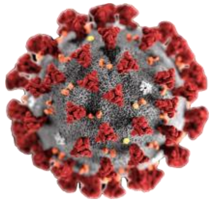
Potential Involvement of neuronal and muscle systems in the response to and recovery from SARS-Cov2/COVID19

Thomas Clanton (APK)

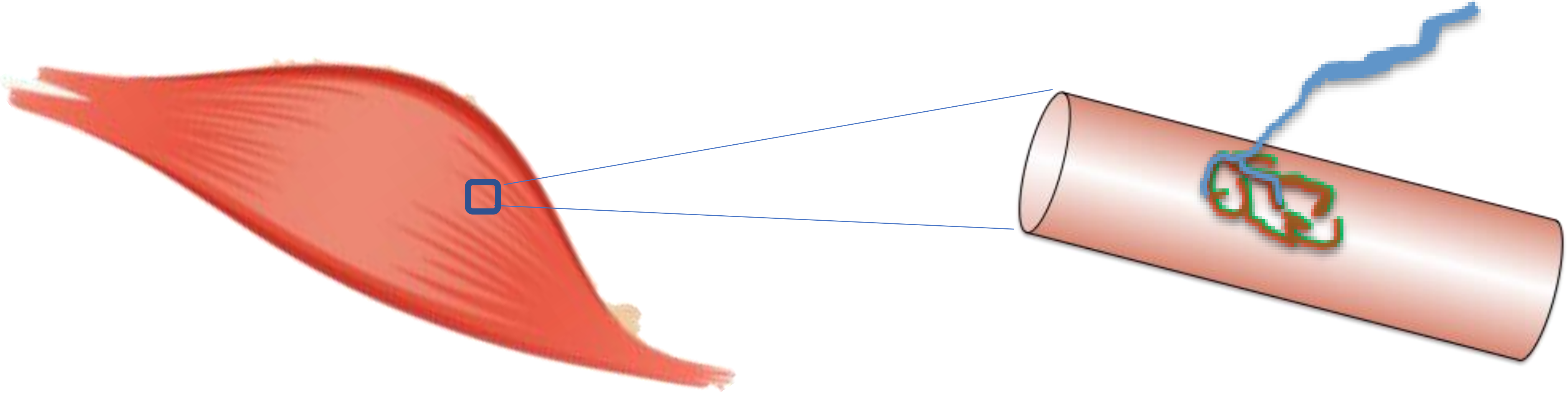
Russell Hepple (PT)

Why should we care about skeletal muscle impact with SARS-CoV2/Covid-19?

- You need muscle to breathe
- You need muscle to eat
- You need muscle to move
- You need muscle to fight infection

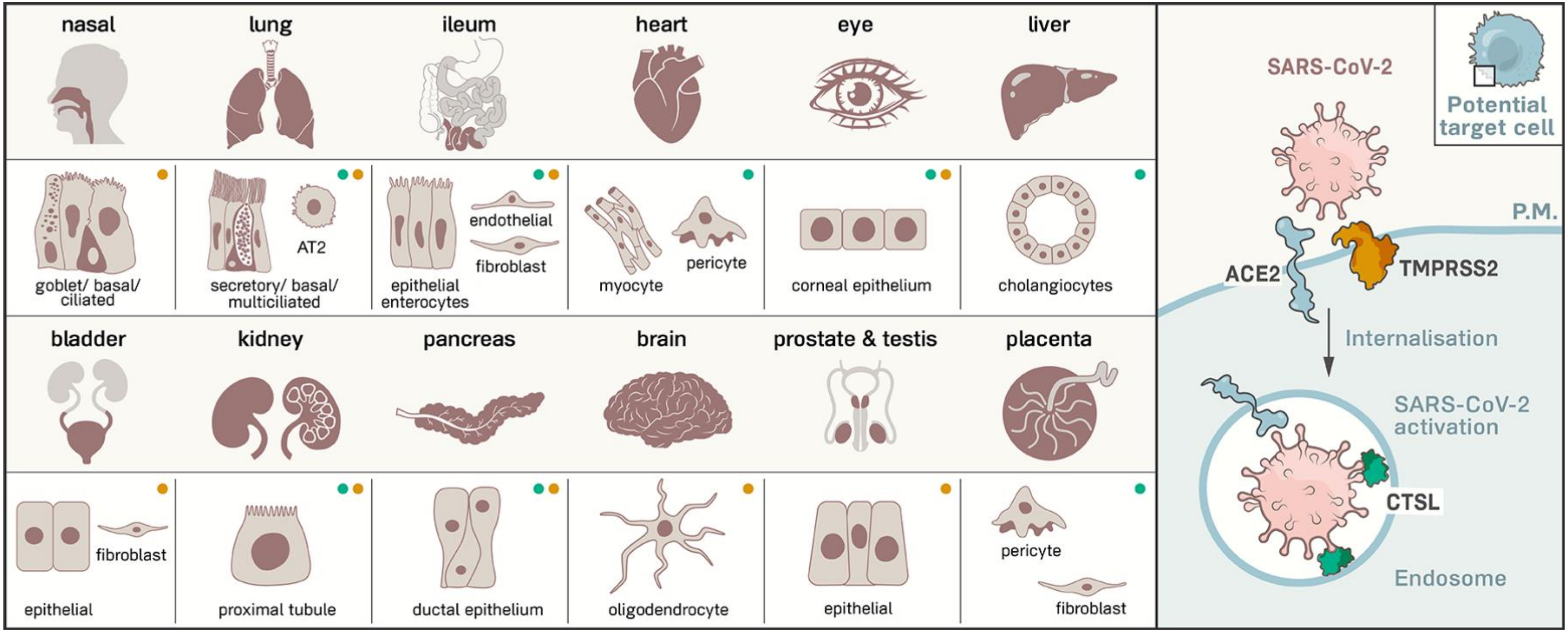


Mechanisms of SARS-CoV2/Covid-19 affect on skeletal muscle



We need to consider direct impact on muscle fibers and effects mediated through damage to motoneurons/neuromuscular junction

SARS-Cov2 receptors are ubiquitous throughout the body (ACE2 receptor, TMPRSS2)



The Scientist

…skeletal muscle expresses the ACE2 receptor, too. It is up-regulated by exercise and has anti-inflammatory actions (Frantz et al. 2017).

What do we know about skeletal muscle impact with SARS-CoV2/Covid-19?

- Not much but an interesting picture is emerging…
- Myalgia is now amongst the symptoms recommended by the CDC to recognize covid-19 (CDC)
- In some cases, the muscle impact looks quite severe…

Rhabdomyolysis

- Urine looks like a cola product
- Is the consequence of rapid degradation of muscle, resulting in muscle proteins appearing at high levels in the blood
- Can occur with muscle crush injury, high intensity/eccentric exercise, exercise in the heat, and with a variety of infections
- Symptoms include muscle pain, nausea, confusion, cardiac arrhythmia
- Main diagnostic feature is high CK in blood, which indicates cardiac or skeletal muscle damage, or both
- Can lead to kidney failure

Volume 26, Number 7—July 2020

Research Letter

EMERGING INFECTIOUS DISEASES®

Rhabdomyolysis as Potential Late Complication Associated with COVID-19

Min Jin and Qiaoxia Tong✉

60 y old man brought into hospital with fever, SARS-CoV2 confirmed

Parameter (reference range)	Day 1	Day 3	Day 6	Day 9†	Day 10	Day 11	Day 12‡	Day 15	Day 17	Day 20
				Rhabdomyolysis						
Myoglobin (0–140 µg/L)	ND	ND	ND	>12,000	12,550	7,905	3,280	928	152	86
Creatine kinase (38–174 U/L)	47	ND	ND	11,842	17,434	14,318	11,067	2,954	1,447	251
LDH (109–245 U/L)	280	ND	ND	2,347	2,137	1,979	1,754	1,265	923	597

JAMA Neurology | Original Investigation

Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China

Ling Mao; Huijuan Jin; Mengdie Wang; Yu Hu; Shengcai Chen; Quanwei He; Jiang Chang; Candong Hong; Yifan Zhou; David Wang; Xiaoping Miao; Yanan Li, MD, PhD; Bo Hu, MD, PhD

- 214 patients with Covid-19 in Wuhan
- 126 patients had nonsevere infection; 88 patients were severe
- Patients with severe infection had neurological manifestations, including evidence for skeletal muscle injury

Table 1. Clinical Characteristics of Patients With COVID-19

Characteristic	No. (%) Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	P value[a]
Age, mean (SD), y	52.7 (15.5)	58.2 (15.0)	48.9 (14.7)	
Age, y				
<50	90 (42.1)	24 (27.3)	66 (52.4)	<.001
≥50	124 (57.9)	64 (72.7)	60 (47.6)	
Sex				
Female	127 (59.3)	44 (50.0)	83 (65.9)	.02
Male	87 (40.7)	44 (50.0)	43 (34.1)	
Skeletal muscle injury	23 (10.7)	17 (19.3)	6 (4.8)	<.001

Guillain-Barre Syndrome

By Dr Jana –

The NEW ENGLAND JOURNAL of MEDICINE

Guillain–Barré Syndrome Associated with SARS-CoV-2

Toscano et al.

- 5 patients in hospitals in northern Italy
- “first symptoms…were lower-limb weakness and paresthesia in four patients and…ataxia and paresthesia in one patient”
- “The interval between the onset of symptoms of Covid-19 and the first symptoms of Guillain-Barre syndrome ranged from 5 to 10 days”
- “On electromyography, fibrillation potentials were present…findings were generally consistent with an axonal variant of Guillain-Barre syndrome”
- “Guillain-Barre syndrome with Covid-19 should be distinguished from critical illness neuropathy and myopathy, which tend to appear later…than Guillain-Barre syndrome”

What can we learn from other viruses/infectious agents?

