

Diaphragm weakness in the critically ill: Basic mechanisms and therapeutic opportunities

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NEW YORK & MONTREAL

SCALE COMPARISON



Disclosure Statement of Financial Interest

- LungPacer, Inc (scientific advisory panel)
- Novartis (consultant)

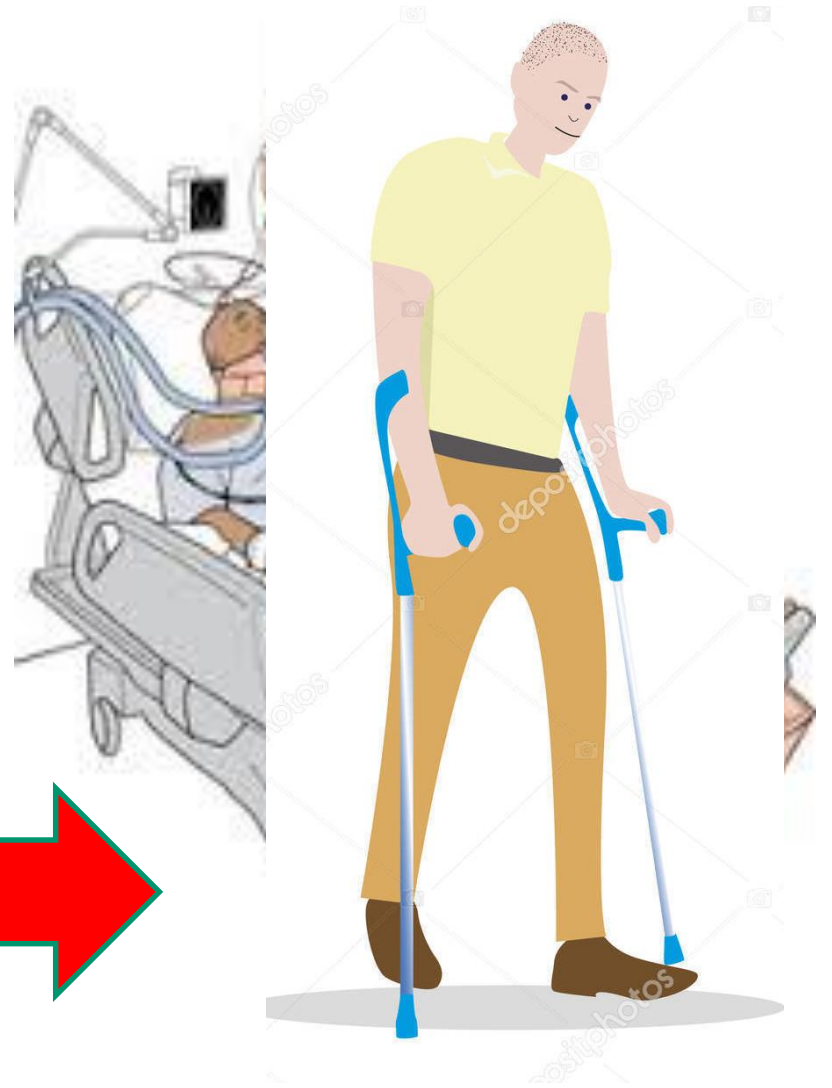
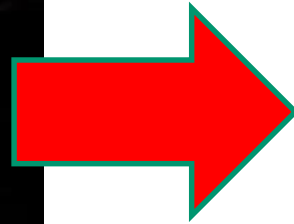
Funding:



Canadian Institutes
of Health Research

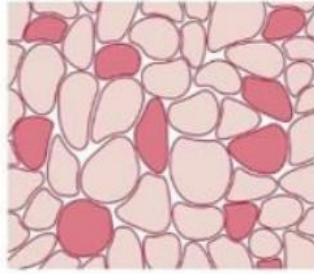
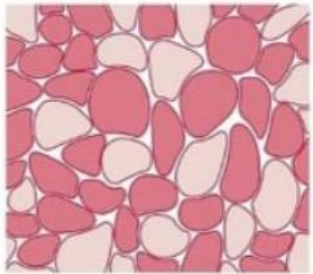
*Fonds de la recherche
en santé*

Québec 



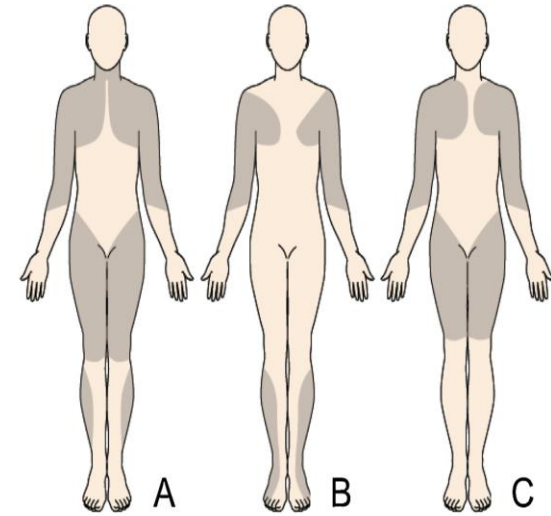
ICU Patient (clipart)

Muscles are not created equal



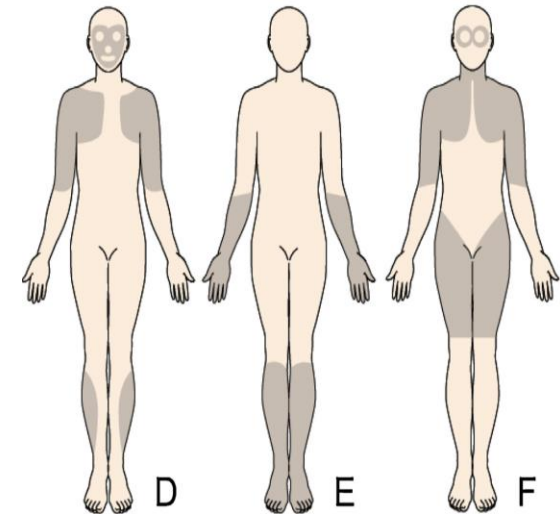
Type I (slow) fiber Atrophy

- Immobilization
- Denervation
- Microgravity

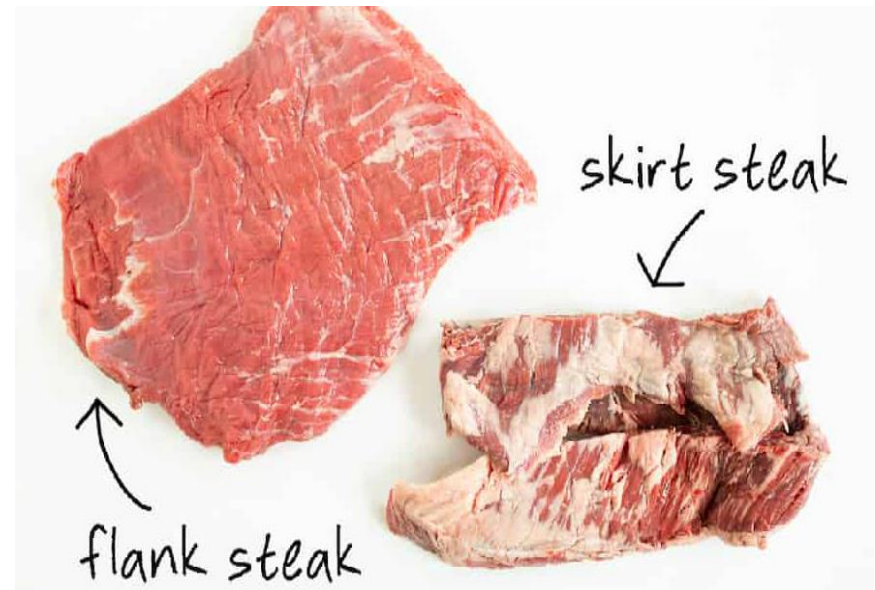
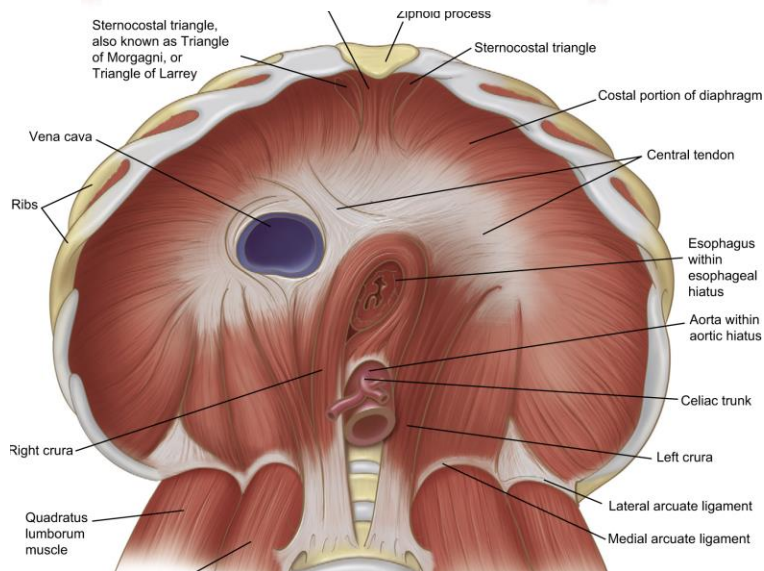
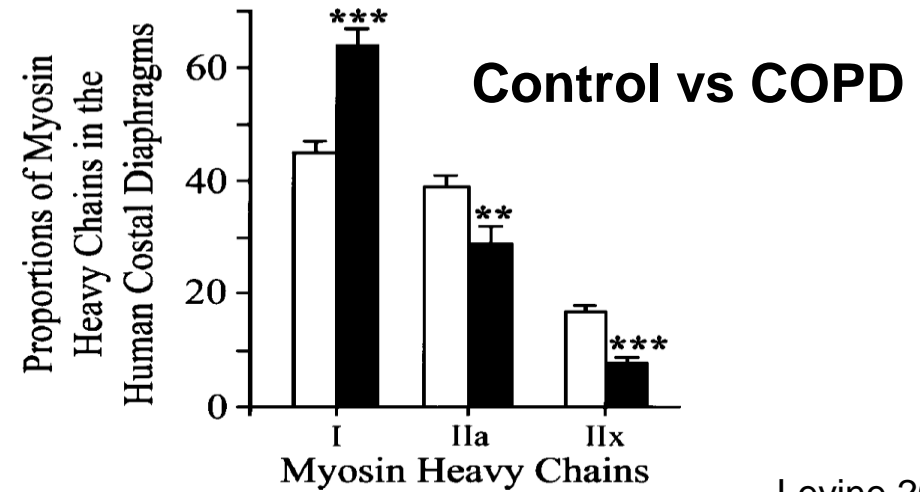
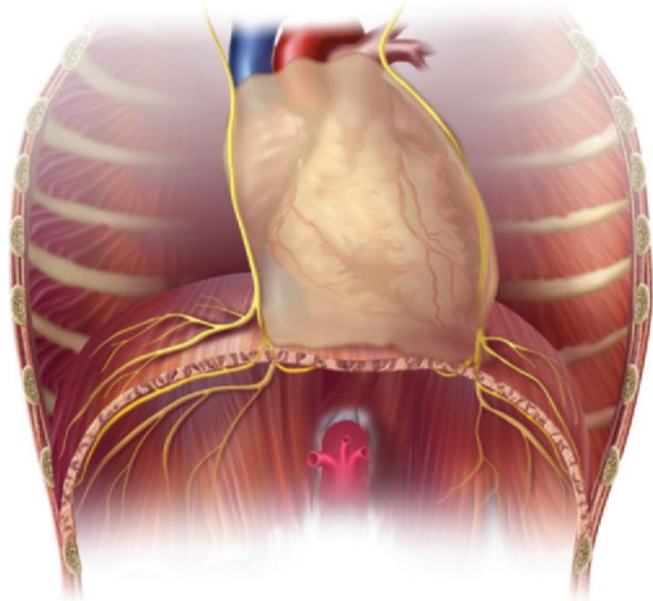


Type II (fast fiber) Atrophy

- Cancer cachexia
- Malnutrition
- Corticosteroids



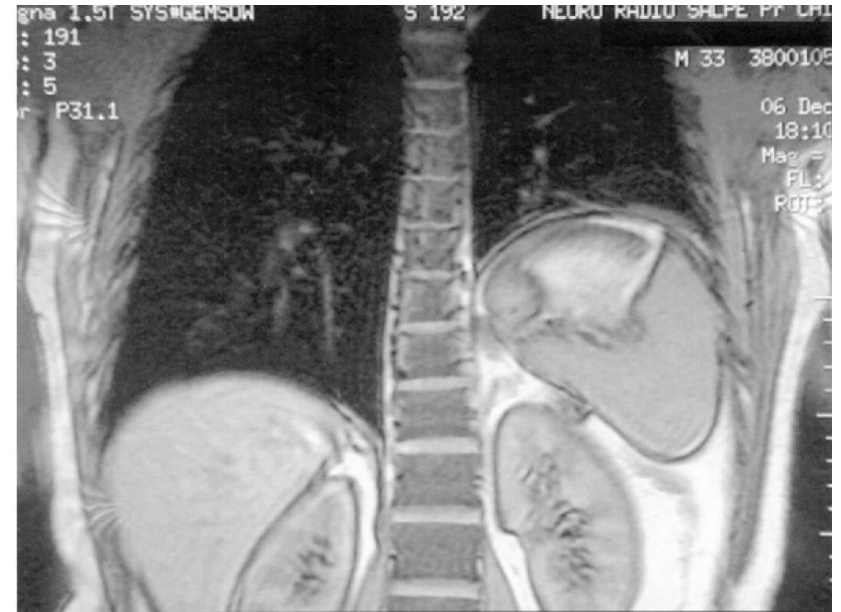
The diaphragm



Unique « evolutionary » features of the diaphragm

- **Anatomical Separator**

Function: Acts to mechanically uncouple thoracic and abdominal cavity pressures



- **Continuous Activity:** Phasic activity during wakefulness and sleep, therefore “not meant to be inactive”

A Fundamental Question



- Is the diaphragm either **more or less vulnerable** than limb muscles to certain insults ?
- In the ICU: Exaggerated responses to **inflammation** and **muscle inactivity** ?

