonary, Allergy and Critical Care Medicine, Respiratory Institute, and.
5. Pathobiology Division, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio.

PMID: 33792518 PMCID: PMC8009011 (available on 2022-04-01)
DOI: 10.1513/AnnalsATS.202005-581CME

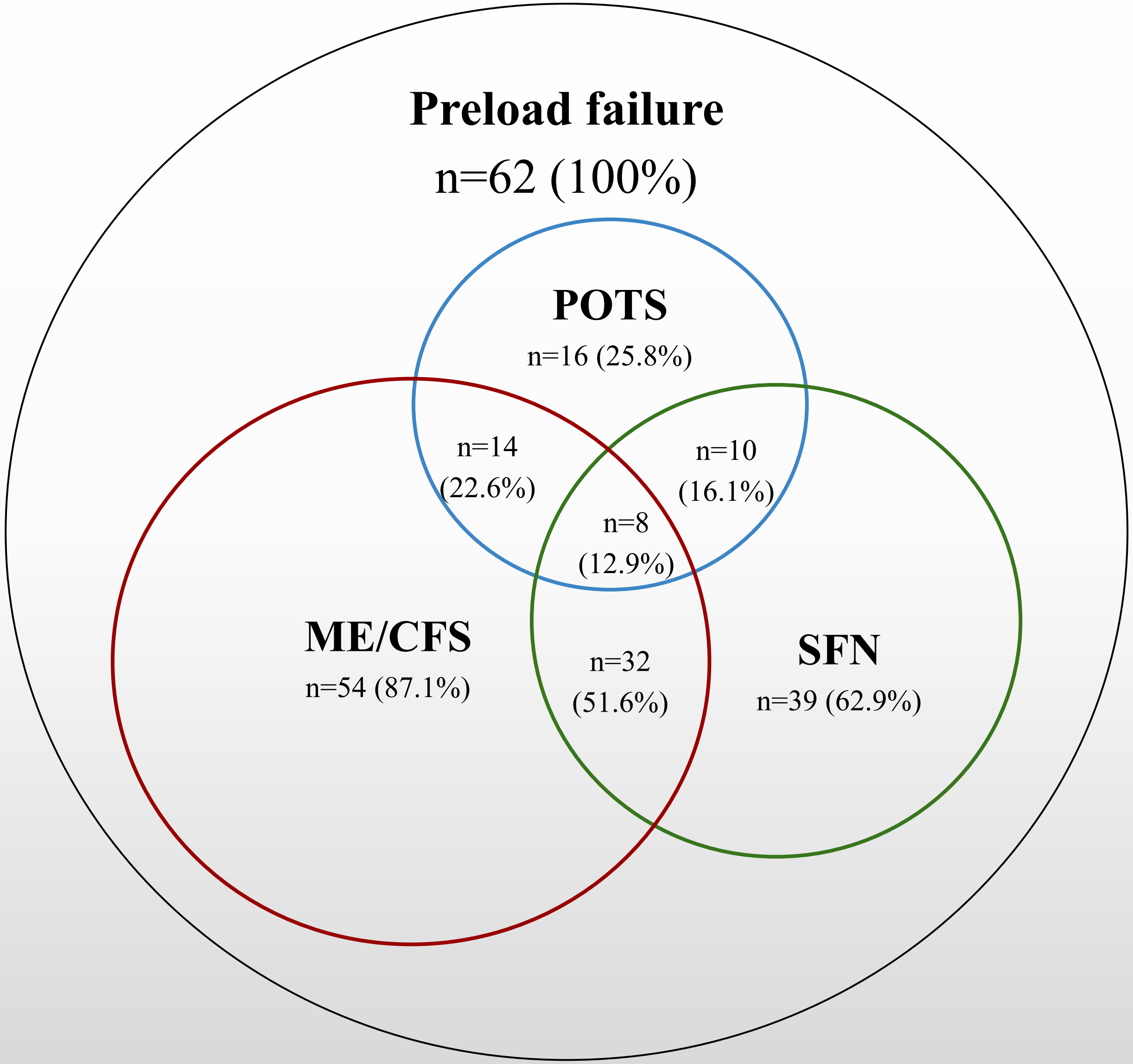
Dyspnea in low-preload states is an underrecognized but growing diagnosis in patients with unexplained dyspnea. Patients can often experience debilitating symptoms at rest and with exertion, as low measured preload often leads to decreased cardiac output and ultimately dyspnea.