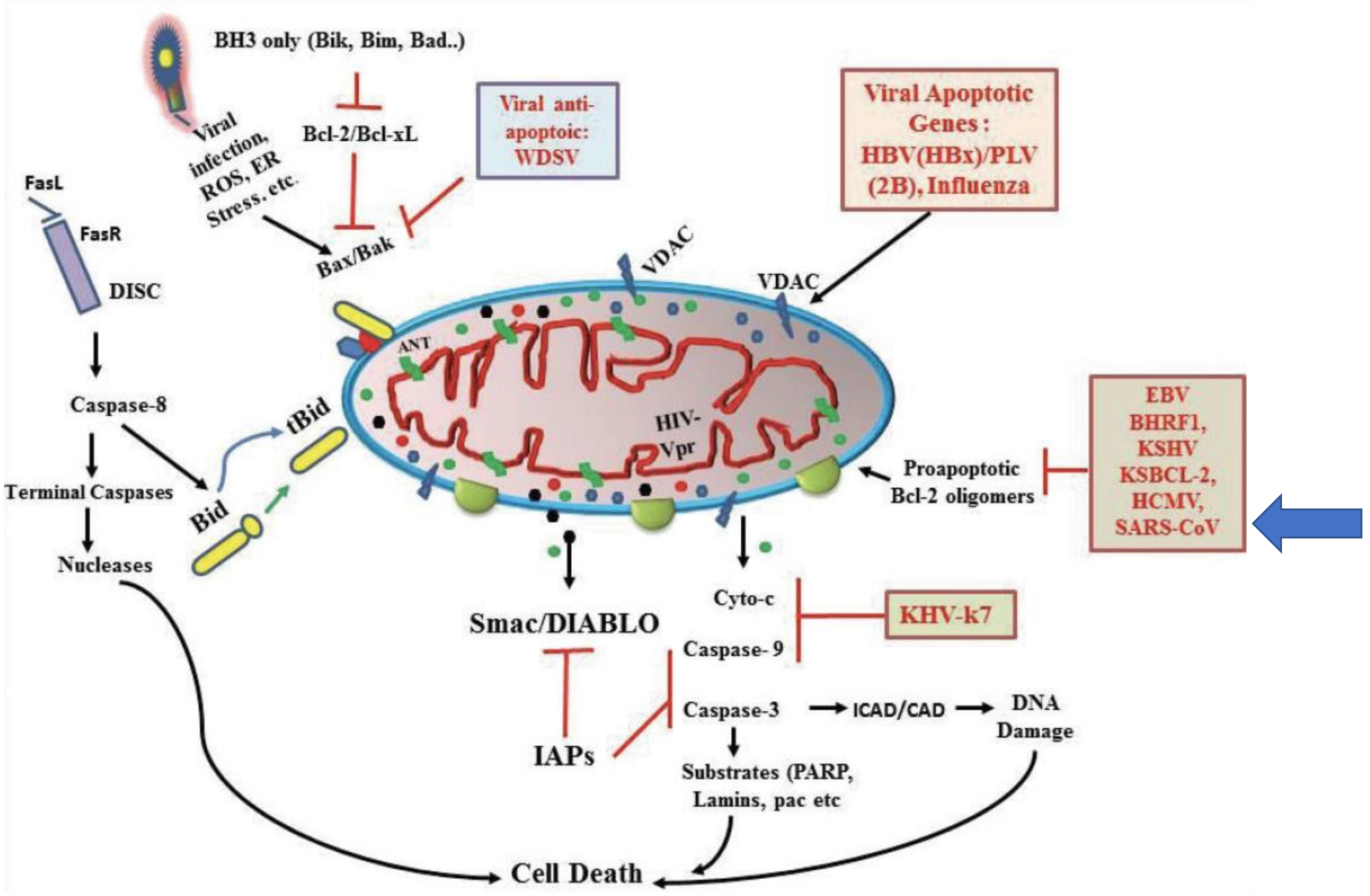
- Many viruses can directly impact muscle (Polio, Influenza A&B, non-Polio enterovirus, Zika…)
- The bacteria causing tetanus and botulism can both affect neurotransmission (Surana et al. 2018)
- Inflammation/’cytokine storm’ causes neuromuscular junction denervation (Liu et al. 2016)
- Conclusion: muscle is often affected in cases of infection

Discussion

- By what mechanisms could viral infection affect skeletal muscle function, including impacts on the motoneuron/neuromuscular junction?

Cellular Mechanisms of Viral Impact on Skeletal Muscle: Mitochondria may be key

- Mitochondria are plentiful in skeletal muscle, and particularly enriched in subsarcolemmal region of muscle fiber, and on both sides of neuromuscular junction
- Many viruses can enter mitochondria to activate apoptotic pathways
- Mitochondrial abnormalities are reported in postviral fatigue syndromes (Behan et al. 1991)
- Viral-mediated mitochondrial impairment has been implicated in myositis (Boehler et al. 2019)



Reshi et al. Modulation of Mitochondria During Viral Infections. InTechOpen. dx.doi.org/10.5772/intechopen.73036, 2018

Part 2:

What do we know about recovery of muscle function, exercise tolerance and quality of life following COVID19 infections.

A comprehensive analysis of physical and mental recovery from severe Covid-19 has not been performed!

All that is available are qualitative reports and case studies:

1) Neurological impairment
2) Muscle weakness
2) Cardiovascular impairment (Cardiomyopathy)
3) Acute Kidney injury
4) CNS and neuromotor impairment (weakness)
5) Pulmonary complications (e.g. fibrosis) and dyspnea
6) Poor quality of life

MOST OF THESE REPORTS ARE POORLY DOCUMENTED

The **assumption** is that patients with a prolonged ICU recovery on a ventilator will exhibit signs of:

PICS: Persistent Inflammation (immunosuppression) and catabolism Syndrome First described at UF in 2012

Related term: Post Intensive Care Syndrome (PICS) -(PM&R specialists)

CIM: Critical Illness Myopathy (CIM) Pulmonologists/Intensivists

ICUAW: ICU acquired weakness, Pulmonologists, Intensivists

Critical illness polyneuromyopathy or polyneuropathy

Originally defined by University of Florida Researchers!   Department of Surgery

J Trauma Acute Care Surg. **2012** Jun;72(6):1491-501. doi: 10.1097/TA.0b013e318256e000.

Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care.

Gentile LF[1], Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, Moldawer LL, Moore FA.

Author information

Abstract

Surgical intensive care unit (ICU) stay of longer than 10 days is often described by the experienced intensivist as a "complicated clinical course" and is frequently attributed to persistent immune dysfunction. "Systemic inflammatory response syndrome" (SIRS) followed by "compensatory anti-inflammatory response syndrome" (CARS) is a conceptual framework to explain the immunologic trajectory that ICU patients with severe sepsis, trauma, or emergency surgery for abdominal infection often traverse, but the causes, mechanisms, and reasons for persistent immune dysfunction remain unexplained. Often involving multiple-organ failure (MOF) and death, improvements in surgical intensive care have altered its incidence, phenotype, and frequency and have increased the number of patients who survive initial sepsis or surgical events and progress to a persistent inflammation, immunosuppression, and catabolism syndrome (PICS). Often observed, but rarely reversible, these patients may survive to transfer to a long-term care facility only to return to the ICU, but rarely to self-sufficiency. We propose that PICS is the dominant pathophysiology and phenotype that has replaced late MOF and prolongs surgical ICU stay, usually with poor outcome. This review details the evolving epidemiology of MOF, the clinical presentation of PICS, and our understanding of how persistent inflammation and immunosuppression define the pathobiology of prolonged intensive care. Therapy for PICS will involve innovative interventions for immune system rebalance and nutritional support to regain physical function and well-being.

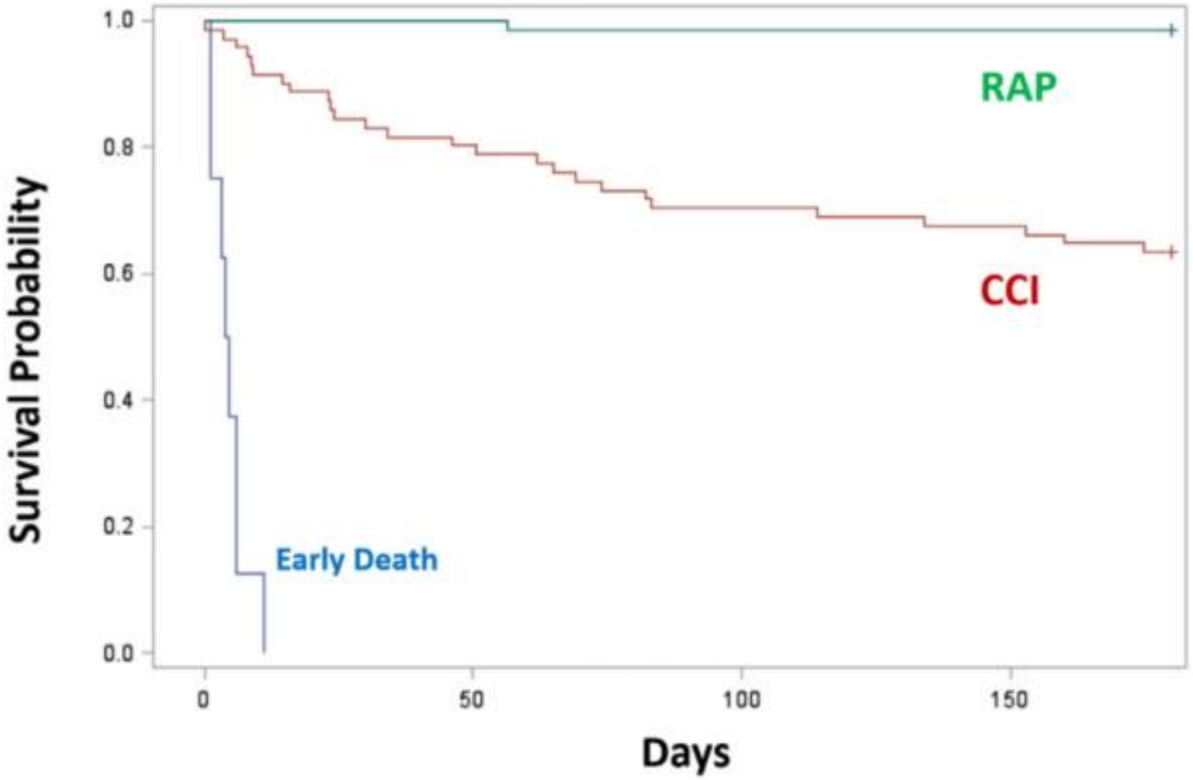


FIGURE 3 | Survival of CCI ($n = 71$) or RAP ($n = 66$) patients 6 months after sepsis. Trajectories were classified as early death (blue), RAP (green), and CCI (red). Kaplan–Meier analysis demonstrated significant differences ($p < 0.01$) in survival between groups. Abbreviations: CCI, chronic critical illness; RAP, rapid recovery.