Drugs

- Corticosteroids
- Neuromuscular blockers
- Sedatives

Metabolic

- Undernutrition
- Overnutrition (eg. TPN)
- Acute Hyperglycemia
- Hypoxia, Hypercapnia

Other Comorbidities

- Cancer
- Diabetes
- COPD

Aging and Frailty

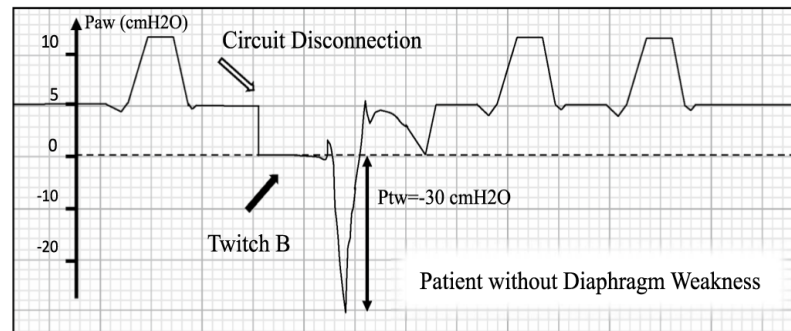
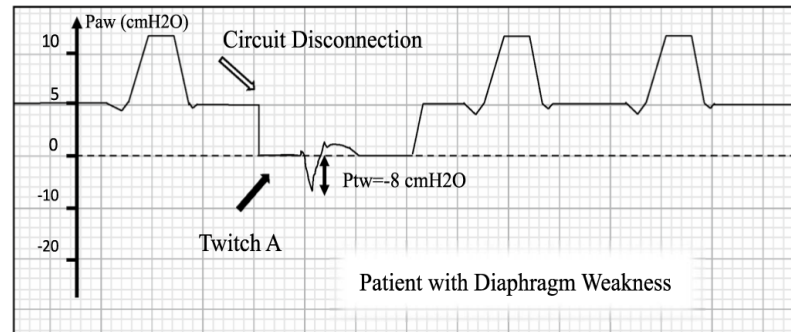
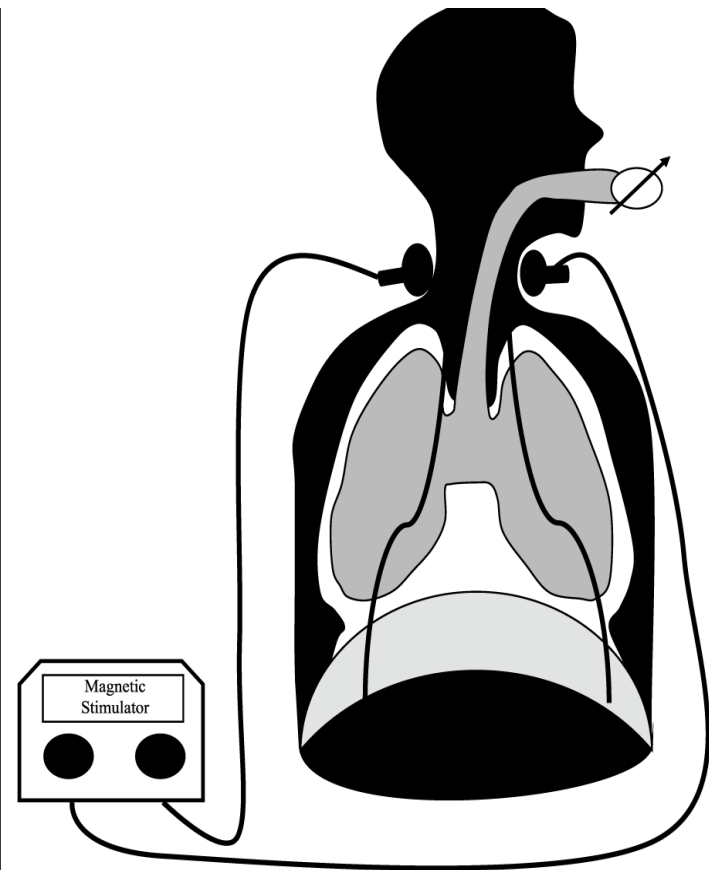
Systemic Inflammation

- SEPSIS

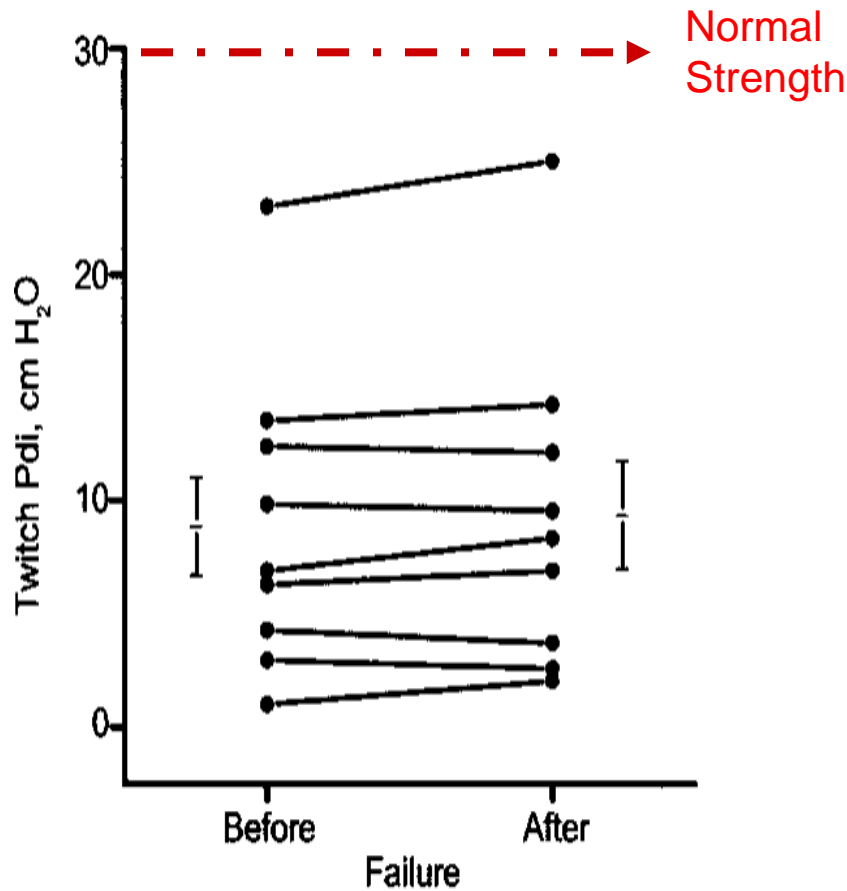
Muscle Inactivity

- MECHANICAL VENTILATION

Phrenic nerve stimulation to objectively measure diaphragm strength in ICU patients



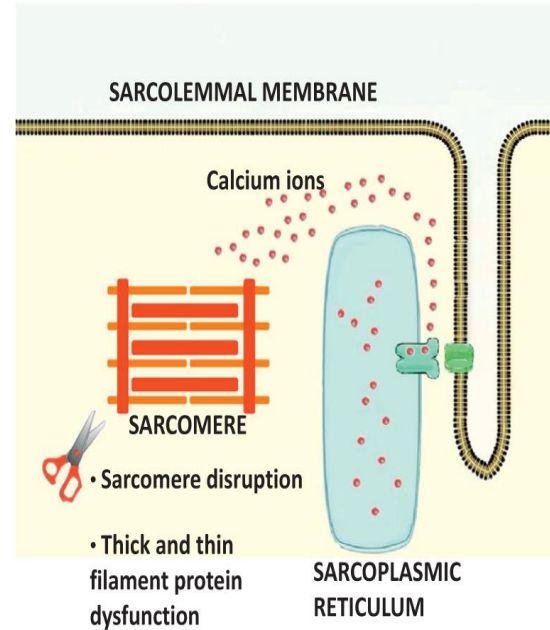
Weaning failure is associated with diaphragm weakness rather than fatigue



Laghi, AJRCCM 2003

1) Impairment of muscle quality

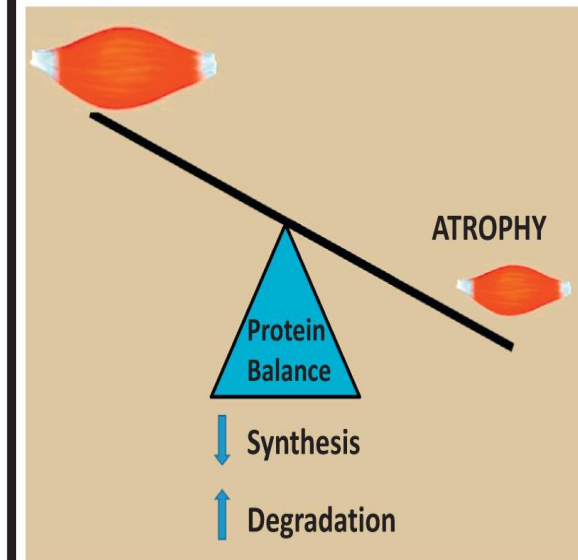
- Defective contractile mechanisms



- Abnormal calcium leakage from sarcoplasmic reticulum release channel

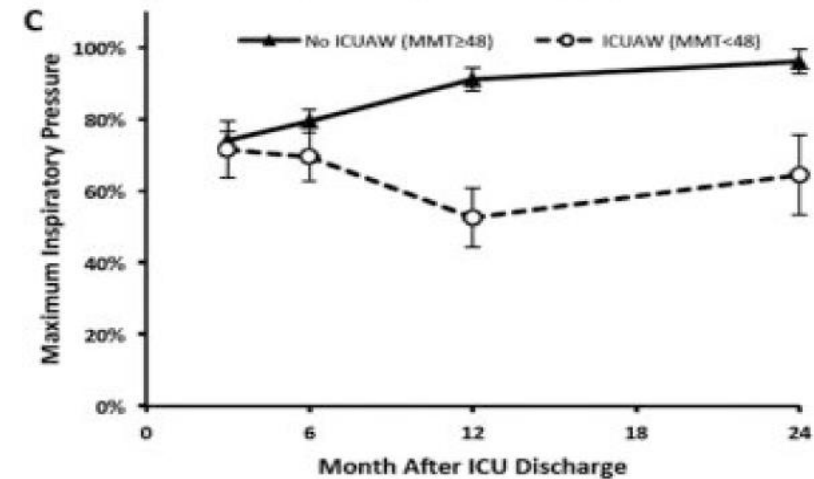
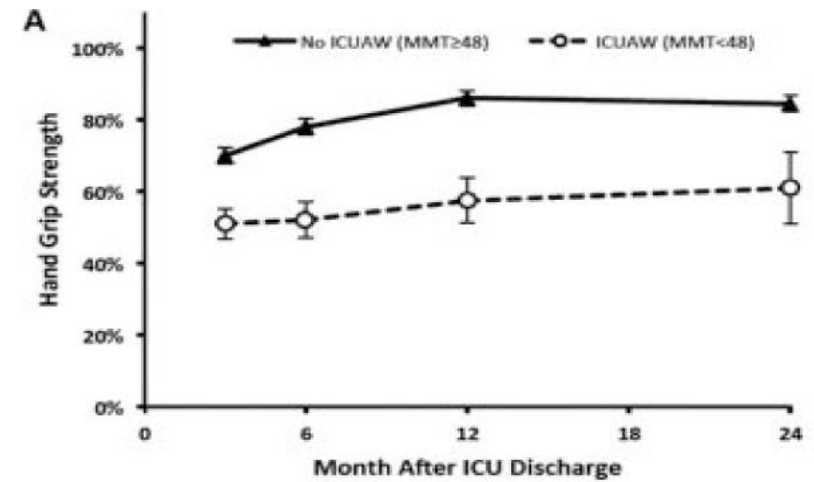
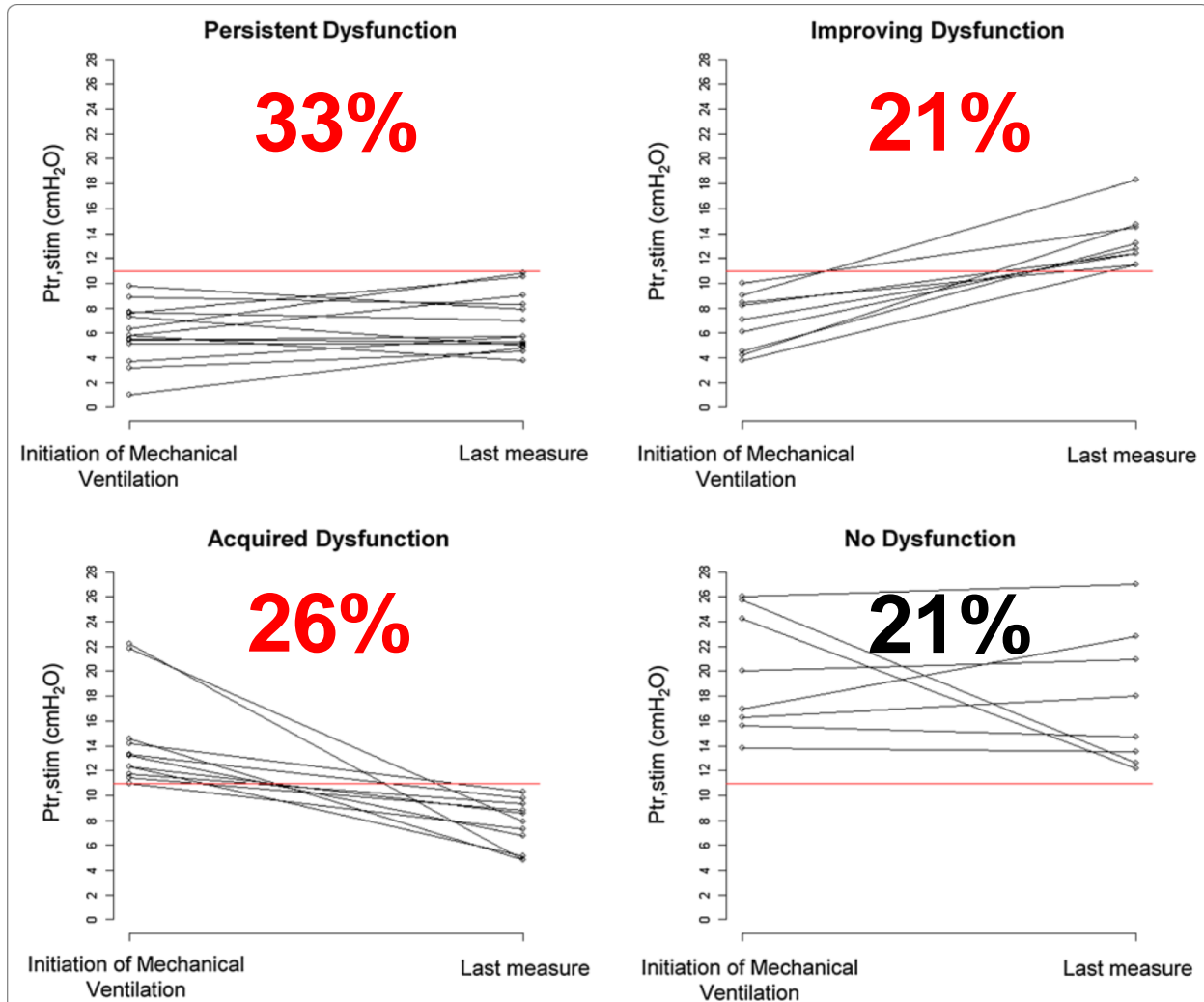
2) Decreased muscle quantity