Ann Am Thorac Soc 2021 Apr;18(4):573-581.

EUROPEAN RESPIRATORY JOURNAL
RESEARCH LETTER
J. MOTIEJUNAITE ET AL.

Hyperventilation as one of the mechanisms of persistent dyspnoea in SARS-CoV-2 survivors

Commonalities Among ME/CFS, Preload Failure, POTS and SFN



Unpublished Data

In ME/CFS & Long COVID:

- Vascular dysregulation contributes to exertional intolerance
- Small fiber neuropathy is prevalent
- Acute exercise activates the inflammasome
- Skeletal muscle mitochondrial dysfunction?
- Dyspnea/hyperventilation, overlap w/ POTS
- Repurposed drugs useful

> Chest. 2022 May 6;S0012-3692(22)00890-X. doi: 10.1016/j.chest.2022.04.146.
Online ahead of print.

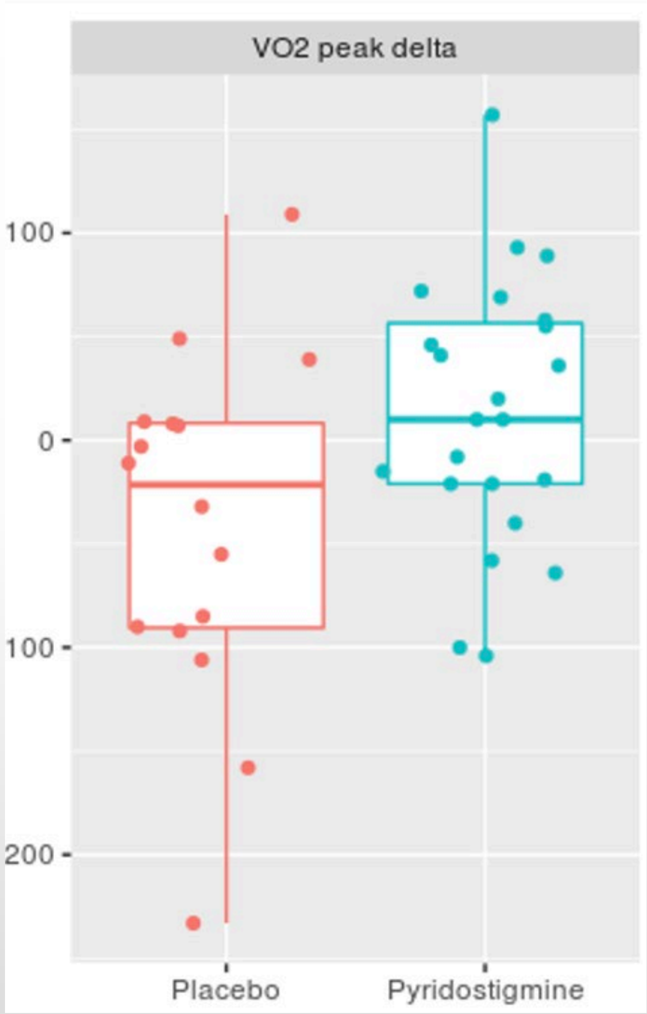
Neurovascular Dysregulation and Acute Exercise Intolerance in ME/CFS: A Randomized, Placebo-Controlled Trial of Pyridostigmine

Phillip Joseph [1], Rosa Pari [2], Sarah Miller [3], Arabella Warren [3], Mary Catherine Stovall [3], Johanna Squires [3], Chia-Jung Chang [4], Wenzhong Xiao [4], Aaron B Waxman [3], David M Systrom [5]