CCI: Chronic Critical Illness patients

> 14 days hospital stay

Low grade organ dysfunction particularly AKI

Chronic inflammation

and immunosuppression

Latent, recurrent infections

Atrophy and muscle weakness

Expression of MDSCs:

Myeloid derived suppressor cells

40% of CCI patients die within one year

Front Immunol. 2018; 9: 1511. PMCID: PMC6036179
Published online 2018 Jul 2. doi: 10.3389/fimmu.2018.01511 PMID: 30013565

Chronic Critical Illness and the Persistent Inflammation, Immunosuppression, and Catabolism Syndrome

Russell B. Hawkins,[1] Steven L. Raymond,[1] Julie A. Stortz,[1] Hiroyuki Horiguchi,[1] Scott C. Brakenridge,[1] Anna Gardner,[2] Philip A. Efron,[1] Azra Bihorac,[1,3] Mark Segal,[1,3] Frederick A. Moore,[1] and Lyle L. Moldawer[1,*]

SIRS: Systemic Inflammatory Response Syndrome "Cytokine Storm"

Front Immunol. 2018; 9: 1511.
Published online 2018 Jul 2. doi: 10.3389/fimmu.2018.01511
PMCID: PMC6036179
PMID: 30013565

Chronic Critical Illness and the Persistent Inflammation, Immunosuppression, and Catabolism Syndrome

Russell B. Hawkins,[1] Steven L. Raymond,[1] Julie A. Stortz,[1] Hiroyuki Horiguchi,[1] Scott C. Brakenridge,[1] Anna Gardner,[2] Philip A. Efron,[1] Azra Bihorac,[1,3] Mark Segal,[1,3] Frederick A. Moore,[1] and Lyle L. Moldawer[1,*]

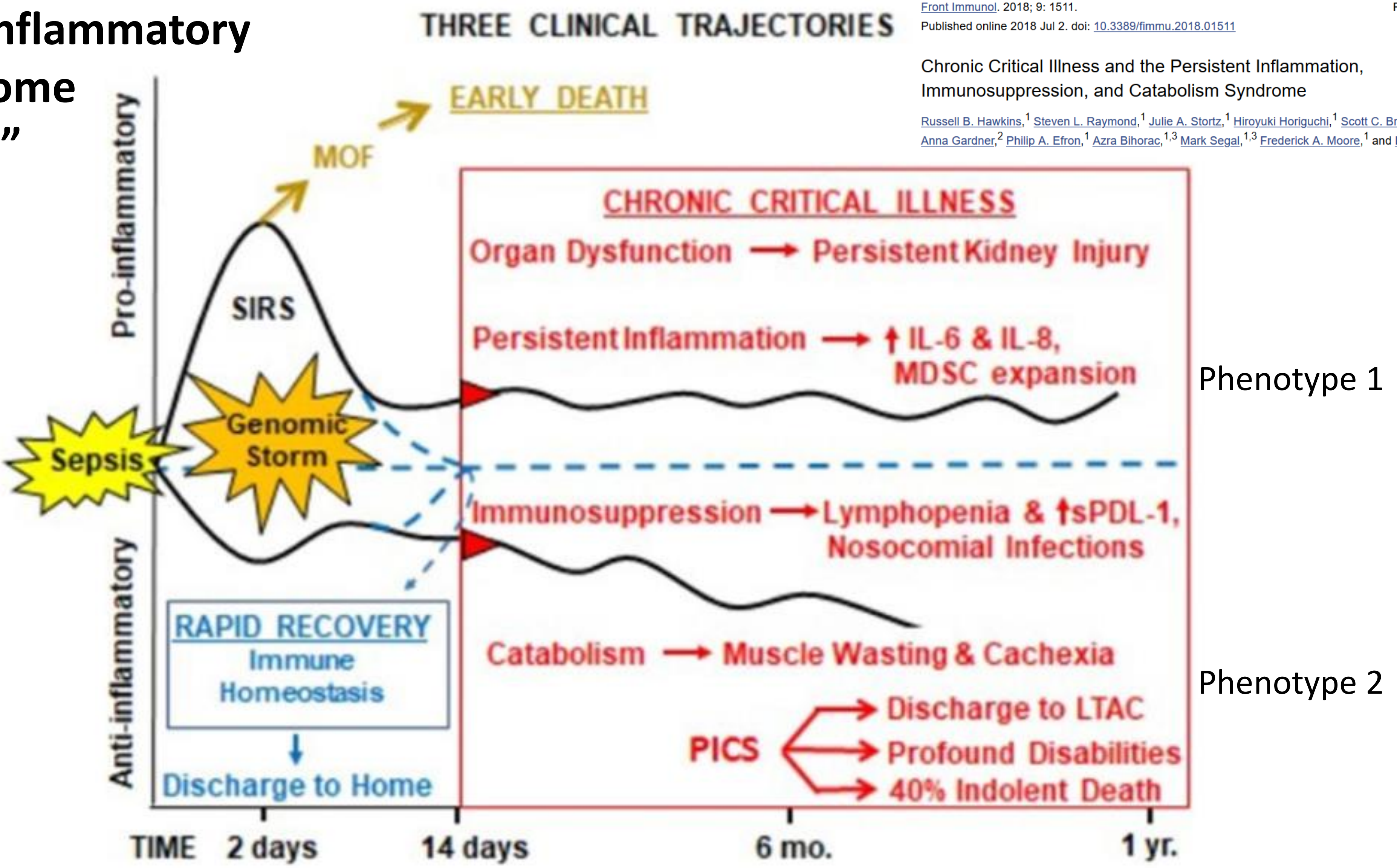


FIGURE 1 | Proposed hypothesis for the PICS. Abbreviations: SIRS, systemic inflammatory response syndrome; MDSC, myeloid-derived suppressor cell; sPDL-1, soluble programmed death ligand-1; LTAC, long-term acute care facility; PICS, persistent inflammation, immunosuppression, and catabolism syndrome.

Do COVID-19 patients that are hospitalized have a long enough ICU stay to induce PICS?

Table 4. Discharge Disposition by 10-Year Age Intervals of Patients Hospitalized With COVID-19

	Patients discharged alive or dead at study end point						Patients in hospital at study end point	
	Died, No./No. (%)		Length of stay among those who died, median (IQR), d[a]	Discharged alive, No./No. (%)		Length of stay among those discharged alive, median (IQR), d[a]		
	Male	Female		Male	Female		No./No. (%)	Length of stay, median (IQR), d[a]
Age intervals, y								
0-9	0/13	0/13	NA	13/13 (100)	13/13 (100)	2.0 (1.7-2.7)	7/33 (21.2)	4.3 (3.1-12.5)
10-19	0/1	0/7	NA	1/1 (100)	7/7 (100)	1.8 (1.0-3.1)	9/17 (52.9)	3.3 (2.8-4.3)
20-29	3/42 (7.1)	1/55 (1.8)	4.0 (0.8-7.4)	39/42 (92.9)	54/55 (98.2)	2.5 (1.8-4.0)	52/149 (34.9)	3.2 (1.9-6.4)
30-39	6/130 (4.6)	2/81 (2.5)	2.8 (2.4-3.6)	124/130 (95.4)	79/81 (97.5)	3.7 (2.0-5.8)	142/353 (40.2)	5.1 (2.5-9.0)
40-49	19/233 (8.2)	3/119 (2.5)	5.6 (3.0-8.4)	214/233 (91.8)	116/119 (97.5)	3.9 (2.3-6.1)	319/671 (47.5)	4.9 (2.9-8.2)
50-59	40/327 (12.2)	13/188 (6.9)	5.9 (3.1-9.5)	287/327 (87.8)	175/188 (93.1)	3.8 (2.5-6.7)	594/1109 (53.6)	4.9 (2.8-8.0)
60-69	56/300 (18.7)	28/233 (12.0)	5.7 (2.6-8.2)	244/300 (81.3)	205/233 (88.0)	4.3 (2.5-6.8)	771/1304 (59.1)	5.0 (2.4-8.2)
70-79	91/254 (35.8)	54/197 (27.4)	5.0 (2.7-7.8)	163/254 (64.2)	143/197 (72.6)	4.6 (2.8-7.8)	697/1148 (60.7)	4.5 (2.3-8.2)
80-89	94/155 (60.6)	76/158 (48.1)	3.9 (2.1-6.5)	61/155 (39.4)	82/158 (51.9)	4.4 (2.7-7.7)	369/682 (54.1)	4.1 (2.1-7.4)
≥90	28/44 (63.6)	39/84 (46.4)	3.0 (0.7-5.5)	16/44 (36.4)	45/84 (53.6)	4.8 (2.8-8.4)	106/234 (45.3)	3.2 (1.5-6.4)

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; NA, not applicable.

[a] Length of stay begins with admission time and ends with discharge time, time at death, or midnight on the last day of data collection for the study. It does not include time in the emergency department.

Most recent data from NEW YORK
Published last week.

JAMA | Original Investigation

Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area

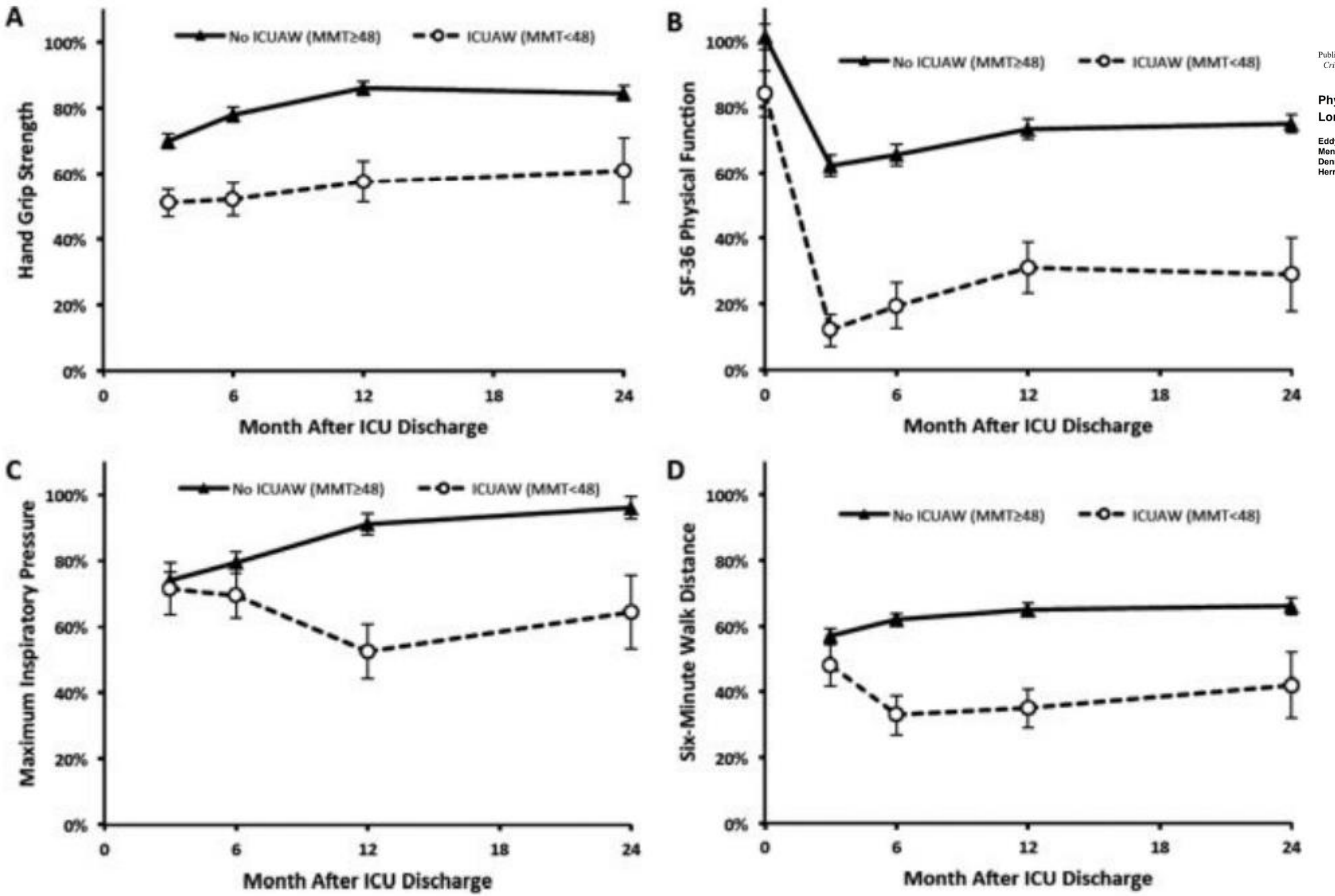
Safiya Richardson, MD, MPH; Jamie S. Hirsch, MD, MA, MSB; Mangala Narasimhan, DO; James M. Crawford, MD, PhD; Thomas McGinn, MD, MPH; Karina W. Davidson, PhD, MASc; and the Northwell COVID-19 Research Consortium