- Altered protein balance

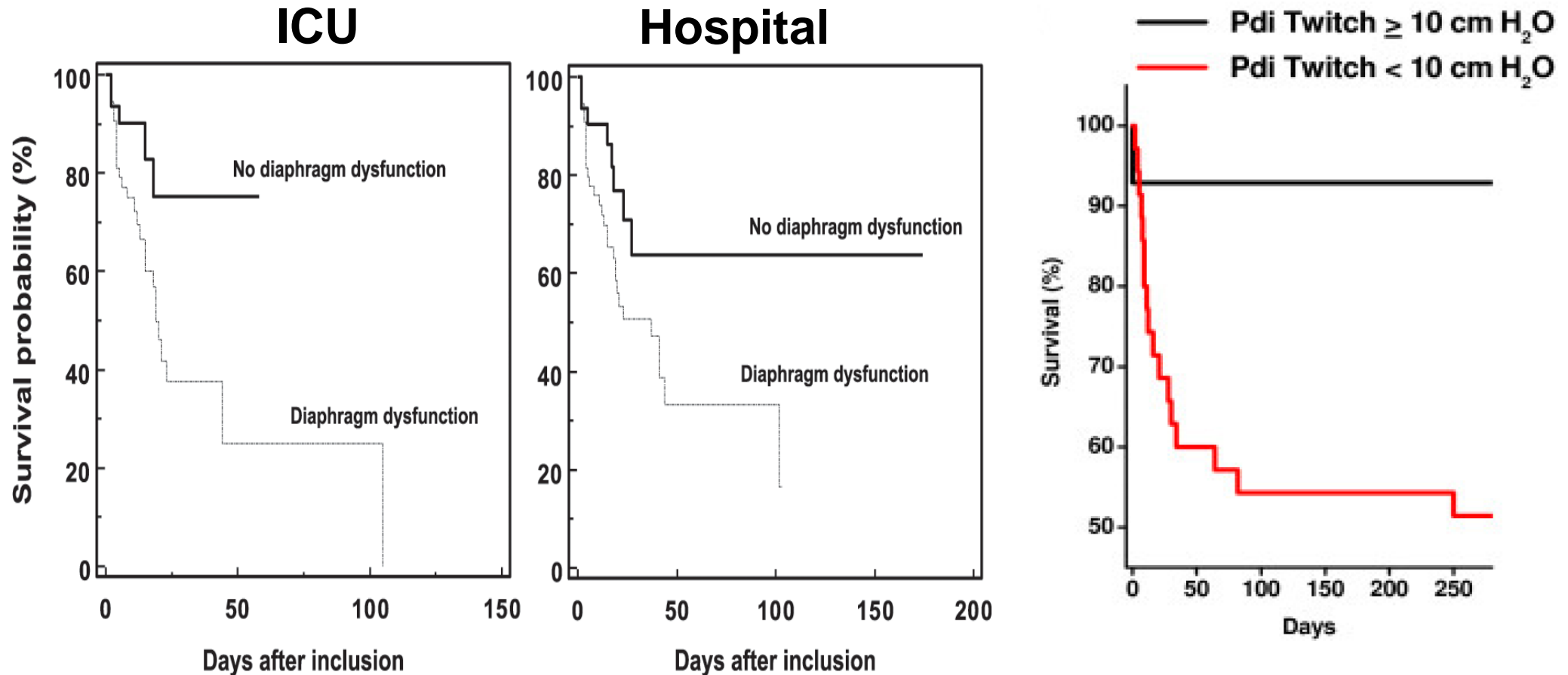


Diaphragm weakness

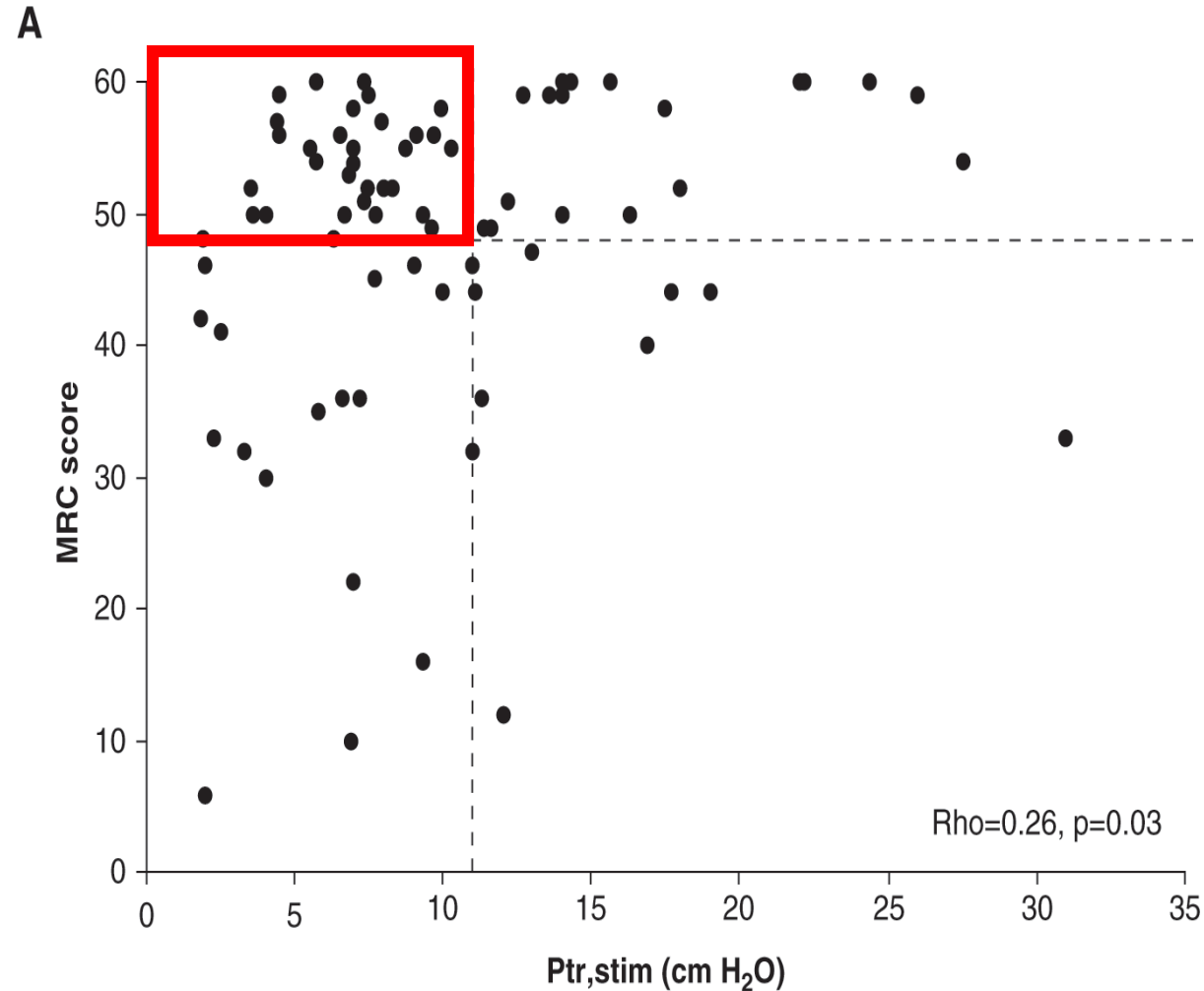
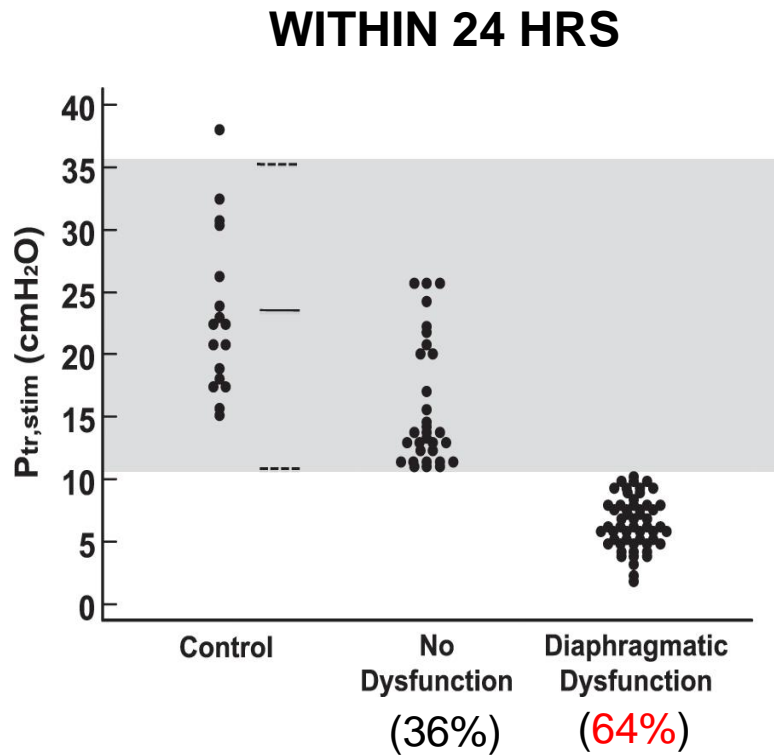
Diaphragm weakness is frequent and long-lasting in mechanically ventilated patients



Diaphragm weakness is associated with increased mortality in ICU



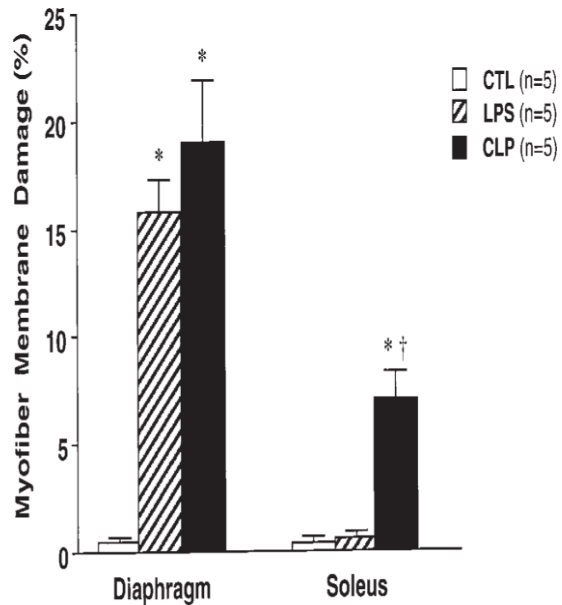
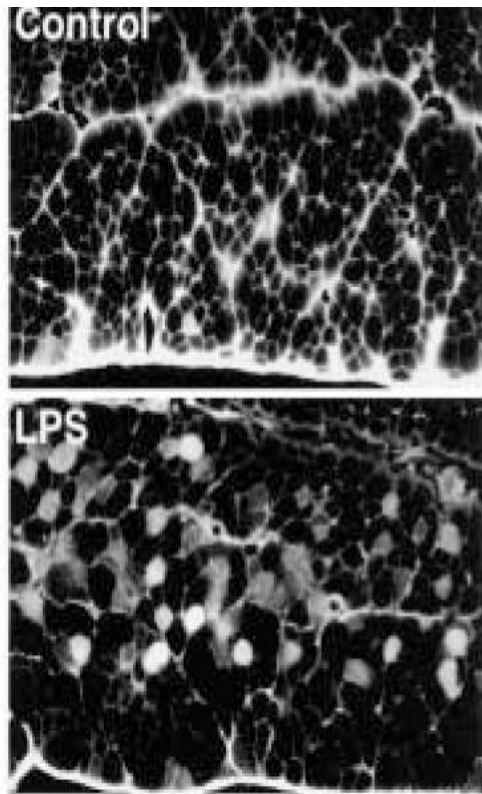
Diaphragm weakness occurs early and correlates poorly with limb muscle strength



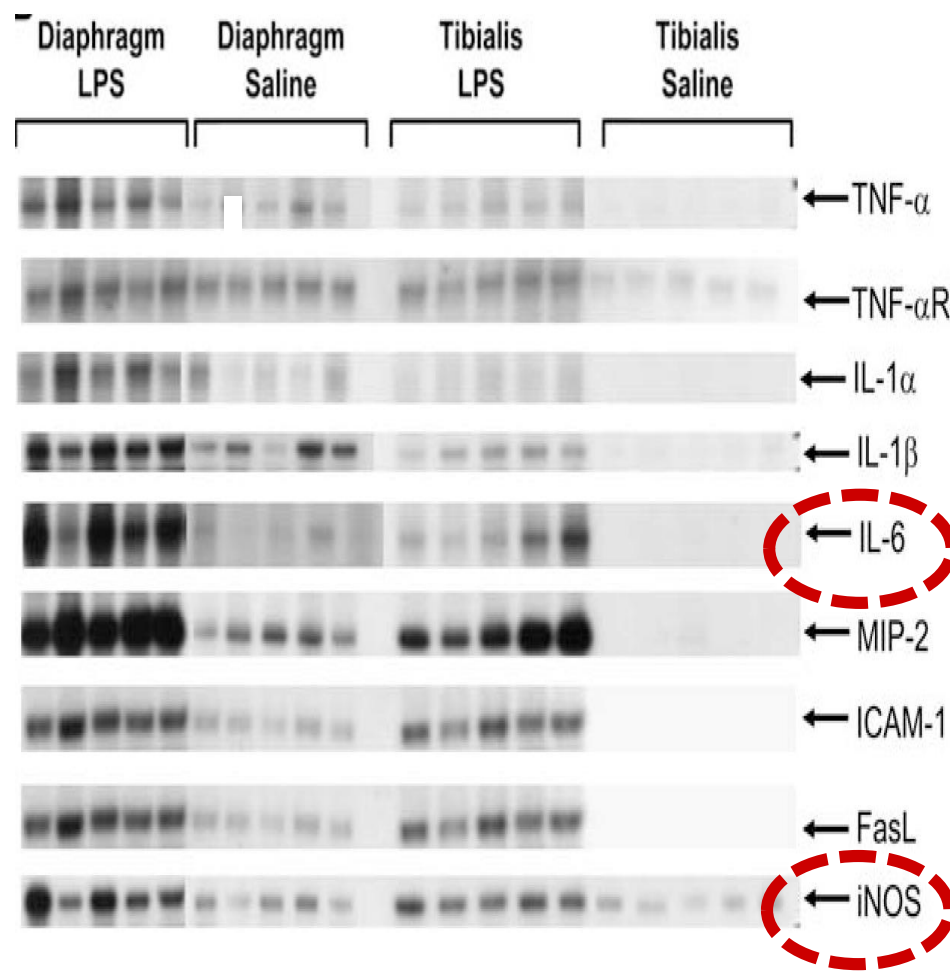
Is the diaphragm more sensitive than limb muscles to **inflammatory stimuli** ?

Diaphragm Sarcolemmal Injury Is Induced by Sepsis and Alleviated by Nitric Oxide Synthase Inhibition

MENG-CHIH LIN, SATORU EBHARA, QASIM EL DWAIRI, SABAH N. A. HUSSAIN, LIYING YANG, STEWART B. GOTTFRIED, ALAIN COMTOIS, and BASIL J. PETROF