Affiliations + expand

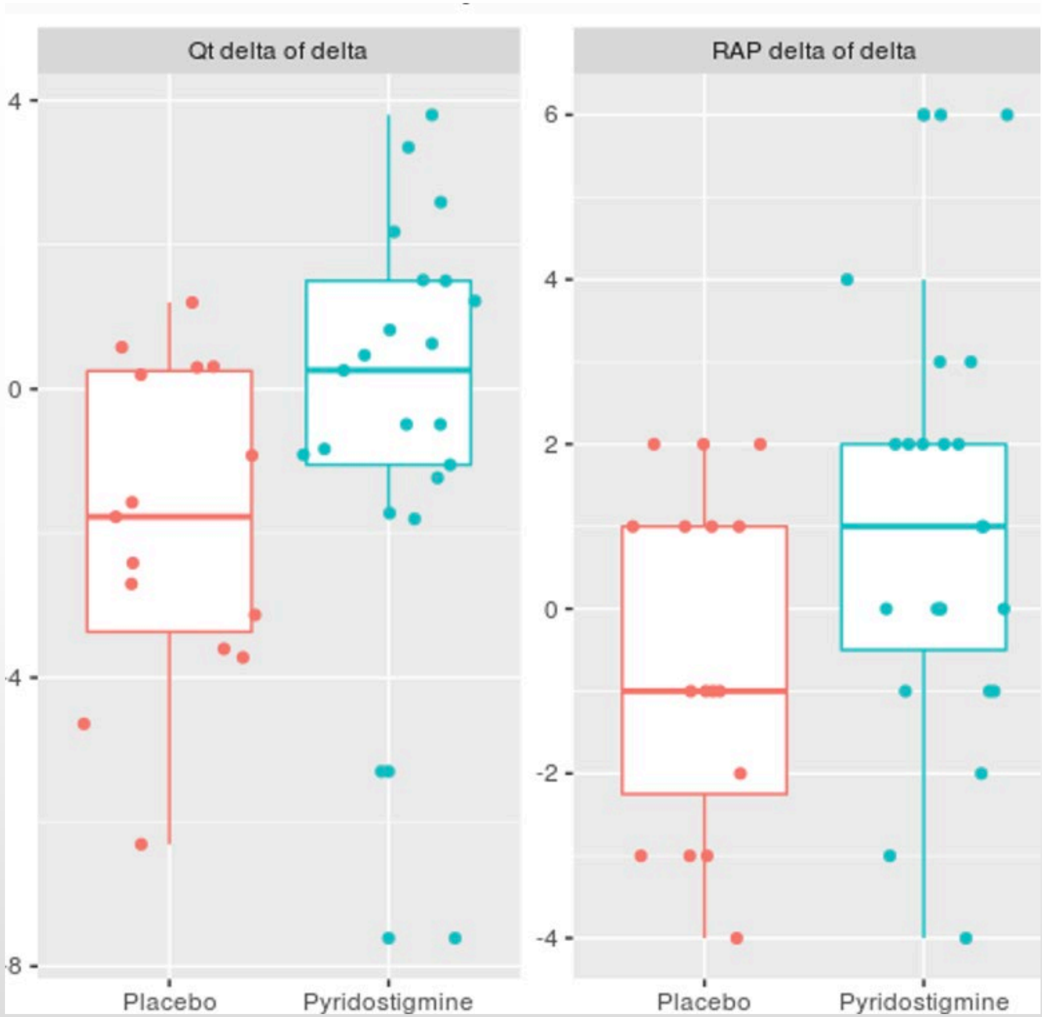
PMID: 35526605 DOI: 10.1016/j.chest.2022.04.146