Critical Illness myopathy or ICUAW:
More associated with ARDS closer to Covid-19 patient descriptions

Focus on muscle and nerve function
Sometimes includes VIDD and failure to wean

Most of the **ARDS** literature uses these terms and applications

Focus on rehab, nutrition, managing glucose, strength testing, physical rehabilitation etc.



Published in final edited form as:
Crit Care Med. 2014 April ; 42(4): 849–859. doi:10.1097/CCM.0000000000000040.

Physical Complications in Acute Lung Injury Survivors: A 2-Year Longitudinal Prospective Study

Eddy Fan, MD, PhD, David W. Dowdy, MD, PhD, Elizabeth Colantuoni, PhD, Pedro A. Mendez-Tellez, MD, Jonathan E. Sevransky, MD, MHS, Carl Shanholtz, MD, Cheryl R. Dennison Himmelfarb, RN, PhD, Sanjay V. Desai, MD, Nancy Ciesla, DPT, Margaret S. Herridge, MD, MPH, Peter J. Pronovost, MD, PhD, and Dale M. Needham, MD, PhD

ICUAW (PICS)

POST ARDS

Multicenter Trial
Led by
Dale Needham

Evidence for involvement of peripheral nerves is COMMON but poorly evaluated over time

Table 1. Clinical variables in critical illness polyneuropathy/myopathy (CIP/CIM) patients and controls

	CIP/CIM		Controls		*p* Value
Age at admission, yrs	44	(21, 59)	24	(18, 35)	.010
ICU days	38	(30, 67)	26	(19, 35)	.001
ICU days before admission	5	(3, 8)	4	(3, 6)	.176
Pa_{O_2}/F_{IO_2} on admission, torr, kPa	75	(57, 143)	92	(76, 152)	.297
	10.0	(7.6, 19.1)	12.2	(10.1, 20.2)	
Ventilator days after admission (28 days)	20	(13, 28)	13	(9, 23)	.018
SAPS II, mean/28 days on ICU	35	(29, 40)	32	(29, 37)	.445
SOFA, mean/28 days on ICU	5	(4, 6)	5	(4, 6)	.694
Daily glucose peak level, mean/28 days on ICU, mg/dL	166	(134, 200)	144	(132, 161)	<.001
Patients received stress-dose hydrocortisone, n (%)	20 of 27 (74)		12 of 18 (67)		.739

ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sepsis-related Organ Failure Assessment. Data are median and quartiles (p25, p75) tested using Mann-Whitney U test and chi-square test (stress-dose hydrocortisone).

However, electromyography (EMG) testing will demonstrate abnormalities showing an initial primary axonal degeneration of the motor neurons, followed by the sensory neural fibers and this coincides with acute and chronic changes of denervation noted on muscle biopsies in affected patients.[39]

Critical illness polyneuropathy and myopathy in patients with acute respiratory distress syndrome*

Sven Bercker, MD; Steffen Weber-Carstens, MD; Maria Deja, MD; Claudia Grimm, MD; Steffen Wolf, MD; Friedrich Behse, MD; Thilo Busch, PhD; Konrad J. Falke, MD; Udo Kaisers, MD

Crit Care Clin. 2011 Jul;27(3):685-704.
Recovery and long-term outcome in acute respiratory distress syndrome.
Herridge MS[1].

Strategies toward Rehabilitation in Critical Illness myopathy:

ACC
Acute and Critical Care
Check for updates
Acute and Critical Care 2019 February 34(1):1-13
https://doi.org/10.4266/acc.2019.00444
| pISSN 2586-6052 | eISSN 2586-6060

Pulmonary and Physical Rehabilitation in Critically Ill Patients

Myung Hun Jang[1], Myung-Jun Shin[1,2], Yong Beom Shin[1,2]

[1]Department of Rehabilitation Medicine, Biomedical Research Institute, Pusan National University Hospital, Busan; [2]Department of Rehabilitation Medicine, Pusan National University School of Medicine, Busan, Korea

Home and Community-Based Physical Therapist Management of Adults With Post–Intensive Care Syndrome

Physical Therapist Management of Adults With PICS

Musculoskeletal

Perspective

James M. Smith, Alan C. Lee, Hallie Zeleznik, Jacqueline P. Coffey Scott, Arooj Fatima, Dale M. Needham, Patricia J. Ohtake

ACC Acute and Critical Care
Acute and Critical Care 2019 February 34(1):1-13
https://doi.org/10.4266/acc.2019.00444
| pISSN 2586-6052 | eISSN 2586-6060

Pulmonary and Physical Rehabilitation in Critically Ill Patients

Myung Hun Jang[1], Myung-Jun Shin[1,2], Yong Beom Shin[1,2]
[1]Department of Rehabilitation Medicine, Biomedical Research Institute, Pusan National University Hospital, Busan; [2]Department of Rehabilitation Medicine, Pusan National University School of Medicine, Busan, Korea

1. Diagnosis: Weakness- Strength
2. Differentiate CIP from CIM

Score 5 questions							/5
A. Open and close your eyes B. Look at me C. Open your mouth and put out your tongue D. Nod your head E. Raise your eyebrows when I have counted up to five							
MRC sum score							
	Right	**Reason**	**EP**	**Left**	**Reason**	**EP**	
Arm abduction							
Forearm flexion							
Wrist extension							
Hip flexion							
Knee extension							
Ankle dorsiflexion							
MRC sum-score				/60			

Table 1. Electrophysiological findings of ICUAW

Critical illness polyneuropathy	Critical illness myopathy
CMAP decreased to <80% of LLN in >2 nerves	CMAP decreased to <80% of LLN in >2 nerves
SNAP decreased to <80% of LLN in >2 nerves	SNAPs are >80% of LLN in >2 nerves
Normal conduction velocity	Normal or near-normal conduction velocity
Abnormal spontaneous activity	Variable spontaneous activity
Large polyphasic MUAPs	Small polyphasic MUAPs in >2 muscle groups
Reduced recruitment/interference pattern	Low-amplitude, full interference pattern
	Muscle inexcitability with direct muscle stimulation

ICUAW: intensive care unit-acquired weakness; CMAP: compound muscle action potential; LLN: lower limit of normal; SNAP: sensory nerve action potential; MUAP: motor-unit action potential.

Early Rehab options in ICU- Results are inconsistent

Exercises for Respiratory Muscle Function:

Deep breathing/incentive spirometry

Respiratory muscle training (inspiratory & expiratory)

Airway secretion maintenance

Positioning to promote drainage

Chest physiotherapy

hyperinflation

cough assistance (mechanical insufflation-exsufflation) with/without "flutter" (Acapella device)

Physical activity and early mobilization

Positioning and joint mobility

Passive ROM and stretching

Cycle ergometer for horizontal position

Neuromuscular electrical stimulation

Tilt table treatment (prepare for standing)

Mobilization sitting on edge of bed, chair, walking in place, eventual ambulation

Resistive muscle training using elastic bands

Pulmonary and Physical Rehabilitation in Critically Ill Patients

Myung Hun Jang[1], Myung-Jun Shin[1,2], Yong Beom Shin[1,2]

[1]Department of Rehabilitation Medicine, Biomedical Research Institute, Pusan National University Hospital, Busan; [2]Department of Rehabilitation Medicine, Pusan National University School of Medicine, Busan, Korea

Figure 7. (A) Upper-body aerobic exercise with fitness equipment. (B, C) Resistive training of upper extremities and bridging exercise using elastic band.

Tipping CJ, Harrold M, Holland A, et al. The effects of active mobilisation and rehabilitation in ICU on mortality and function. Intensive Care Med. 2017 43:171-183

Burtin C, Clerckx B, Robbeets C, et al. Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med. 2009;37(9): 2499-2505.

Gruther W, Kainberger F, Fialka-Moser V, et al. Effects of neuromuscular electrical stimulation on muscle layer thickness of knee extensor muscles in intensive care unit patients. J Rehabil Med. 2010;42 (6):593-597.

	Rehabilitation			Standard Care				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
1.26.1 Early and low dose rehabilitation								
Hanekom 2012	160	43	96	151	55	97	32.8%	9.00 [-4.92, 22.92]
Hodgson 2016	156	27	29	143	27	21	27.6%	13.00 [-2.16, 28.16]
Wolfe 2013	115	78	48	91	83	48	6.1%	24.00 [-8.22, 56.22]
Subtotal (95% CI)			**173**			**166**	**66.6%**	**12.04 [2.27, 21.81]**
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 2 (P = 0.69); I² = 0%								
Test for overall effect: Z = 2.42 (P = 0.02)								
1.26.2 Late and high dose rehabilitation								
Moss 2016	151	31	59	146	45	61	33.4%	5.00 [-8.79, 18.79]
Subtotal (95% CI)			**59**			**61**	**33.4%**	**5.00 [-8.79, 18.79]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.71 (P = 0.48)								
Total (95% CI)			**232**			**227**	**100.0%**	**9.69 [1.71, 17.66]**
Heterogeneity: Tau² = 0.00; Chi² = 1.39, df = 3 (P = 0.71); I² = 0%								
Test for overall effect: Z = 2.38 (P = 0.02)								
Test for subgroup differences: Chi² = 0.67, df = 1 (P = 0.41), I² = 0%								

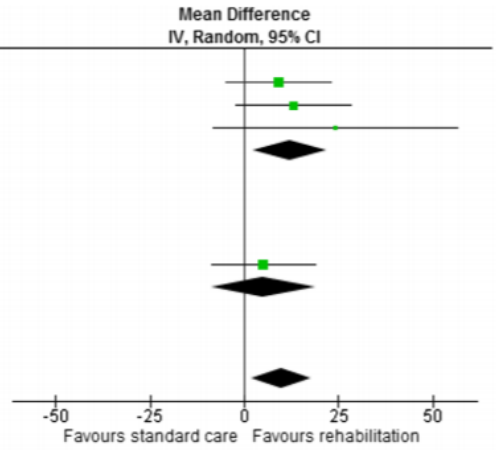


Fig. 4 Forest plot for days alive and out of hospital to 180 days

JAMA. 2018 Jul 24;320(4):368-378. doi: 10.1001/jama.2018.9592.