MC Lin AJRCCM 1998

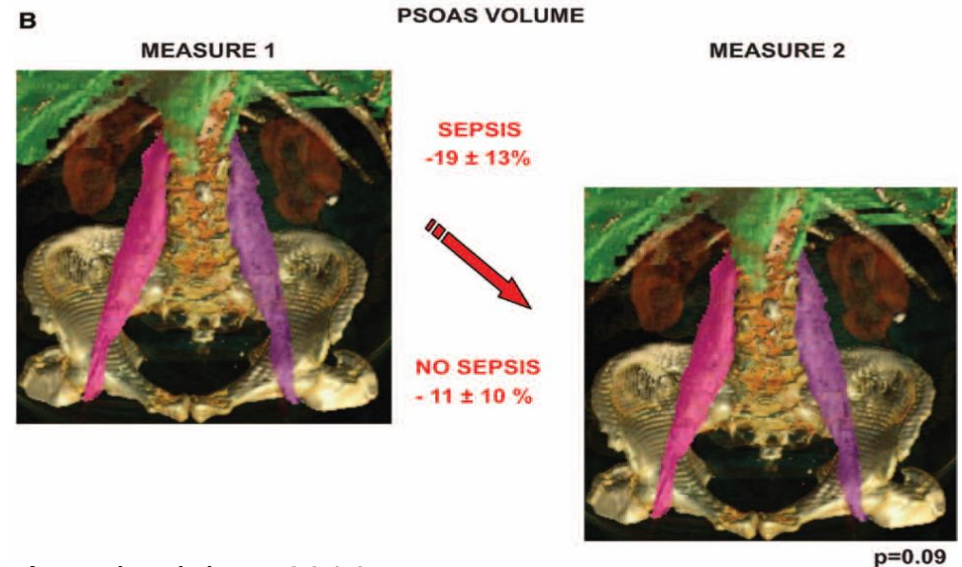
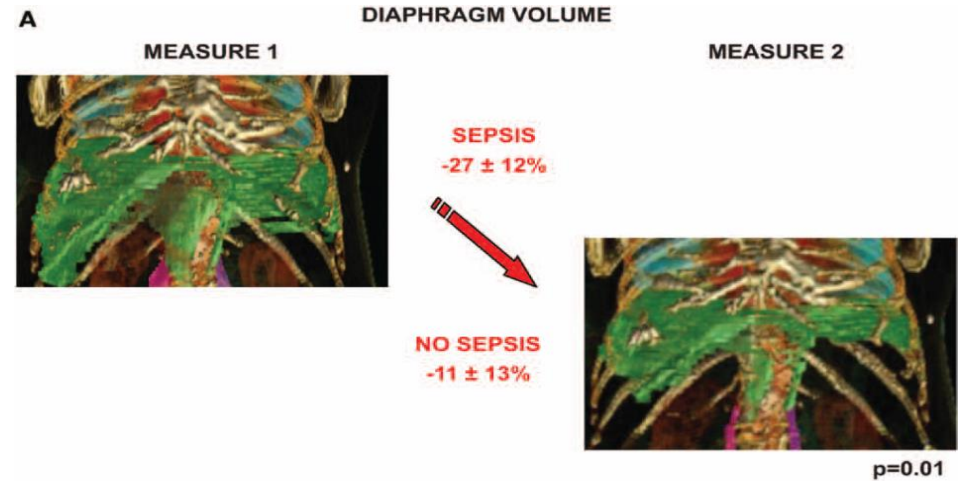
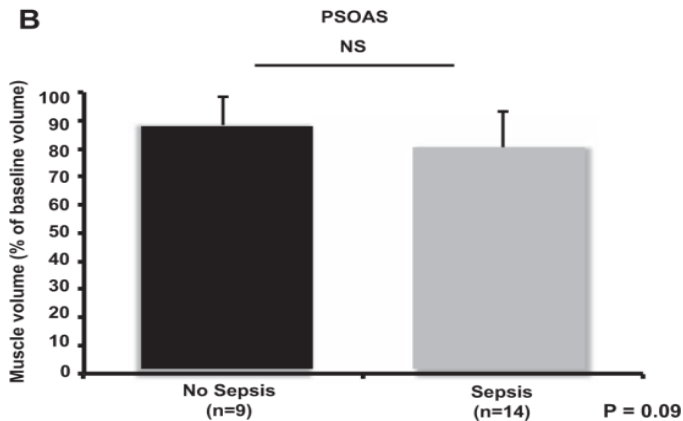
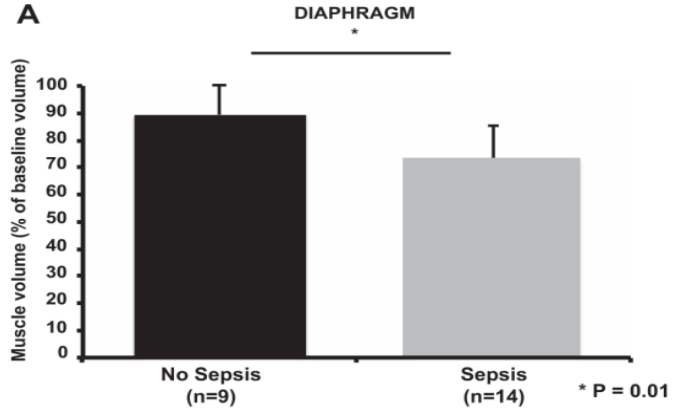


Demoule AJRCCM 2006

Diaphragm more vulnerable to sepsis in humans

Sepsis Is Associated with a Preferential Diaphragmatic Atrophy

A Critically Ill Patient Study Using Tridimensional Computed Tomography



Is the diaphragm more vulnerable to **inactivity** ?

Critical Care Perspective

Ventilator-induced Diaphragmatic Dysfunction (VIDD)

Theodoros Vassilakopoulos and Basil J. Petrof

Respiratory and Critical Care Divisions, McGill University Health Center, and Meakins-Christie Laboratories, McGill University, Montreal, Quebec, Canada; and Critical Care Division, University of Athens Medical School, Evangelismos Hospital, Athens, Greece

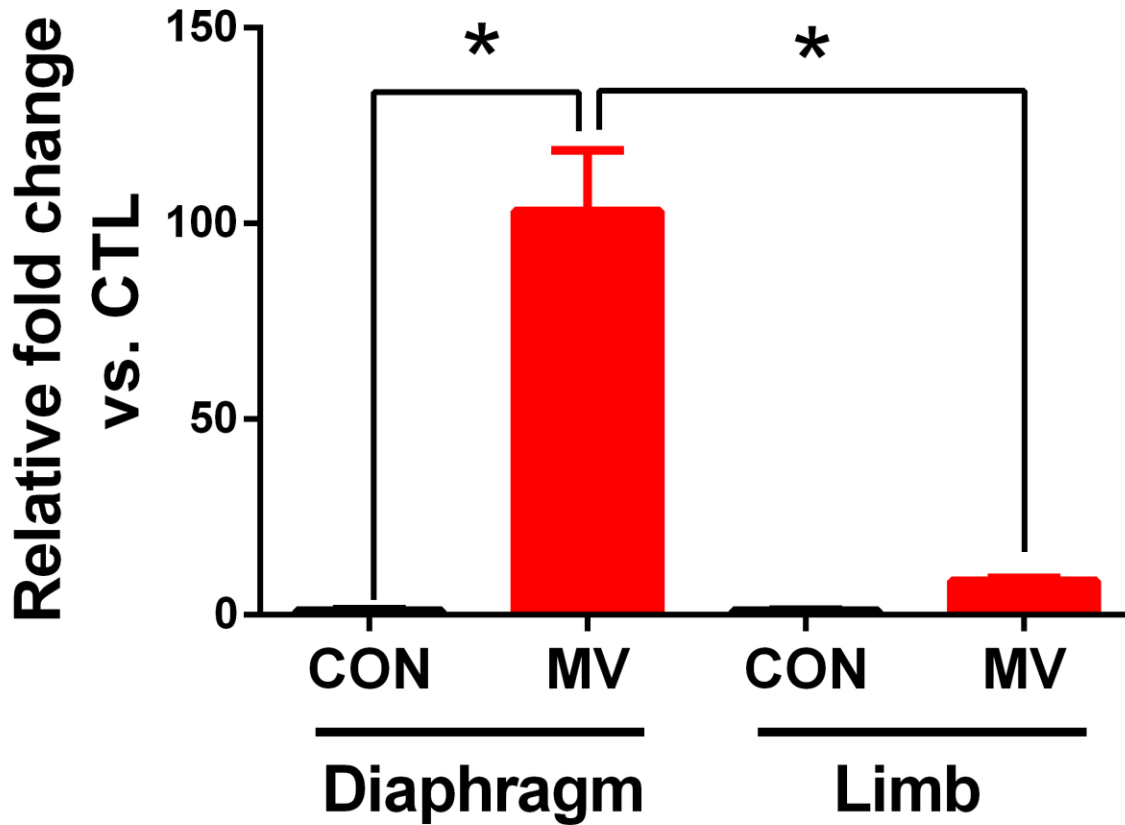
TABLE 1. EXPERIMENTAL STUDIES OF VENTILATOR-INDUCED DIAPHRAGMATIC DYSFUNCTION

First Author (Ref.)	Year	Animal	n (CMV)	Duration	Control	V _T (ml/kg)	RR	PEEP	Force Decline (%)
Le Bourdelles (16)	1994	Rats	18 (9)	48 h	Yes	10	80	1	49
Anzueto (13)	1997	Baboons	7	11 d	No	15	12	2	25*
Radell (14)	2002	Piglets	7	5 d	No	12–15	16–19	3.0–5.0	28–31*
Sassoon (15)	2002	Rabbits	30 (12)	1–3 d	Yes	6–8	40–50	0	51*
Yang (18)	2002	Rats	9 (5)	44–93 h	Yes	5	90	4	48
Shanely (26)	2002	Rats	38 (16)	18 h	Yes	10	80	1	NA
Powers (17)	2002	Rats	39 (15)	12–24 h	Yes	10	80	1	46
Shanely (22)	2003	Rats	14 (6)	18 h	Yes	10	80	1	21
Bernard (19)	2003	Rabbits	17 (7)	49 h	Yes	8	60	2	NA
Capdevila (21)	2003	Rabbits	19 (9)	51 h	Yes	8	60	2	25
Racz (39)	2003	Rats	52 (16)	24 h	Yes	10	55–60	1	NA
Gayán-Ramírez (20)	2003	Rats	31 (12)	24 h	Yes	10	55–60	1	34
Zergeroglu (30)	2003	Rats	52 (22)	3–18 h	Yes	10	80	1	NA

Definition of abbreviations: CMV = controlled mechanical ventilation; control = presence of control group; force decline = percent decline in diaphragmatic force production in mechanically ventilated animals versus control animals or baseline; NA = not available; PEEP = positive end-expiratory pressure; RR = respiratory rate.

* *In vivo* transdiaphragmatic pressure development in response to phrenic nerve stimulation.

Higher IL-6 expression in the diaphragm



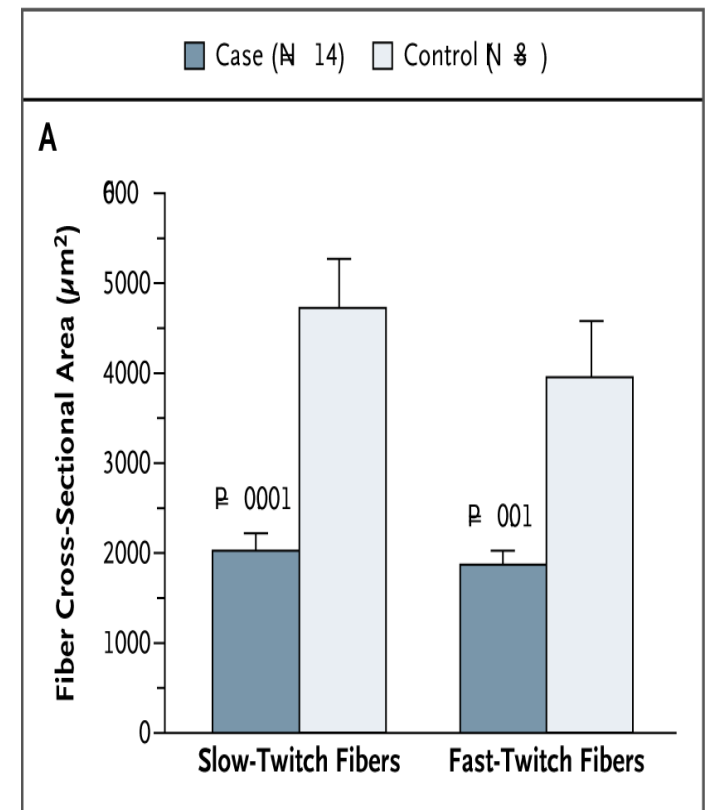
The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

MARCH 27, 2008

VOL. 358 NO. 13

Rapid Disuse Atrophy of Diaphragm Fibers in Mechanically
Ventilated Humans
Levine et al



Main messages so far ...

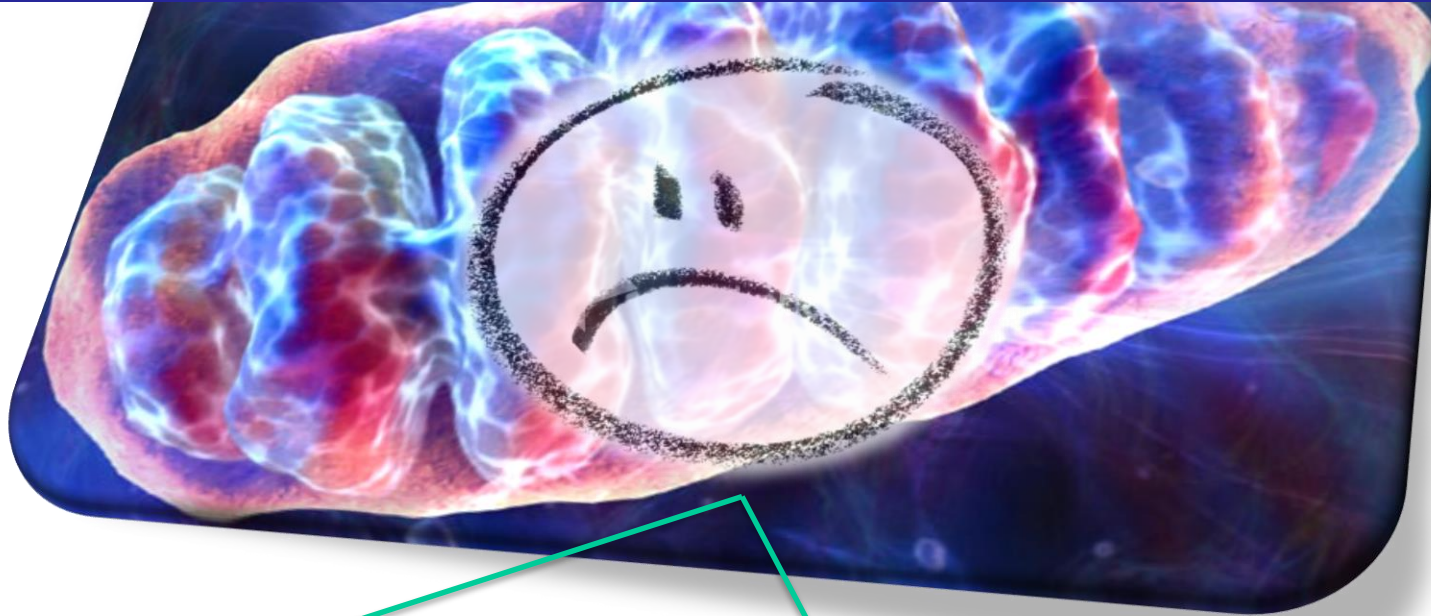
- Diaphragm weakness is very common and occurs rapidly in critically ill, mechanically ventilated patients
- Diaphragm weakness in mechanically ventilated ICU patients is a poor prognostic factor associated with increased mortality
- The diaphragm appears to be more vulnerable to weakness, atrophy and inflammation induced by pathological stimuli such as sepsis and muscle inactivity