V02 peak

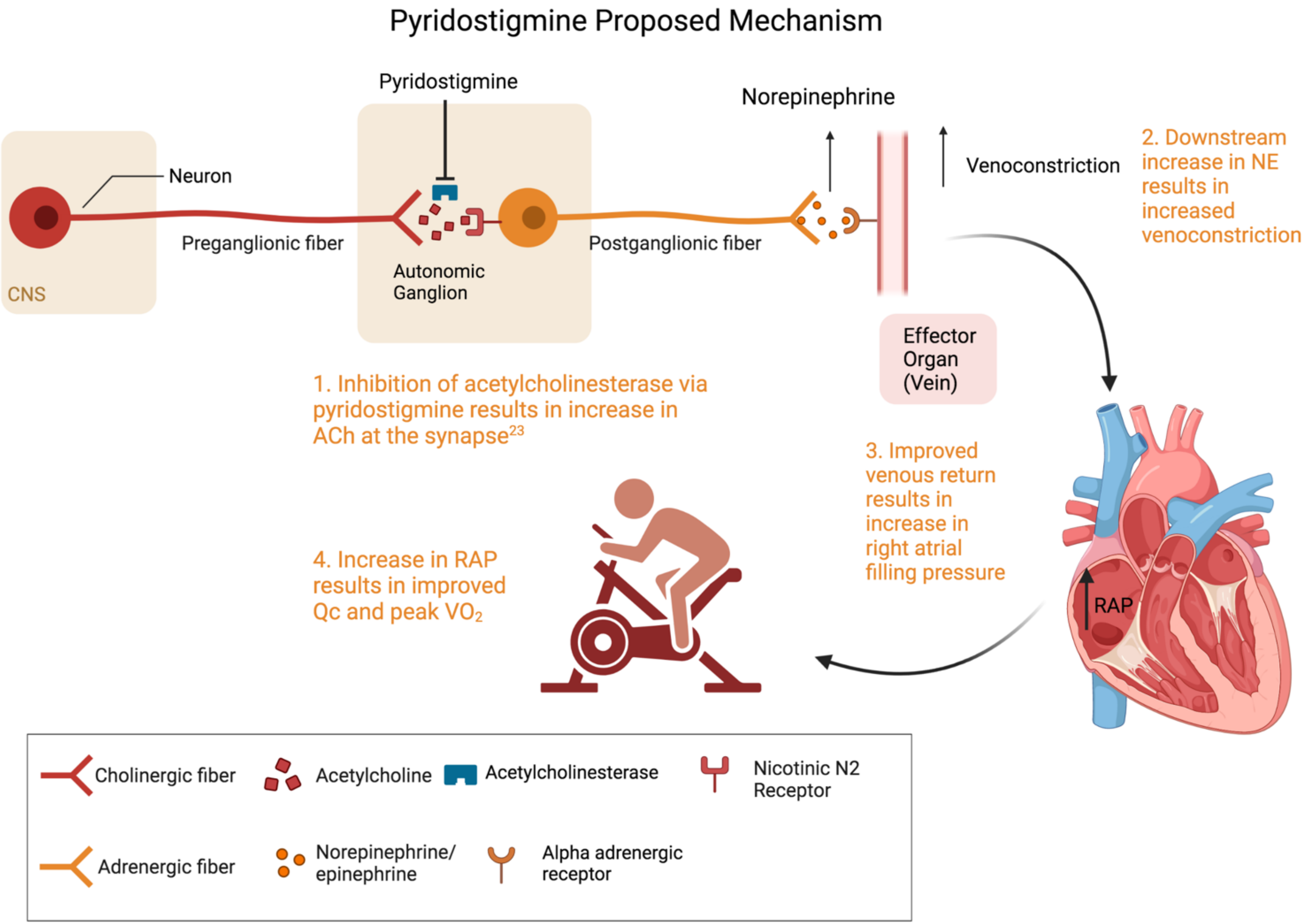


Joseph P, Pari R, Miller S, Warren A, Stovall MC, Squires J, Chang CJ, Xiao W, Waxman AB, Systrom DM. Neurovascular Dysregulation and Acute Exercise Intolerance in ME/CFS: A Randomized, Placebo-Controlled Trial of Pyridostigmine. Chest. 2022 May 6:S0012-3692(22)00890-X. doi: 10.1016/j.chest.2022.04.146. Epub ahead of print. PMID: 35526605.

Peak Cardiac Output and RAP



Joseph P, Pari R, Miller S, Warren A, Stovall MC, Squires J, Chang CJ, Xiao W, Waxman AB, Systrom DM. Neurovascular Dysregulation and Acute Exercise Intolerance in ME/CFS: A Randomized, Placebo-Controlled Trial of Pyridostigmine. Chest. 2022 May 6:S0012-3692(22)00890-X. doi: 10.1016/j.chest.2022.04.146. Epub ahead of print. PMID: 35526605.