Effect of In-Bed Leg Cycling and Electrical Stimulation of the Quadriceps on Global Muscle Strength in Critically Ill Adults: A Randomized Clinical Trial.

Fossat G[1], Baudin F[1], Courtes L[1], Bobet S[1], Dupont A[2], Bretagnol A[1], Benzekri-Lefèvre D[1], Kamel T[1], Muller G[1], Bercault N[1], Barbier F[1], Runge I[1], Nay MA[1], Skarzynski M[1], Mathonnet A[1], Boulain T[1].

Home and Community-Based Physical Therapist Management of Adults With Post–Intensive Care Syndrome

Physical Therapist Management of Adults With PICS

Musculoskeletal

Perspective

James M. Smith, Alan C. Lee, Hallie Zeleznik, Jacqueline P. Coffey Scott, Arooj Fatima, Dale M. Needham, Patricia J. Ohtake

1) Concept: Community Based Rehabilitation options for Individuals with PICS

Specialized Comprehensive Post ICU Clinics

2) Developing national/international consensus and accurate functional outcomes

Improving Long-Term Outcomes Research for Acute Respiratory Failure

R24HL111895

https://www.improvelto.com/

Developed by Dale Needham
At Johns Hopkins

About | Core Outcome Set (COS) | Instruments | Cohort Retention | Statistical Tools | COS Resources | Publications | Media | Account Info

About Us

Dale Needham, FCPA, MD, PhD, Director of the Outcomes After Critical Illness and Surgery (OACIS) Group at Johns Hopkins University School of Medicine, received an R24 grant from the National Heart, Lung and Blood Institute (NHLBI). This R24 project, entitled "Improving Long-Term Outcomes Research for Acute Respiratory Failure" is aimed at creating resources for researchers conducting long-term follow-up of patients surviving acute respiratory failure and acute respiratory distress syndrome (ARF/ARDS).

This R24 project has three Aims in advancing long-term outcomes research for ARF/ARDS:

1) to recommend long-term outcome measures and associated measurement instruments for research in this patient population. (**Click here for:** Methodology Summary, Protocol for Modified Delphi Consensus)

2) to create and disseminate practical tools for maximizing patient cohort retention for longitudinal long-term outcomes research studies.

3) to create and disseminate statistical tools and programs to appropriately address truncation due to mortality when analyzing long-term functional outcomes in this patient population.

VIDEO: Dr. Needham discusses the R24 Project in an ATS Podcast

As a resource to researchers, this project complements a 2009 NIH NHLBI workshop recommendation (PubMed) that patient outcomes after hospital discharge be evaluated in Phase III trials. A subsequent 2018 NIH NHBLI working group (PubMed) has specifically recommended this project's Core Outcome Measurement Set (COMS) for <u>all</u> studies evaluating post-hospital patient outcomes.

If you have any questions, please contact us.

Login

Username or Email

Password

Remember Me

Log In

Discussion

What approaches does UF use now for rehabilitation of PICS patients?

What special needs are Covi-19 patients going to need?

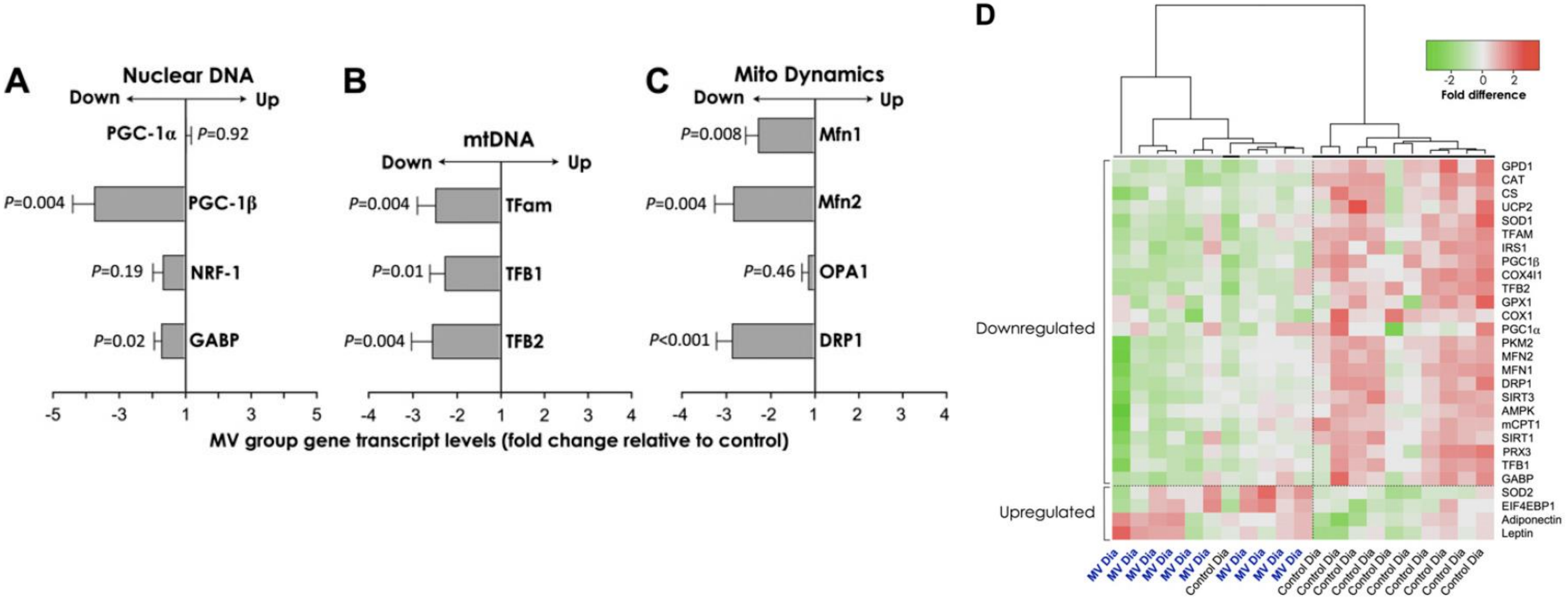
Mechanisms of Skeletal Muscle Atrophy and Dysfunction

Consequences of Skeletal Muscle Atrophy & Dysfunction

- Individuals with muscle atrophy have worse health outcomes, particularly when combined with disease (e.g., COPD, CVD, Diabetes), and increased risk of early mortality
- Major contributor to failure to wean from ventilator
- Impairs mobility and quality of life

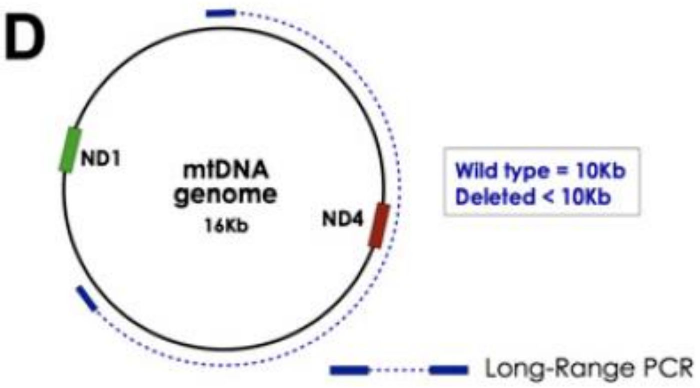
Mitochondrial Dysfunction with Mechanical Ventilation

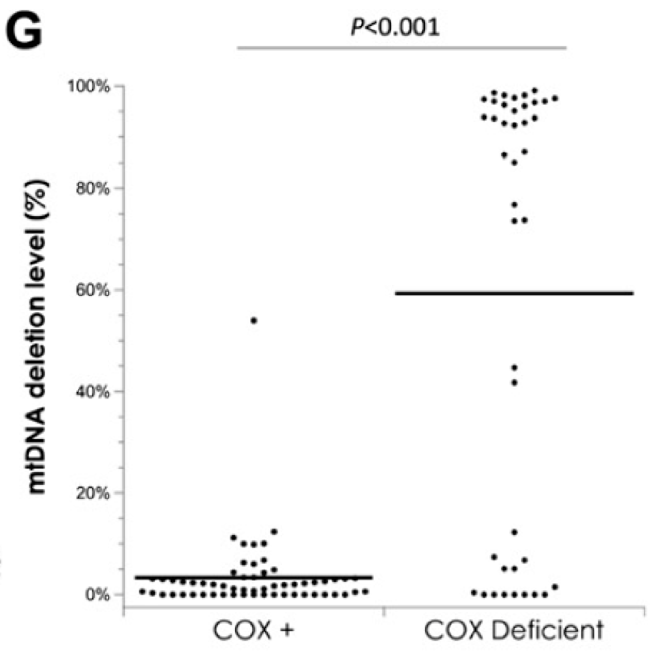
Diaphragm & biceps muscle samples from brain dead organ donors on MV and age-matched controls undergoing thoracic surgery for benign or malignant lung nodules