**What are the major
mechanisms of
VIDD ?**



A central role for mitochondrial dysfunction

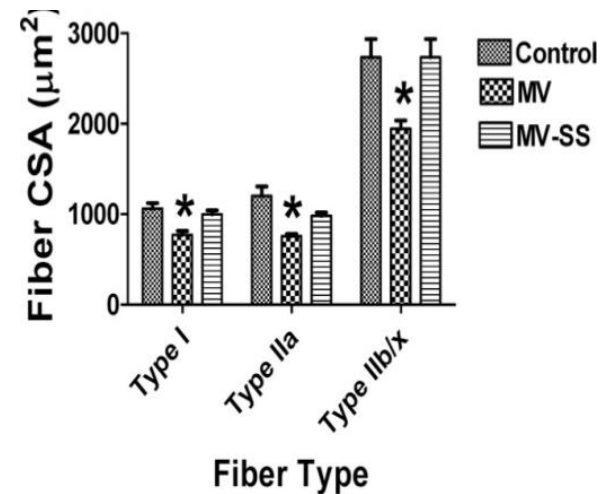
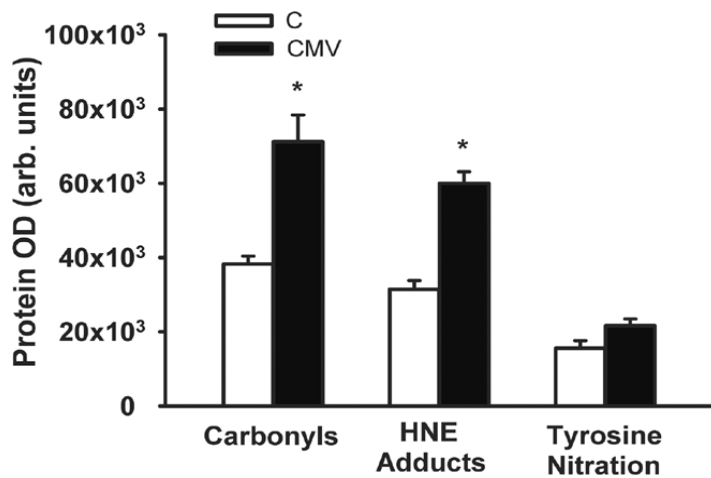
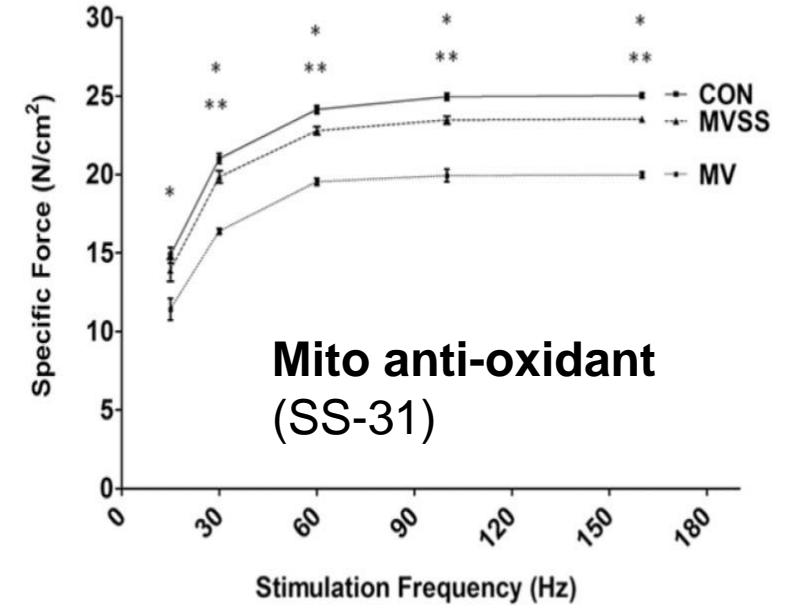
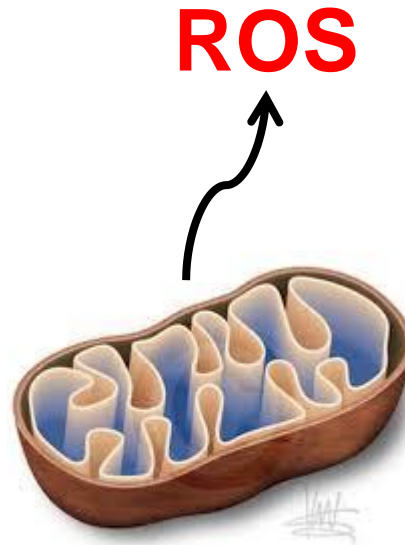
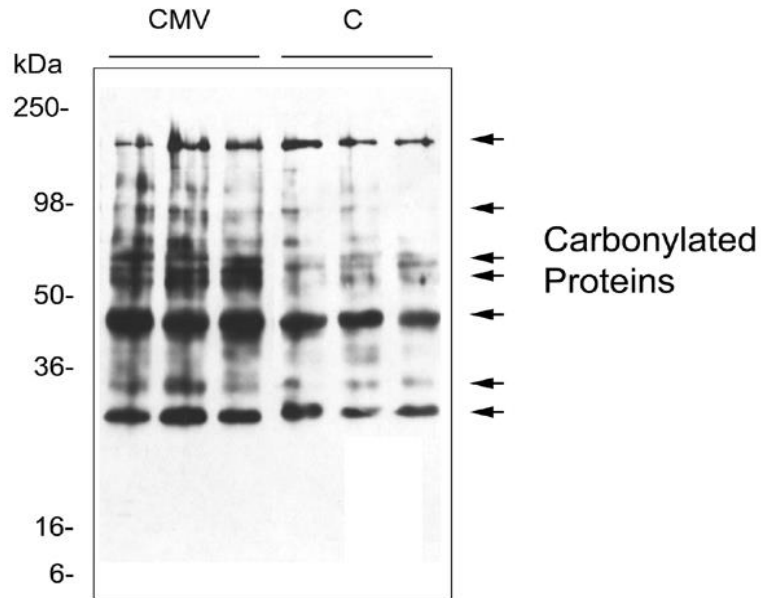


• **Decreased capacity for energy production**

Increased oxidative stress

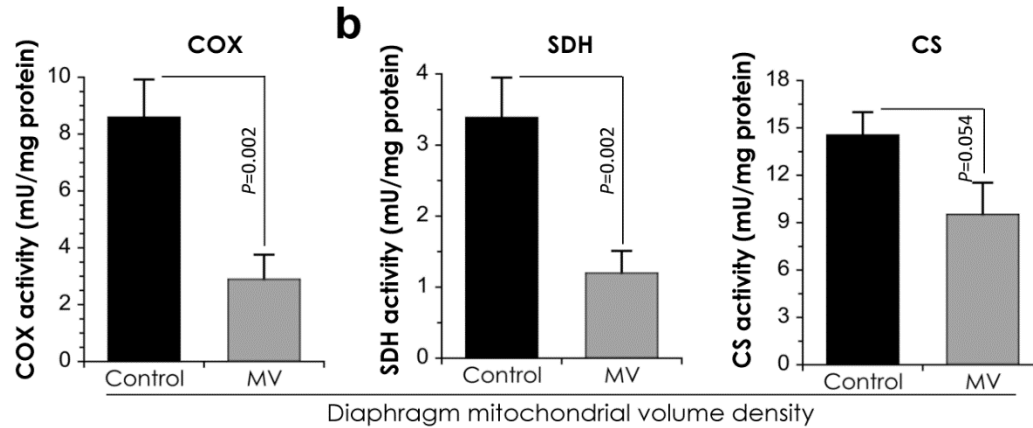
- **Impaired Contractility**
- **Atrophy**

Mitochondria-derived reactive oxygen species (ROS)

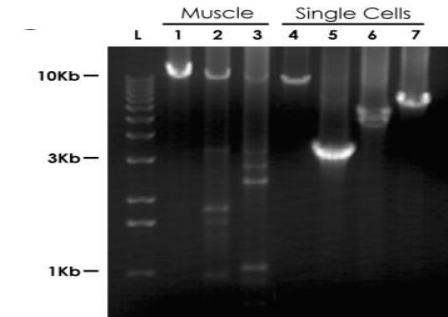
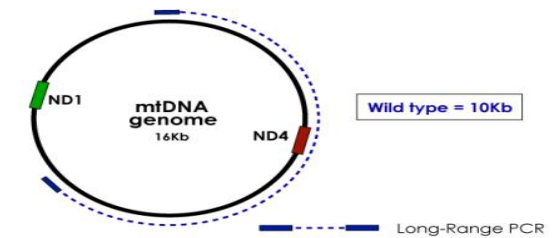
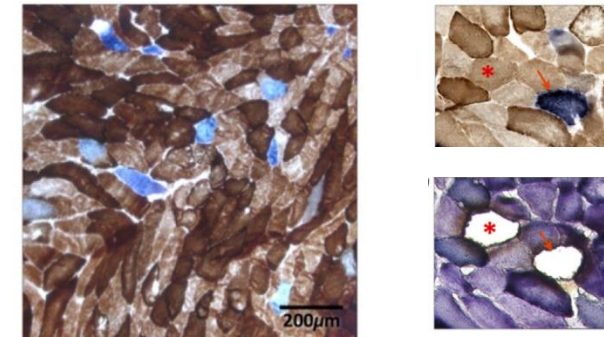
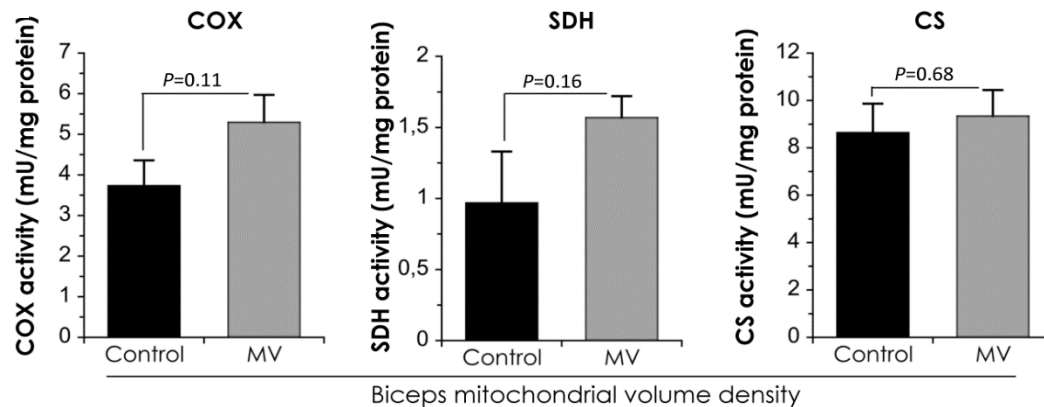


Mitochondrial dysfunction and mt DNA damage in human diaphragms during MV

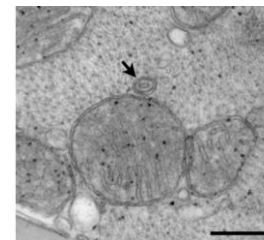
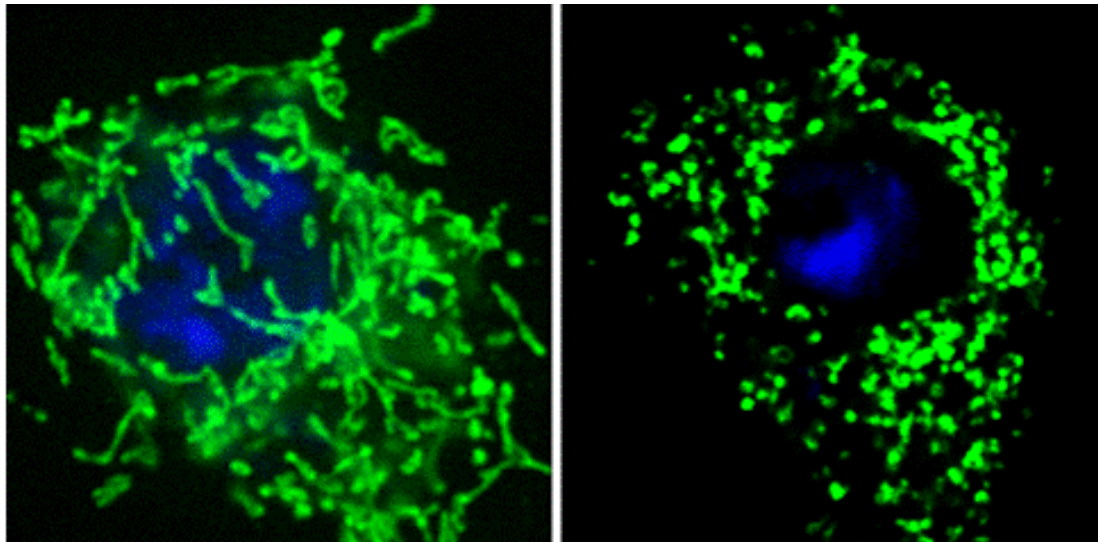
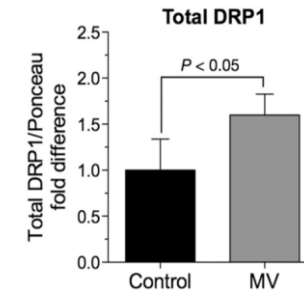
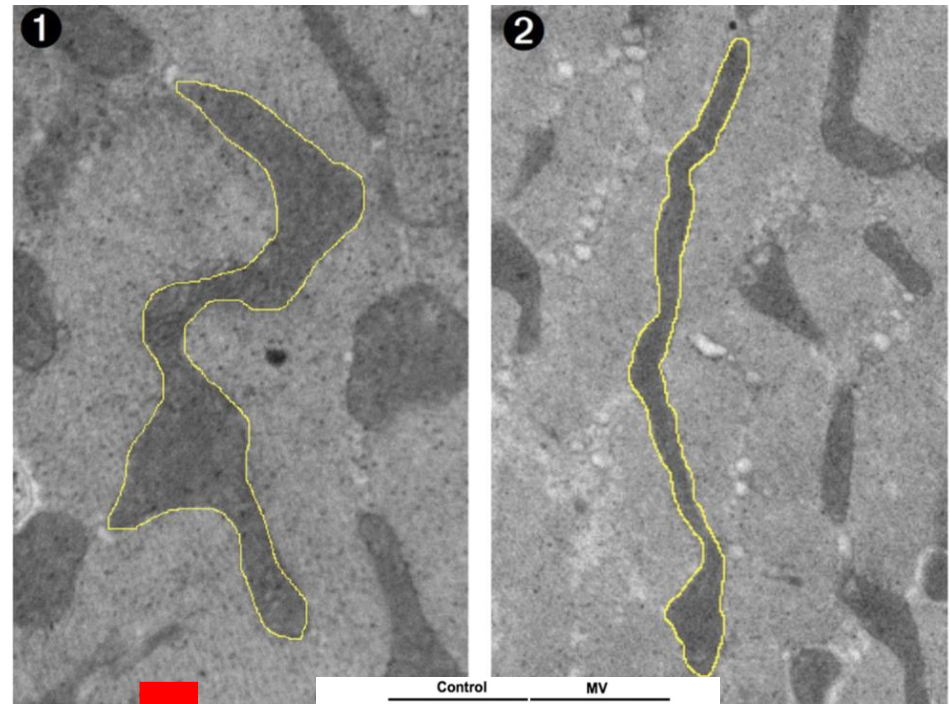
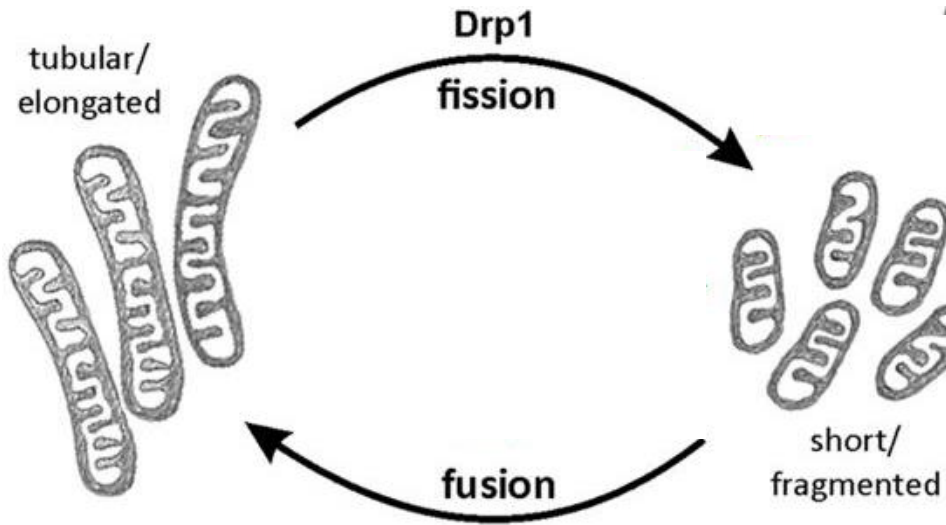
DIAPHRAGM