Pyridostigmine Proposed Mechanism
Pyridostigmine
Norepinephrine
Neuron
Venoconstriction
2. Downstream increase in NE results in increased venoconstriction
Preganglionic fiber
Postganglionic fiber
CNS
Autonomic Ganglion
Effector Organ (Vein)
1. Inhibition of acetylcholinesterase via pyridostigmine results in increase in ACh at the synapse[23]
3. Improved venous return results in increase in right atrial filling pressure
RAP
4. Increase in RAP results in improved Qc and peak VO_2
Cholinergic fiber
Acetylcholine
Acetylcholinesterase
Nicotinic N2 Receptor
Adrenergic fiber
Norepinephrine/ epinephrine
Alpha adrenergic receptor

Repurposed Drugs

- Pyridostigmine (Mestinon)
- Fludrocortisone (Florinef)
- ProAmatine (Midodrine)
- Low dose naltrexone
- IVIg/Hizentra

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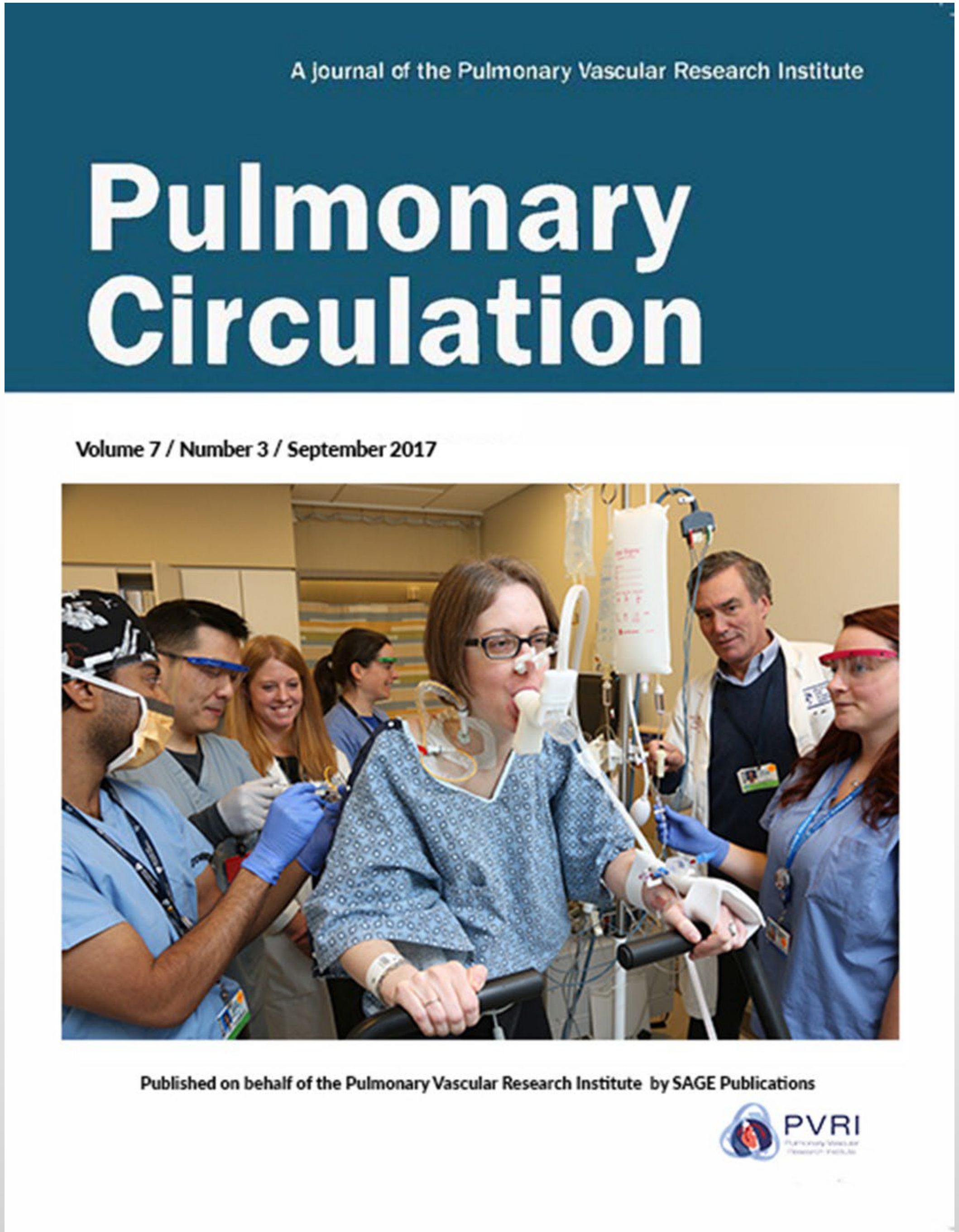

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Solve M.E.

CDMRP

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Questions?