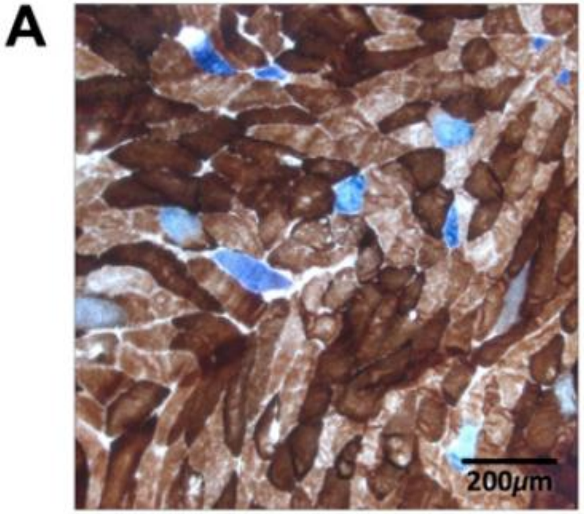


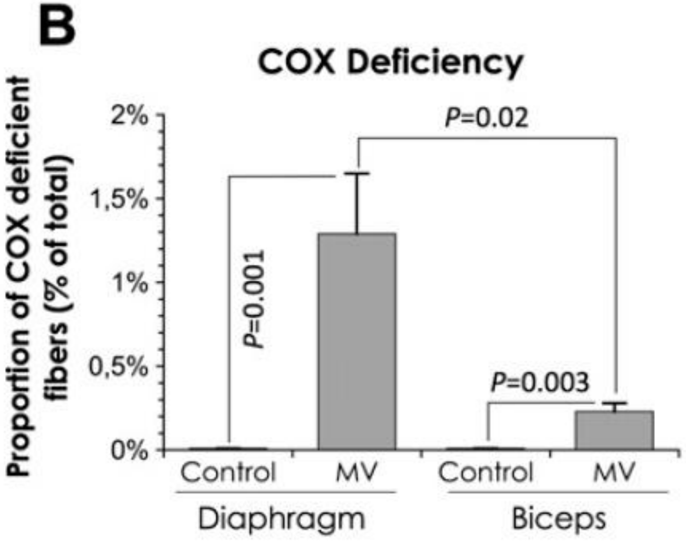
Picard et al. Am J Resp Crit Care Med. 186 (11): 1140-9, 2012

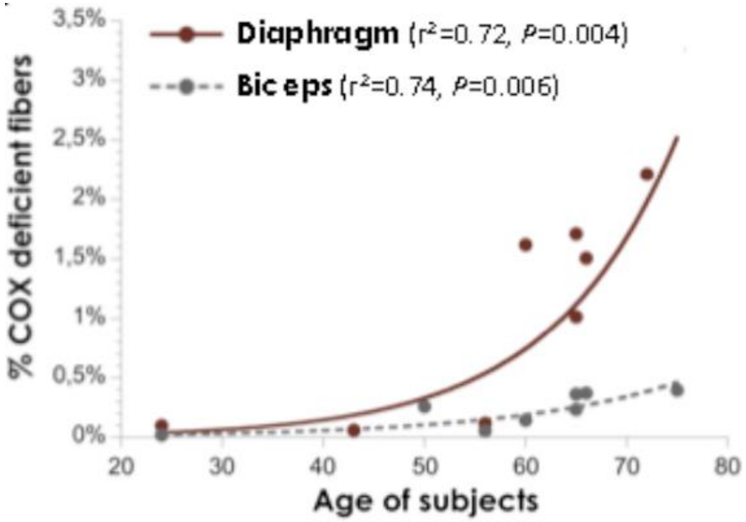
MV causes a massive proliferation of mtDNA mutations





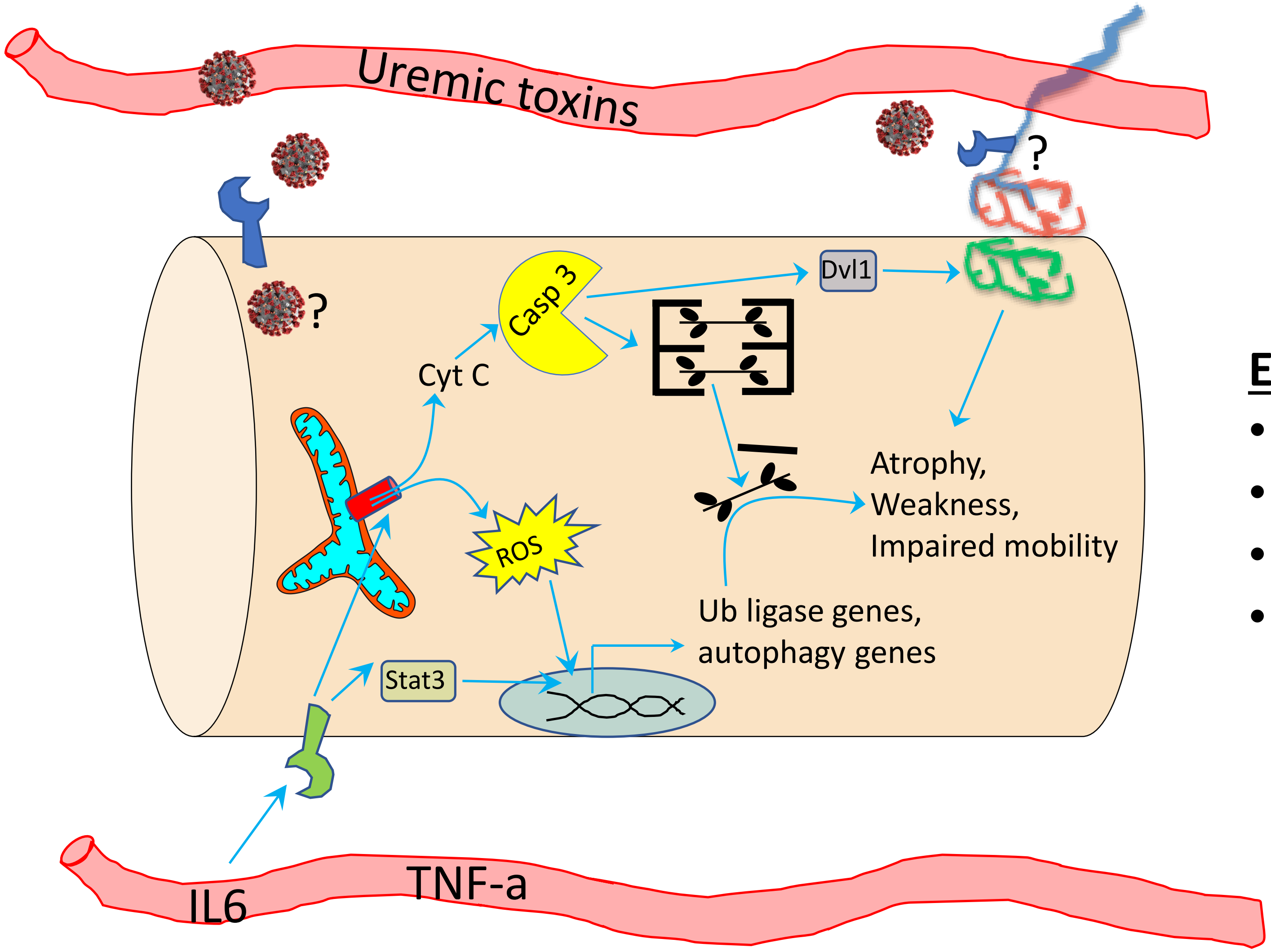






Picard et al. Am J Resp Crit Care Med. 186 (11): 1140-9, 2012

Mechanisms of Muscle Atrophy



Exacerbating Factors:

- Aging
- Sedentary lifestyle
- Kidney disease
- Smoking

Part 4. How skeletal muscle might be involved in the immune responsiveness to COVID 19?

Lessons learned from sepsis.

Clanton leads discussion

Exercise Conditioning Can help to prevent mortality and morbidity from SEPSIS

HUMANS

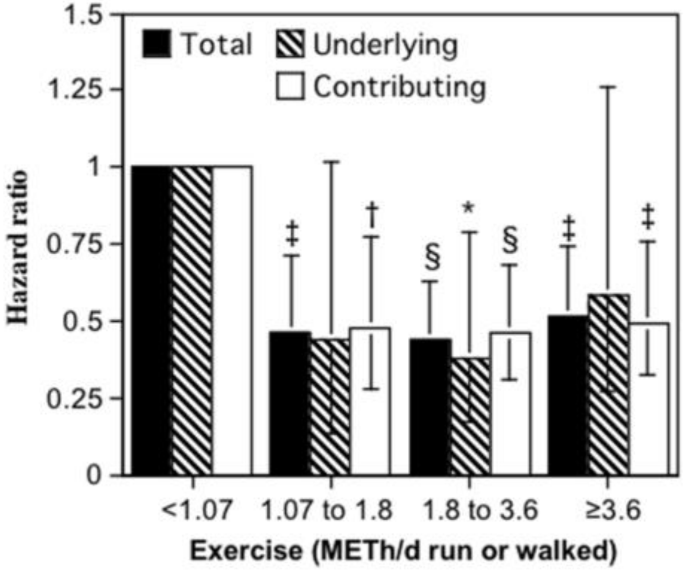
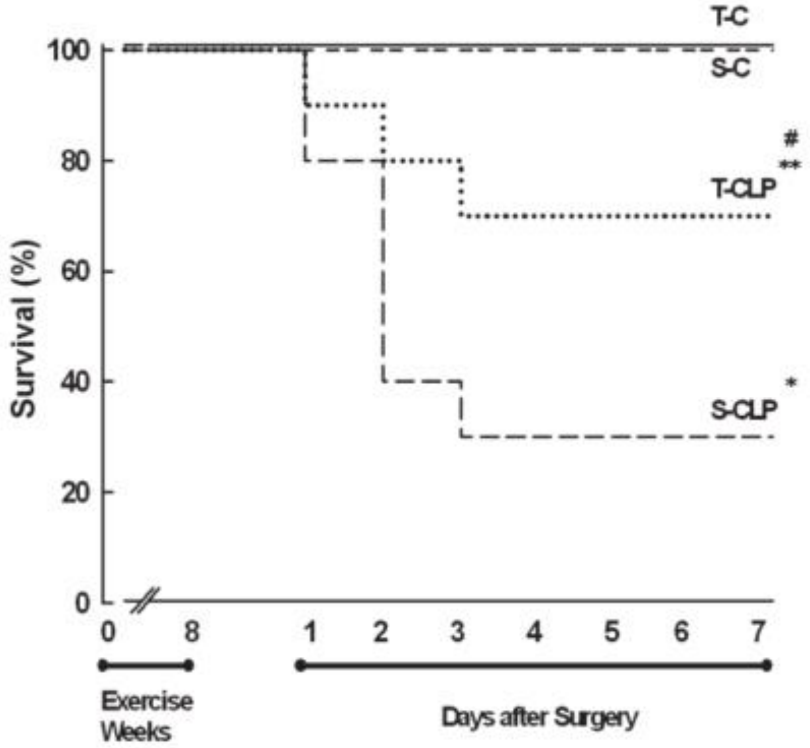


Figure 1. Relative risk of sepsis mortality by METh/d run or walked in 155,484 subjects during an average of 11.6-year mortality surveillance. There was 13.4% of the sample that was inadequately active (<1.07 MET-hours/d), 8.8% that met the exercise recommendations (1.07 to 1.8 MET-hours/d), 29.3% that exceeded the recommendations by 1 to 2-fold, (1.8 to 3.6 MET-hours/d), and 48.5% that exceeded the recommendations by ≥2-fold (≥3.6 MET-hours/d). Brackets designate 95% confidence intervals. Relative risks (i.e., the hazard ratios) were calculated from Cox proportional hazard analyses adjusted for sex, age, race, and cohort effects. Significant risk reductions relative to the inadequate exercise group were coded: * P≤0.05; † P≤0.01, ‡ P≤0.001, and § P≤0.0001.
doi:10.1371/journal.pone.0079344.g001

RATS



Exercise trained

Sedentary

Fig. 3. Kaplan-Meier survival curves during the training protocol and 7 days after surgery. Data represent percentage survival of S (S-C, S-CLP, n = 10/group) and T mice (T-C and T-CLP, n = 10/group). *Significantly different from S-C group ($P < 0.05$). **Significantly different from T-C group ($P < 0.05$). #Significantly different from S-CLP group ($P < 0.05$).