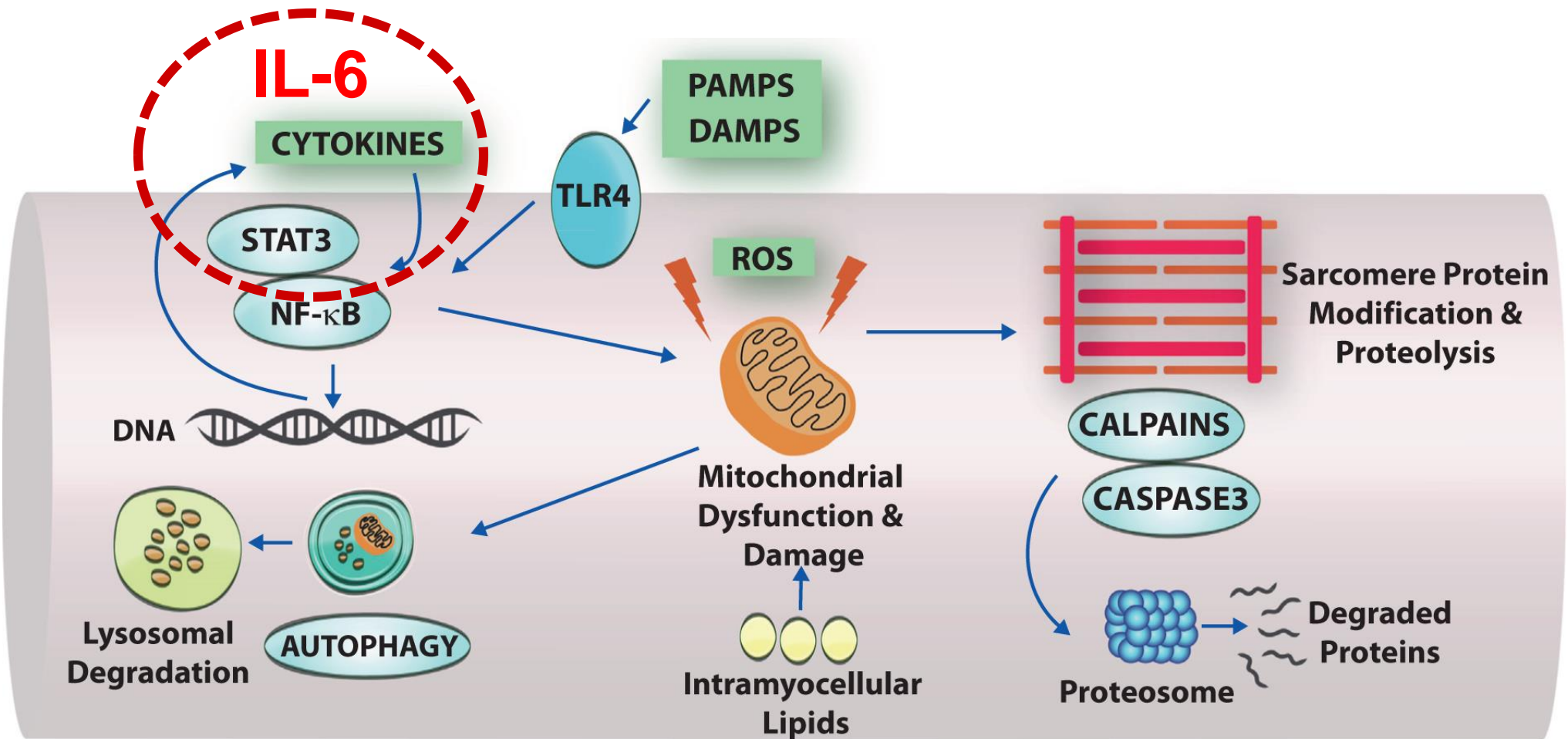
LIMB



Evidence for mitochondrial fragmentation during mechanical ventilation

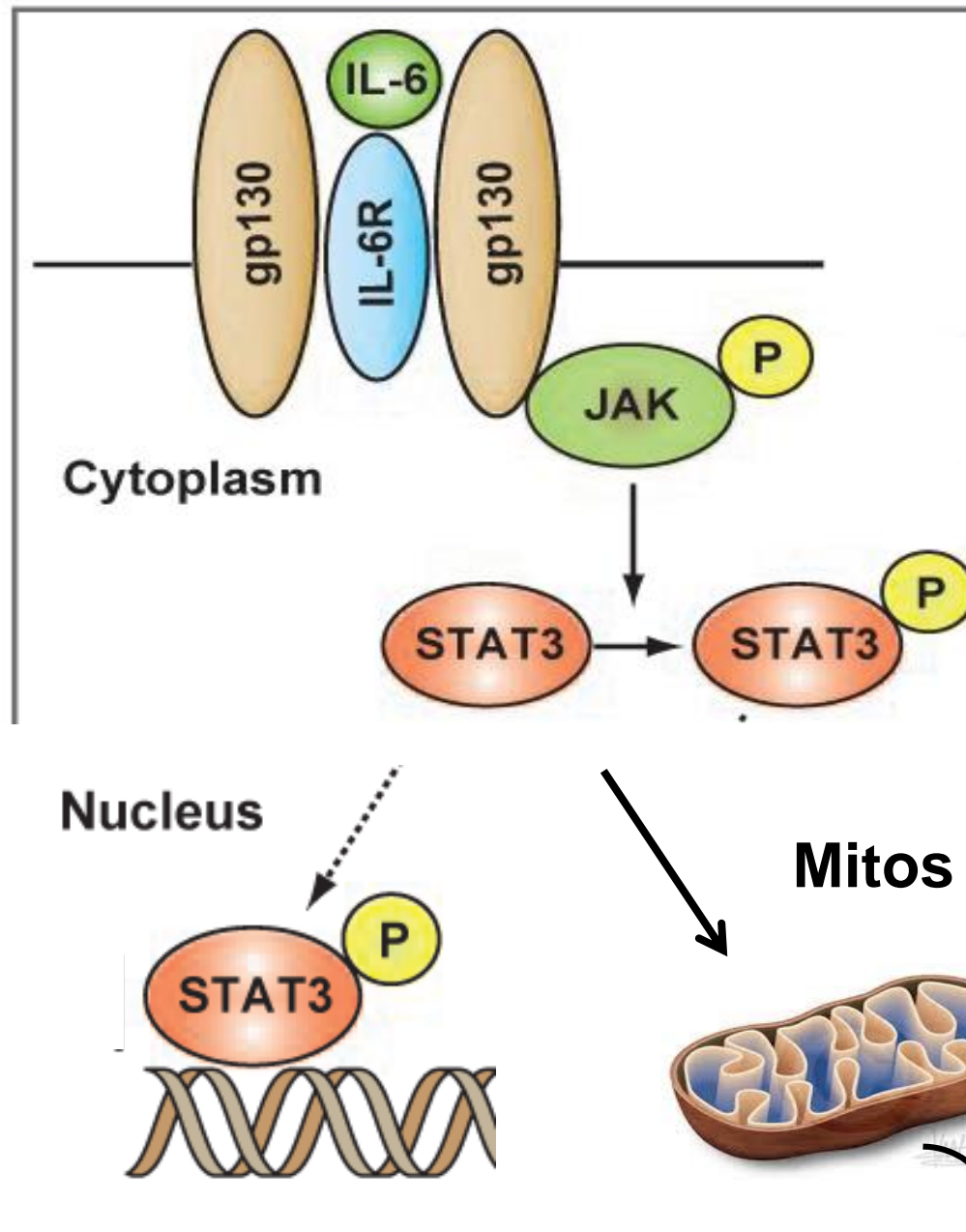
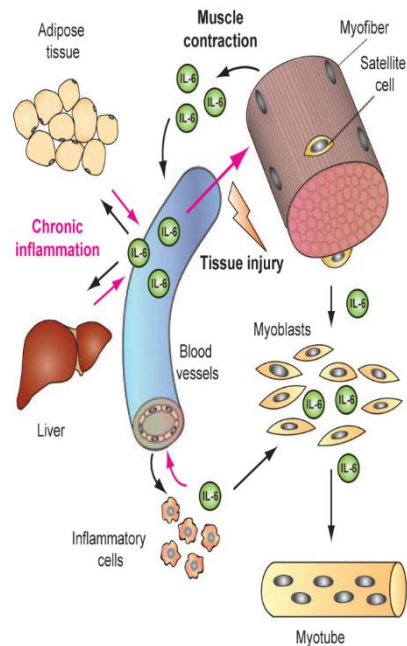


What are the upstream mediators ?

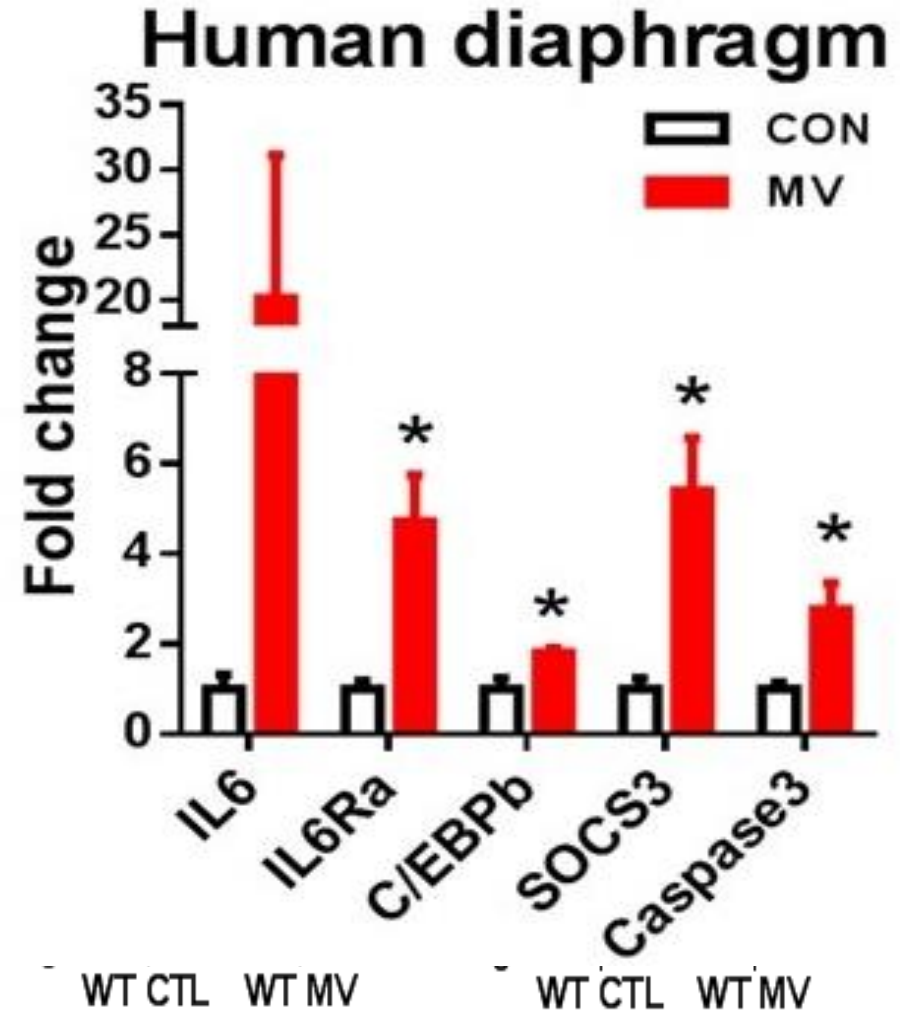
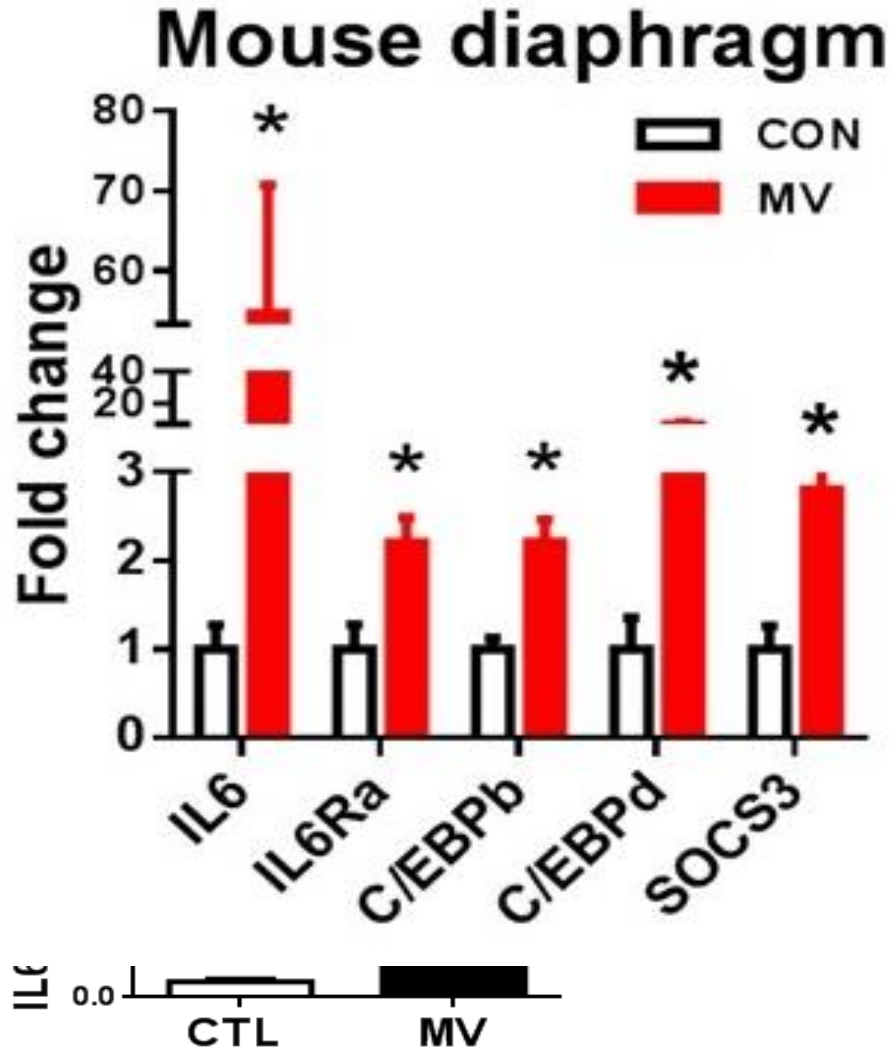