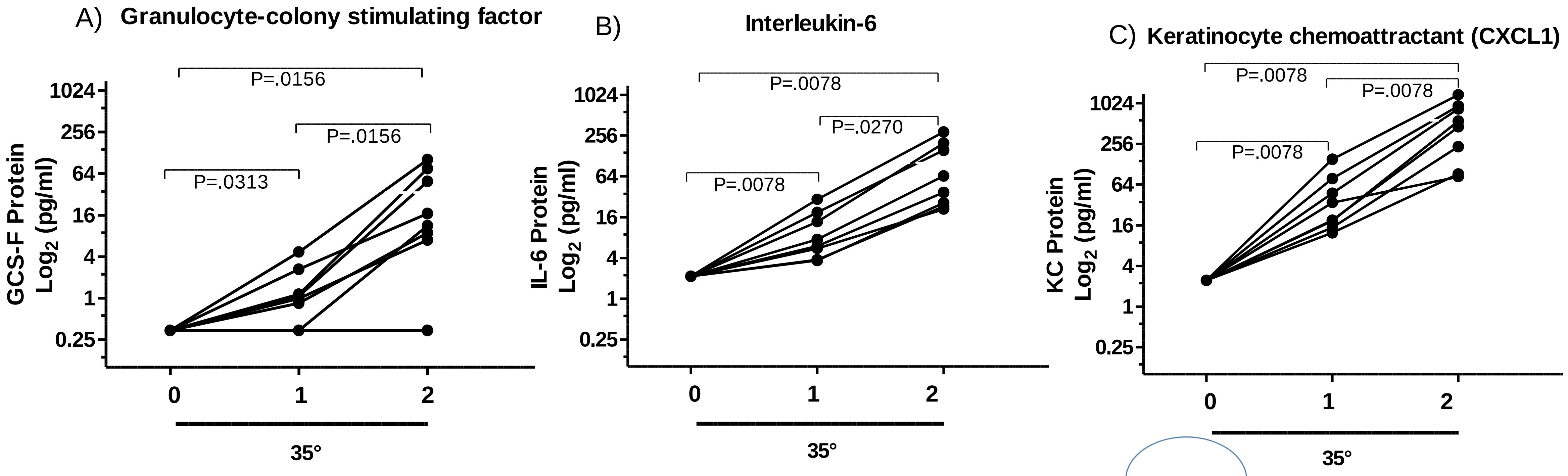
Regular and moderate exercise before experimental sepsis reduces the risk of lung and distal organ injury

Carla C. de Araújo,[1] Johnatas D. Silva,[1] Cynthia S. Samary,[1] Isabela H. Guimarães,[1] Patrícia S. Marques,[1] Gisele P. Oliveira,[1] Luana G. R. R. do Carmo,[1] Regina C. Goldenberg,[2] Ilka Bakker-Abreu,[3] Bruno L. Diaz,[3] Nazareth N. Rocha,[2,4] Vera L. Capelozzi,[5] Paolo Pelosi,[6] and Patricia R. M. Rocco[1]

PT Wallace, PLOS one 2013

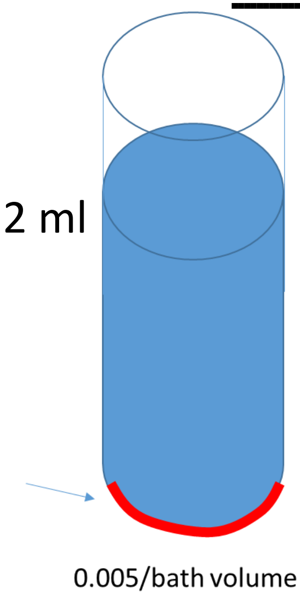
1 MET-hour per day would be walking slowly for 30 min or walking briskly (3 m/h) for 20 min/day

Mouse muscle cytokine secretion in response to LPS exposure



Mouse blood volume 2 ml

Plasma volume ≈1 ml

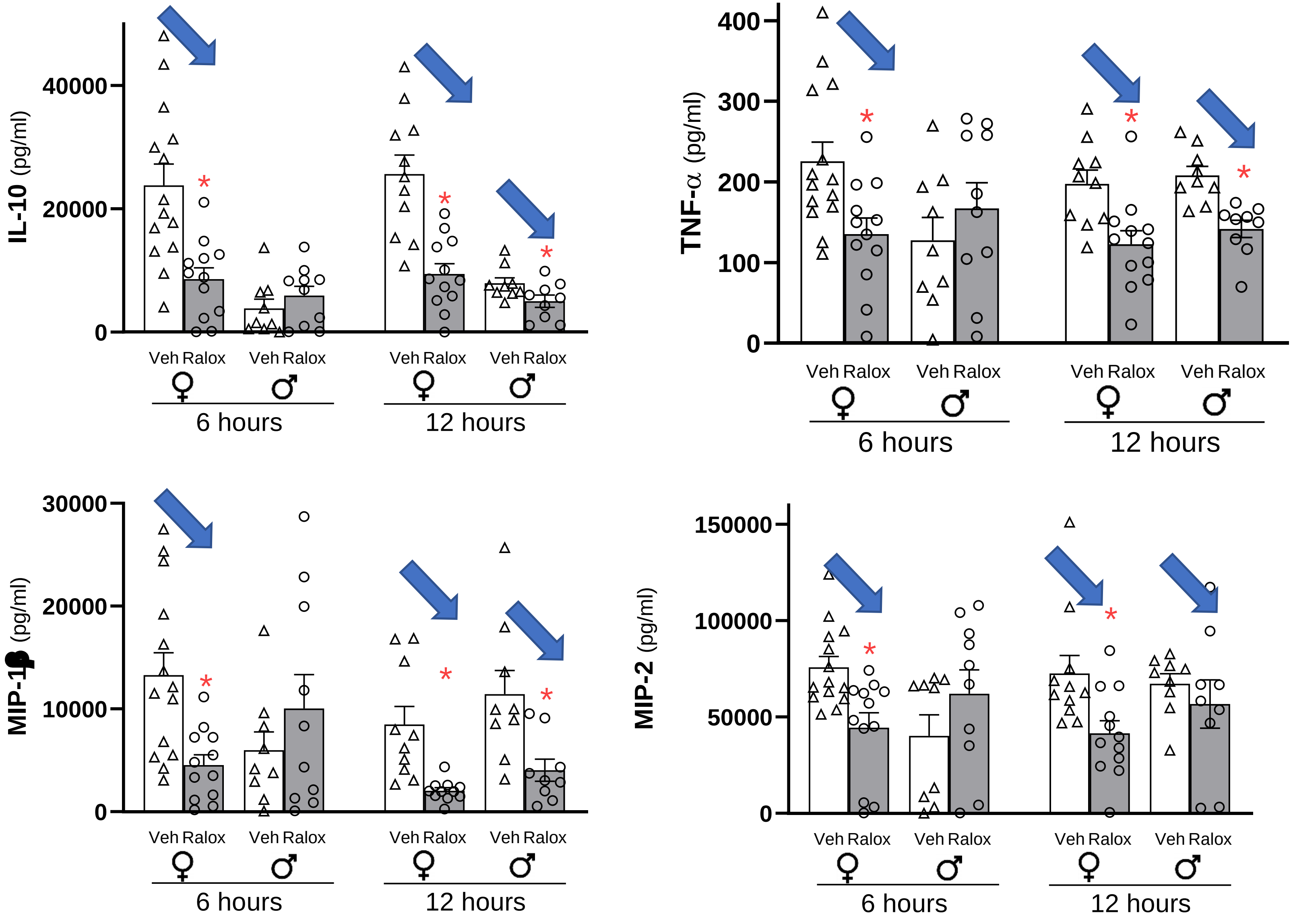


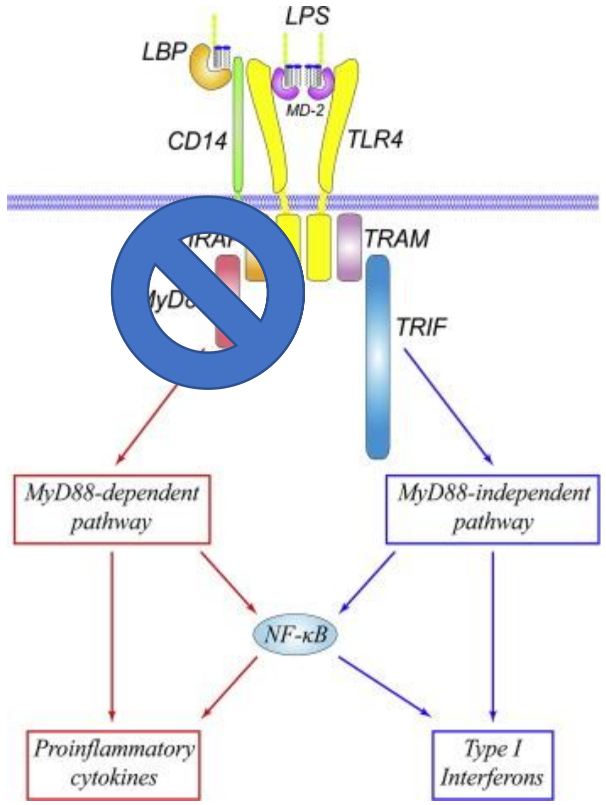
Skeletal muscle = 40% of the lean mass in mouse