Sustained \uparrow IL-6

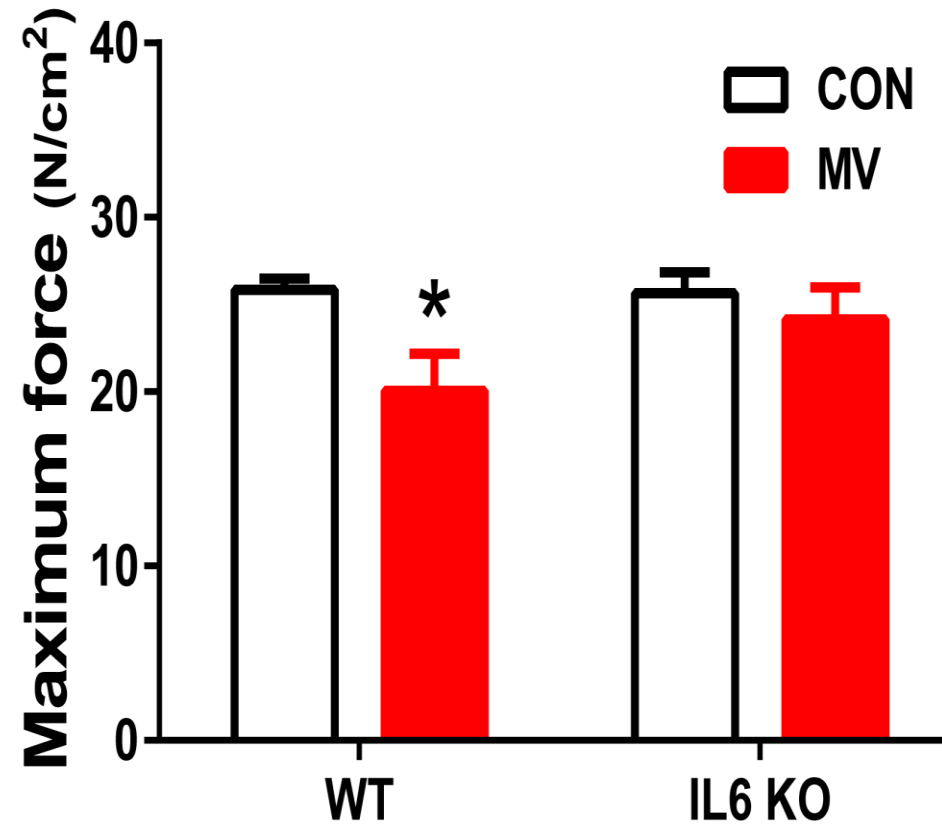
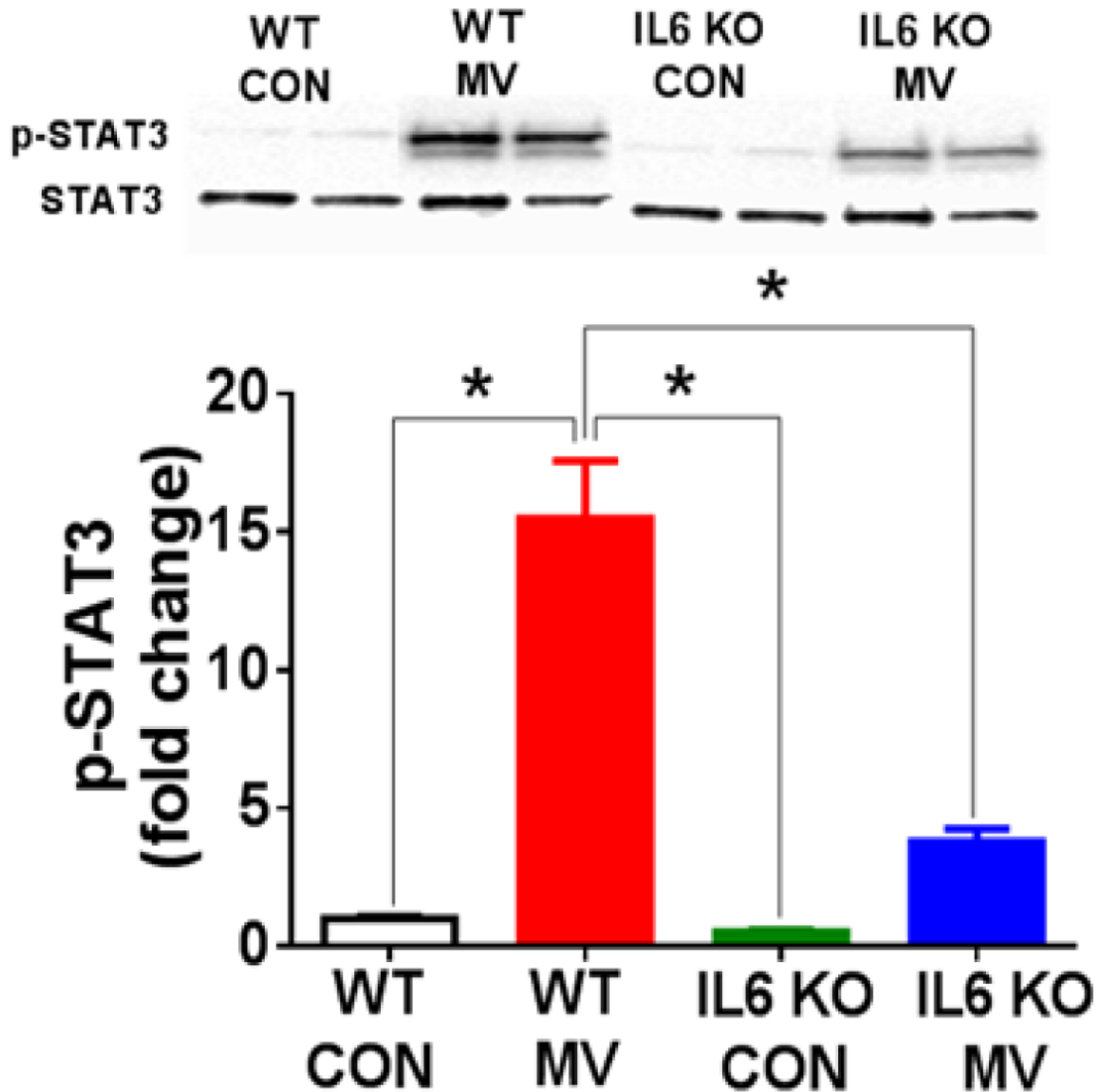
- Impaired Mito Fct
- Autophagy
- Cachexia



Upregulation of the IL6 / STAT3 pathway during mechanical ventilation

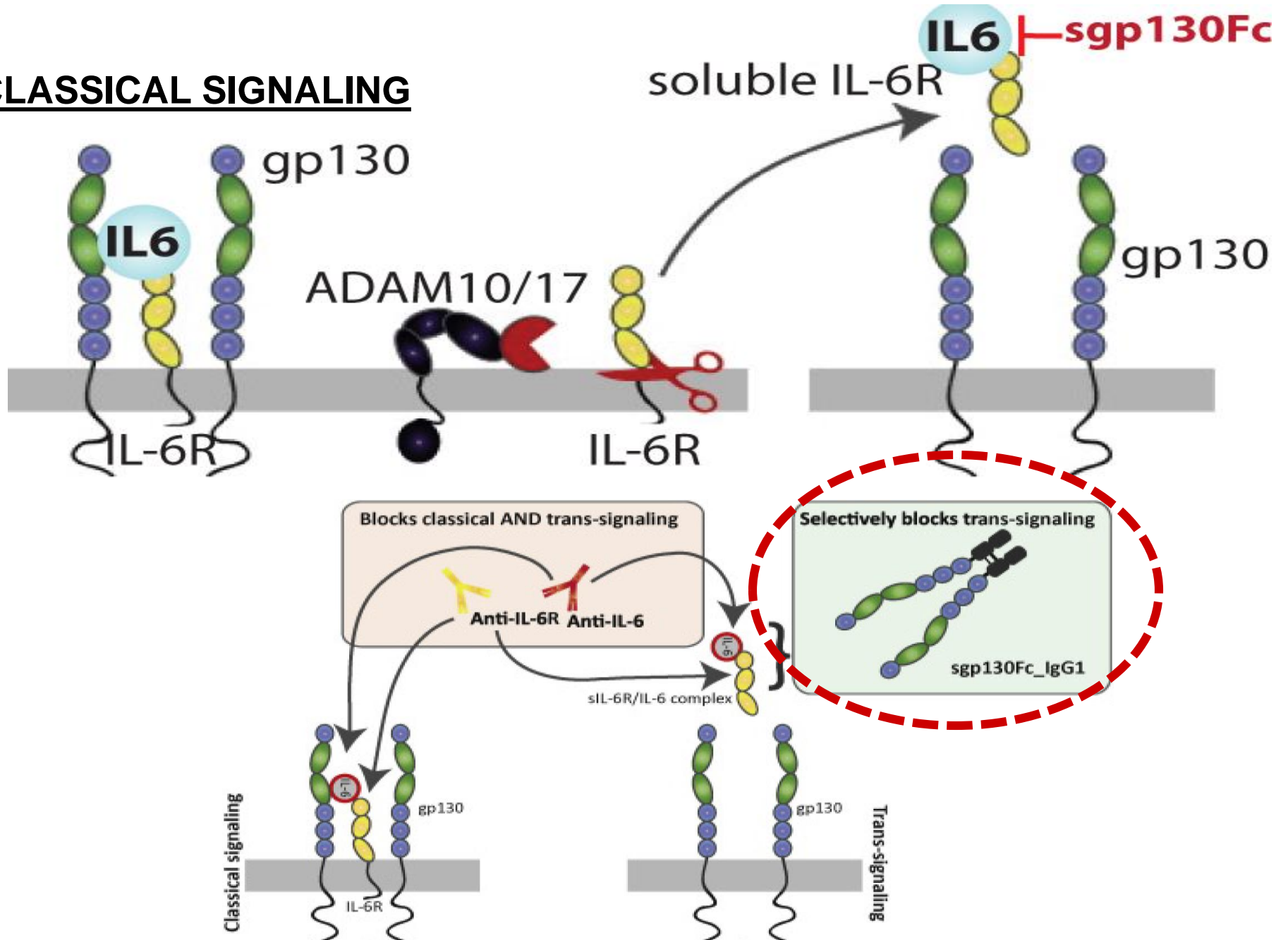


Genetic IL6 KO prevents STAT3 activation and diaphragm weakness during MV

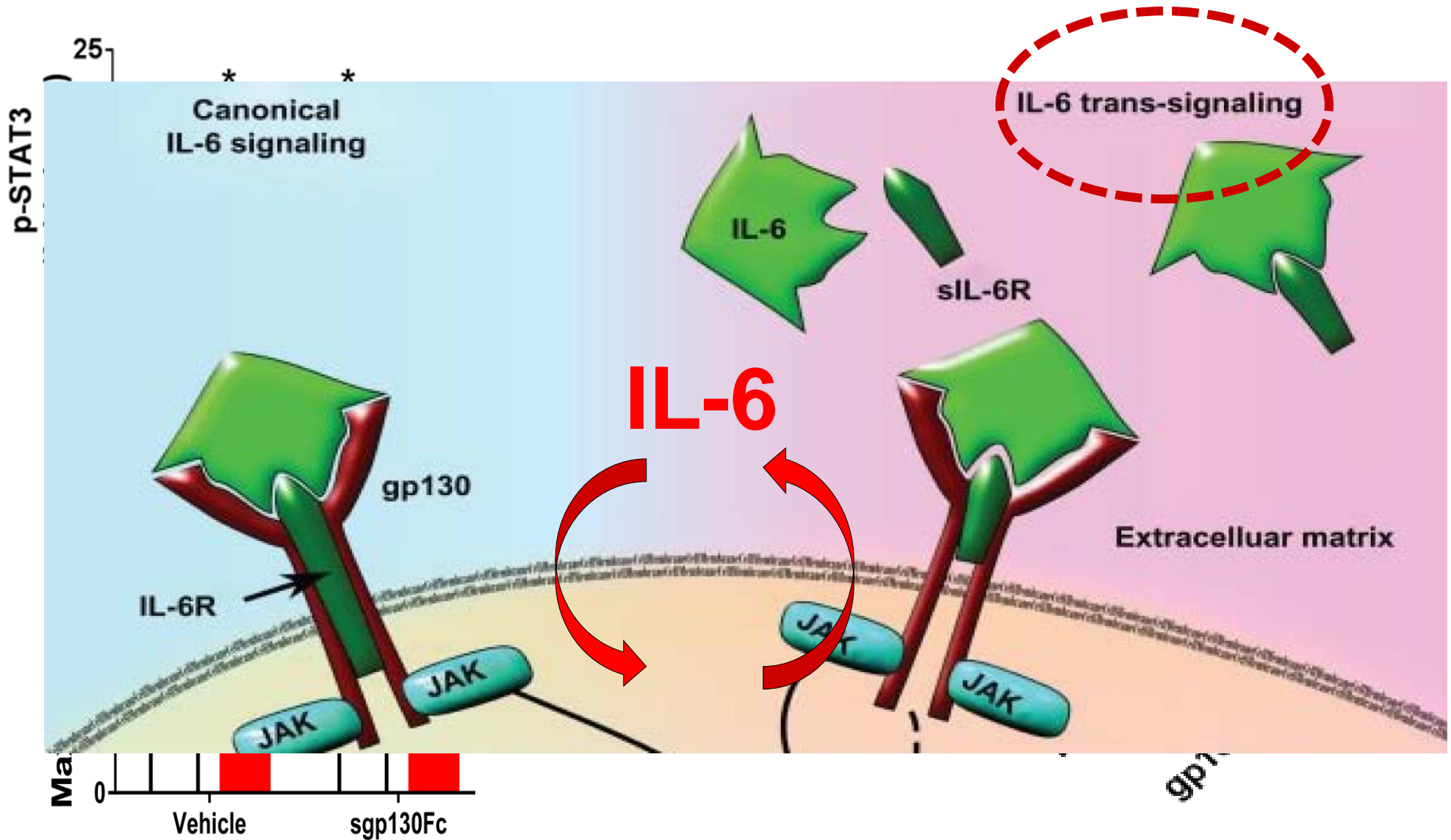


TRANS-SIGNALING

CLASSICAL SIGNALING



Blockade of IL6 trans-signaling prevents STAT3 activation and diaphragm weakness



Main summary points ...

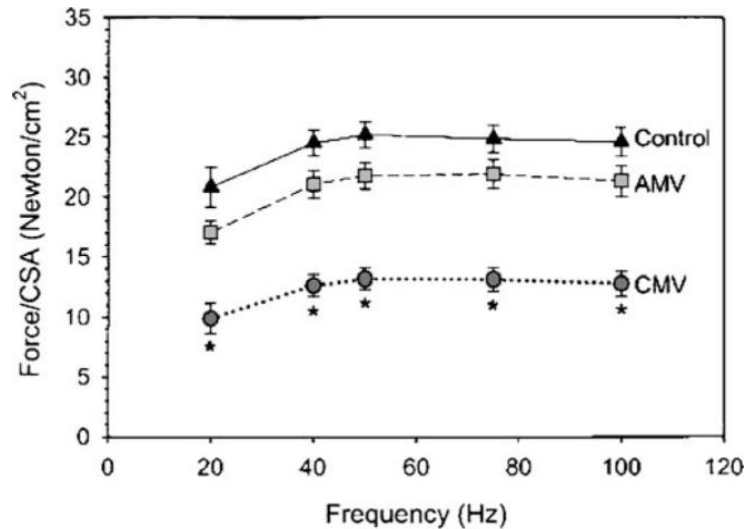
- Mechanical ventilation rapidly induces multiple adverse effects on the diaphragm including reduced force generation, atrophy, oxidative stress, and mitochondrial dysfunction & fission
- IL-6 is an important mediator of STAT3 activation and force loss in the diaphragm during mechanical ventilation
- VIDD can be prevented by inhibiting the non-classical “pathological” IL-6 trans-signaling pathway



**What can we do for
prevention or
therapy ?**

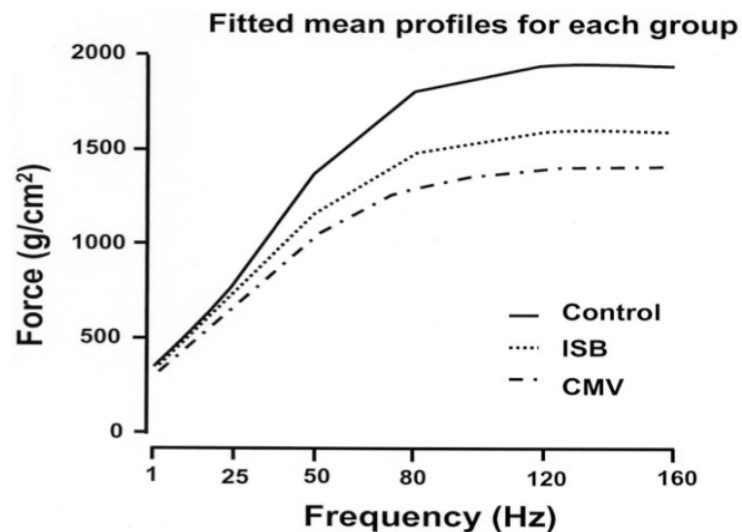


Encourage greater diaphragm activity



Controlled MV versus Assist Control (3 days in rabbits)