1 µg/ml endotoxin

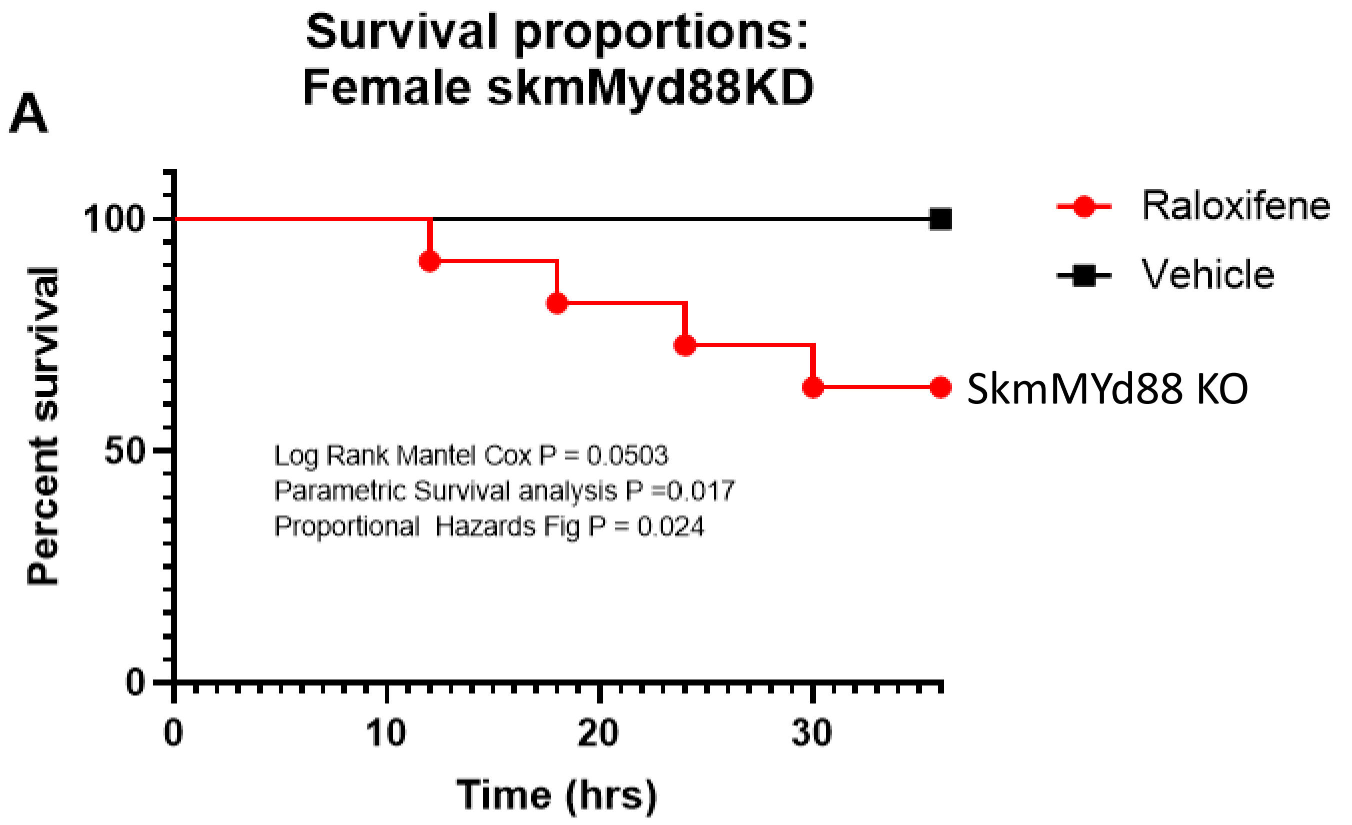
Mattingly et al. Clanton lab, unpublished

Knockout essential function of TLRs in skeletal muscle ONLY



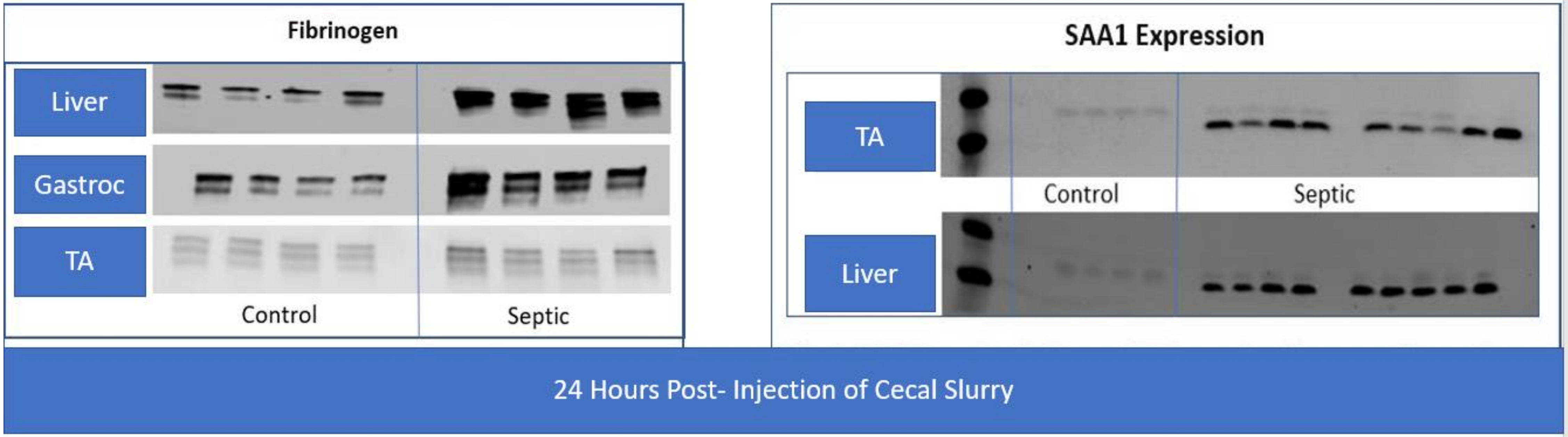


Laitano et al. (in preparation)



Laitano et al. (in preparation)

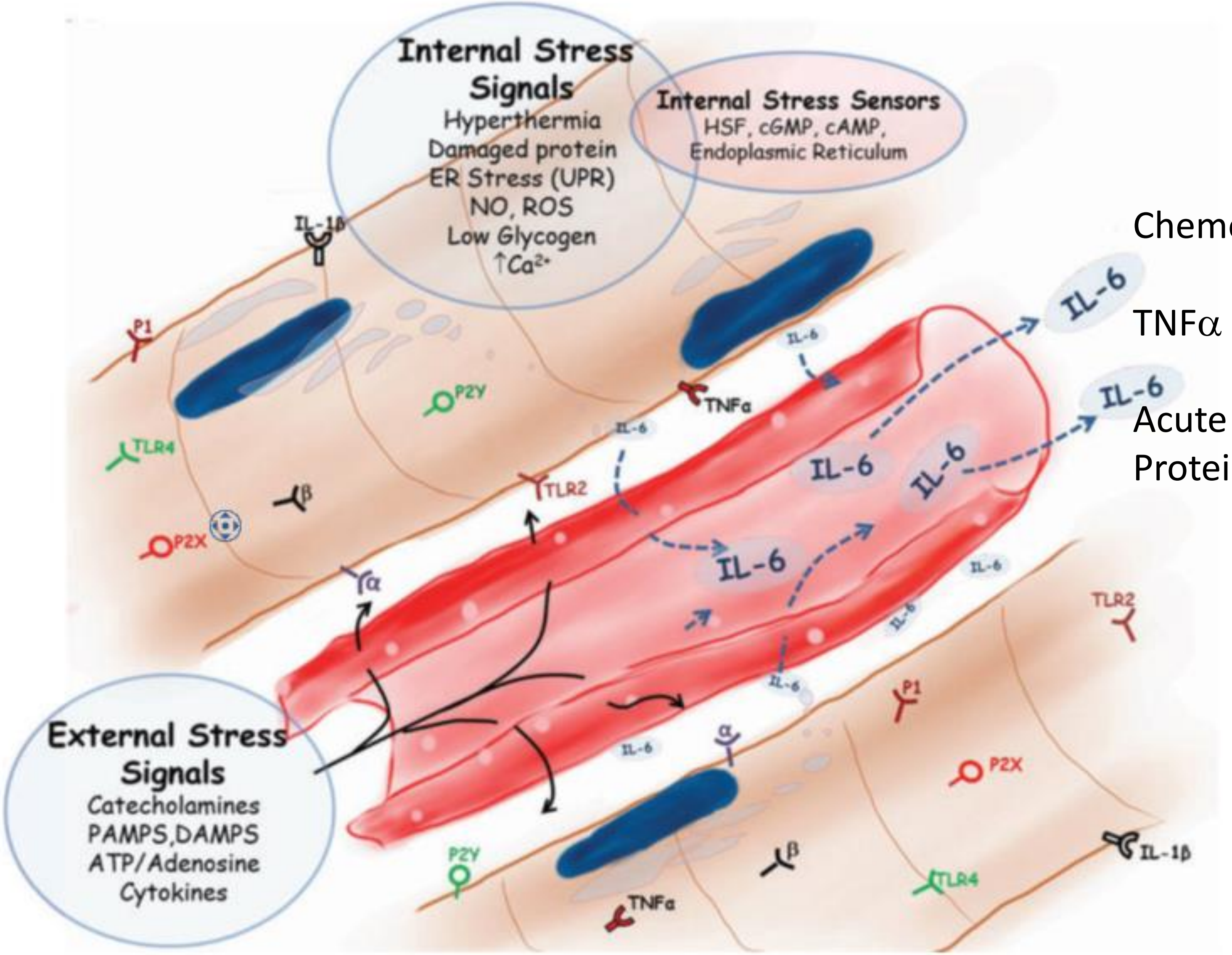
Acute Phase Protein Expression in Skeletal muscle



Acute Phase Protein Presence in Cecal Slurry mouse model

Gerard Robinson, Clanton Lab (unpublished)

HYPOTHESIS: SKELETAL MUSCLE CONTRIBUTES TO THE ACUTE PHASE RESPONSE AND MAY CONTRIBUTE TO SIRS



Welc an Clanton, 2012

Chemokines,

TNFα

Acute Phase Proteins

Systemic Inflammatory Response Syndrome?

Elimination of Pathogens?

Does EXERCISE CONDITIONING or minimal EXERCISE REHABILITATION improve immunological outcomes?

If so, how does it do that and what experiments could be done in humans to evaluate it?

Part 5. What do comorbidities that exacerbate poor outcomes in Covid19 infection tell us about the disease?

HYPERTENSION
OBESITY
DIABETES

JAMA | Original Investigation

Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area

Safiya Richardson, MD, MPH; Jamie S. Hirsch, MD, MA, MSB; Mangala Narasimhan, DO; James M. Crawford, MD, PhD; Thomas McGinn, MD, MPH; Karina W. Davidson, PhD, MASc; and the Northwell COVID-19 Research Consortium

Discussion question:

What studies of patient histories and outcomes in Covid 19 could be done to help understand these co-morbidities.