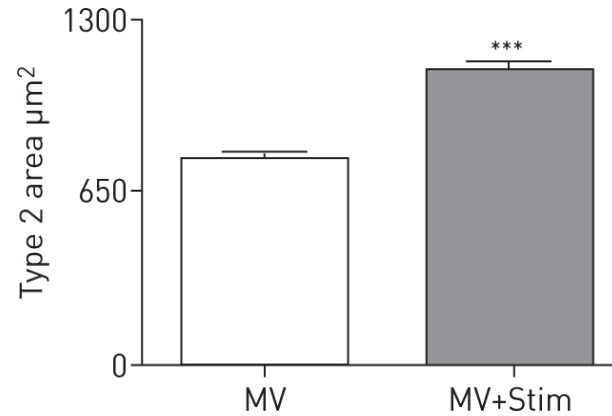
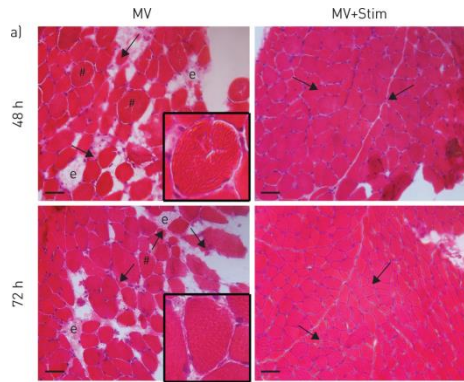
Sassoon, AJRCCM 2004



Controlled MV versus Intermittent Spontaneous Breathing (24 hours – 60 min ISB q5h in rats)

Gayan-Ramirez, Crit Care Med 2005

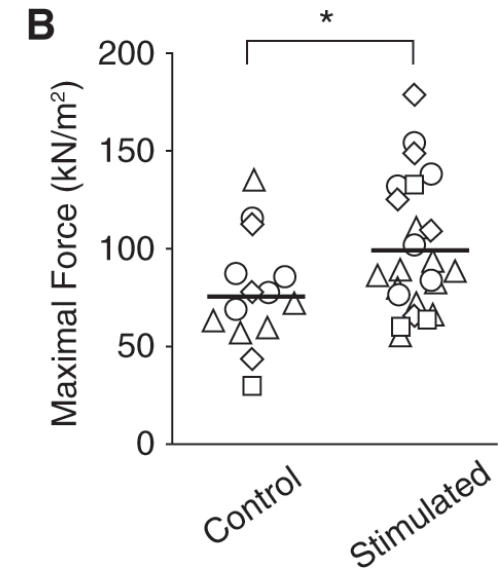
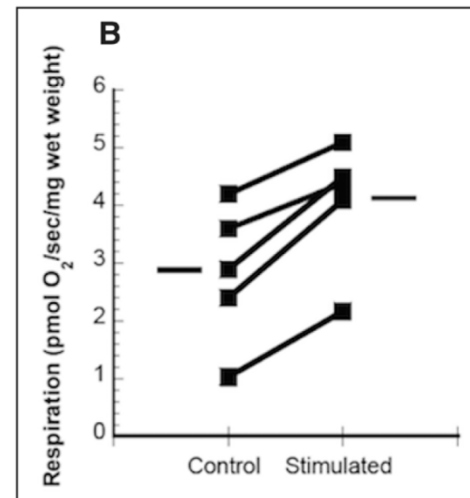
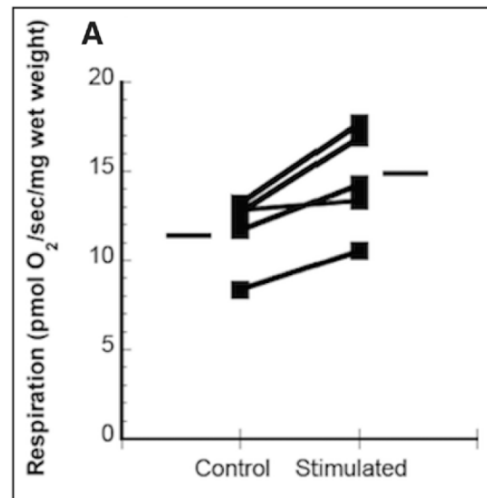
Intermittent phrenic nerve stimulation



ANIMALS

Masmoudi, ERJ 2013

HUMANS

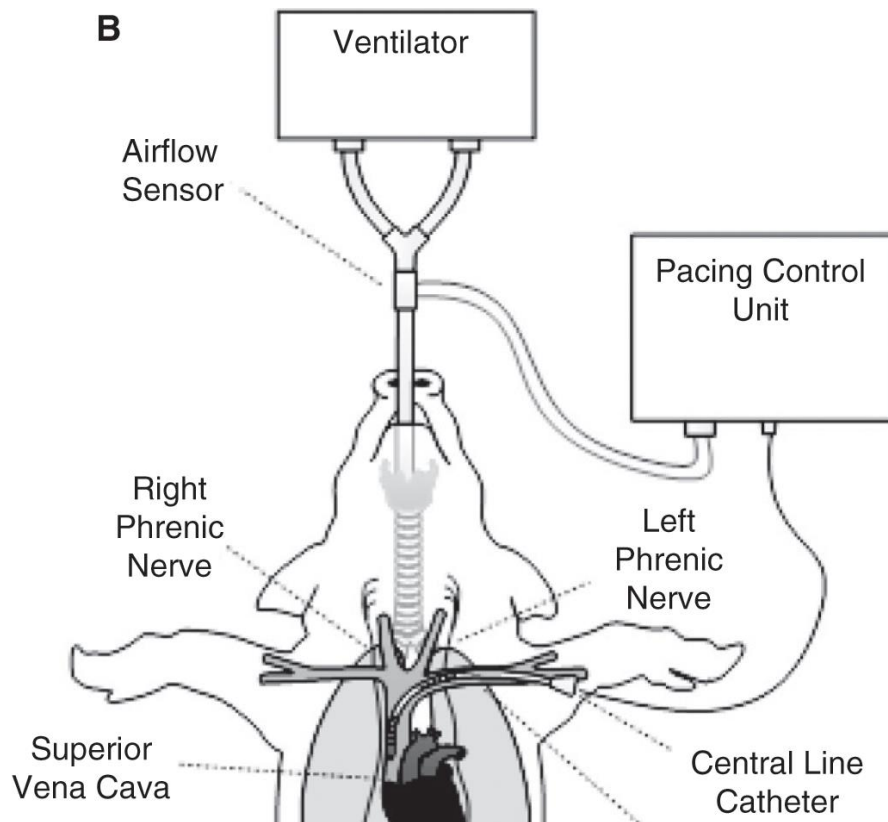


Martin, Crit Care Med 2014

Ahn, AJRCCM 2014

Transvenous pacing of phrenic nerves

Mitigation of Ventilator-induced Diaphragm Atrophy Phrenic Nerve Stimulation



Reynolds, AJRCCM 2017

STUDY PROTOCOL

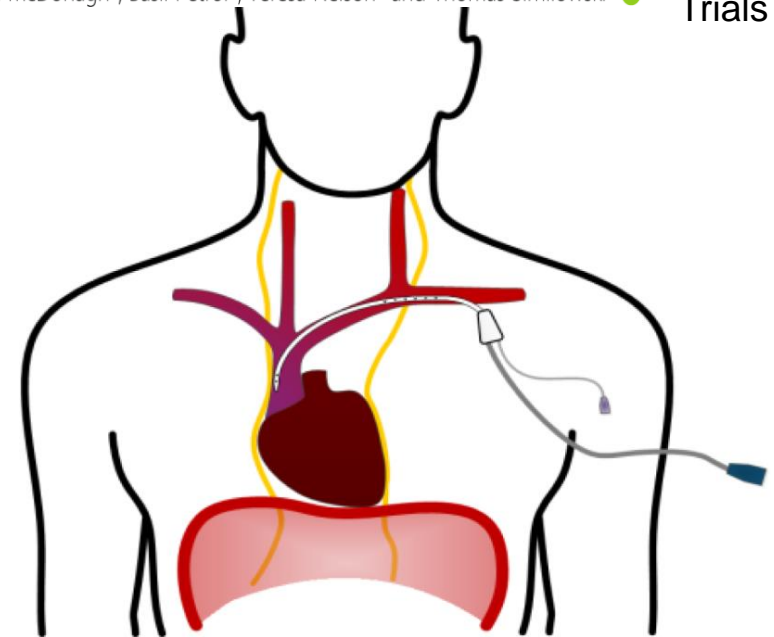
Open Access



Temporary transvenous diaphragm pacing vs. standard of care for weaning from mechanical ventilation: study protocol for a randomized trial

Douglas Evans^{1,10}, Deborah Shure², Linda Clark¹, Gerard J. Criner³, Martin Dres⁴, Marcelo Gama de Abreu⁵, Franco Laghi⁶, David McDonagh⁷, Basil Petrof⁸, Teresa Nelson⁹ and Thomas Similowski^{4*}

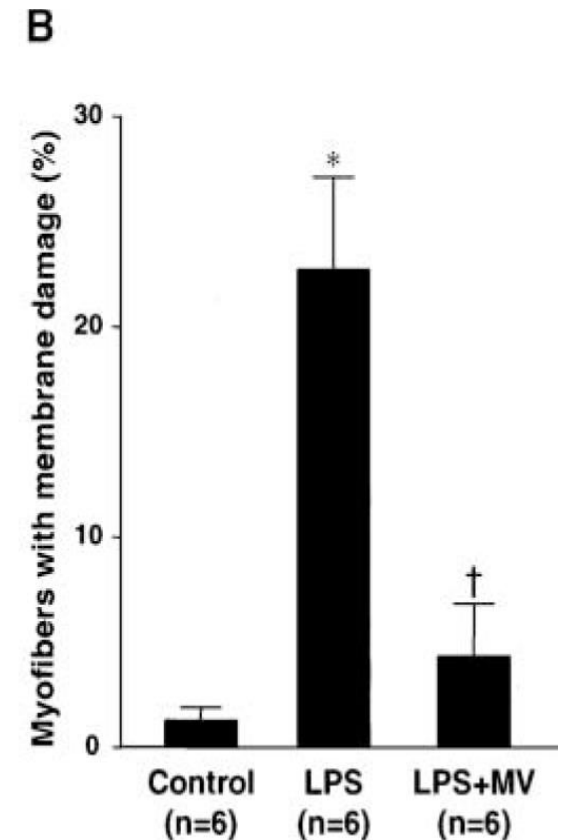
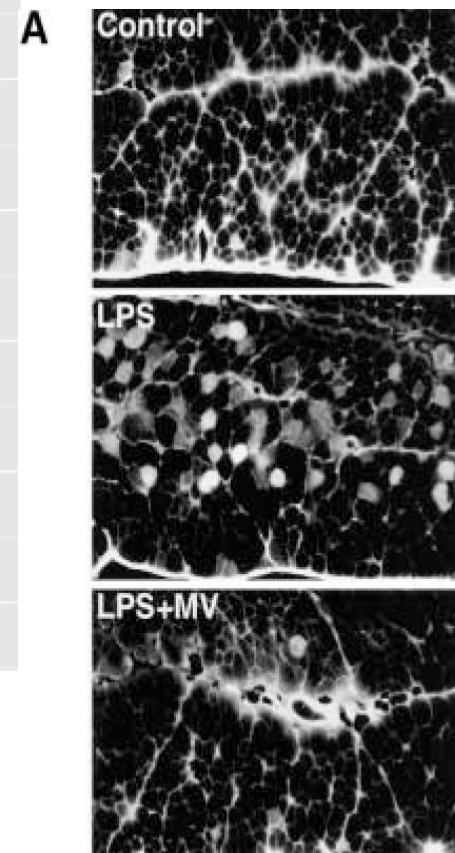
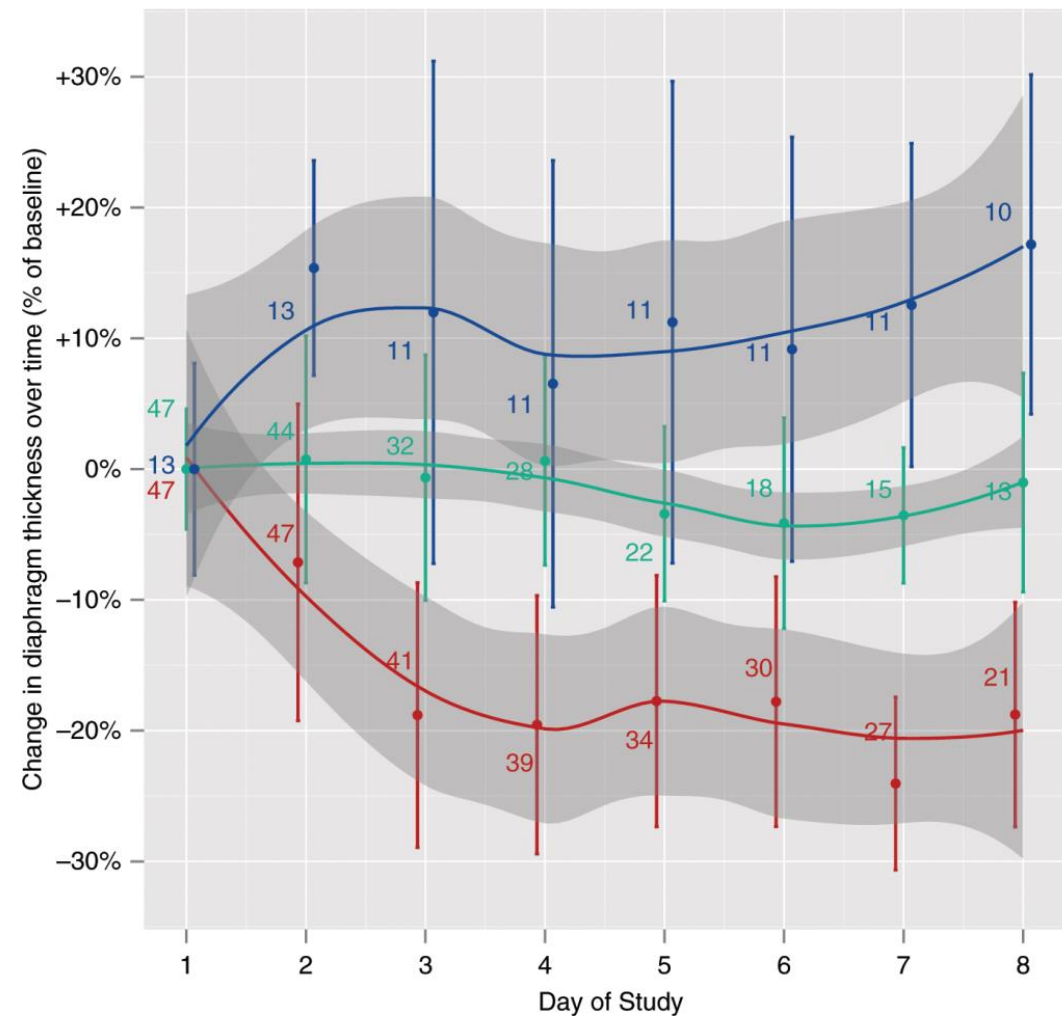
Trials 2019



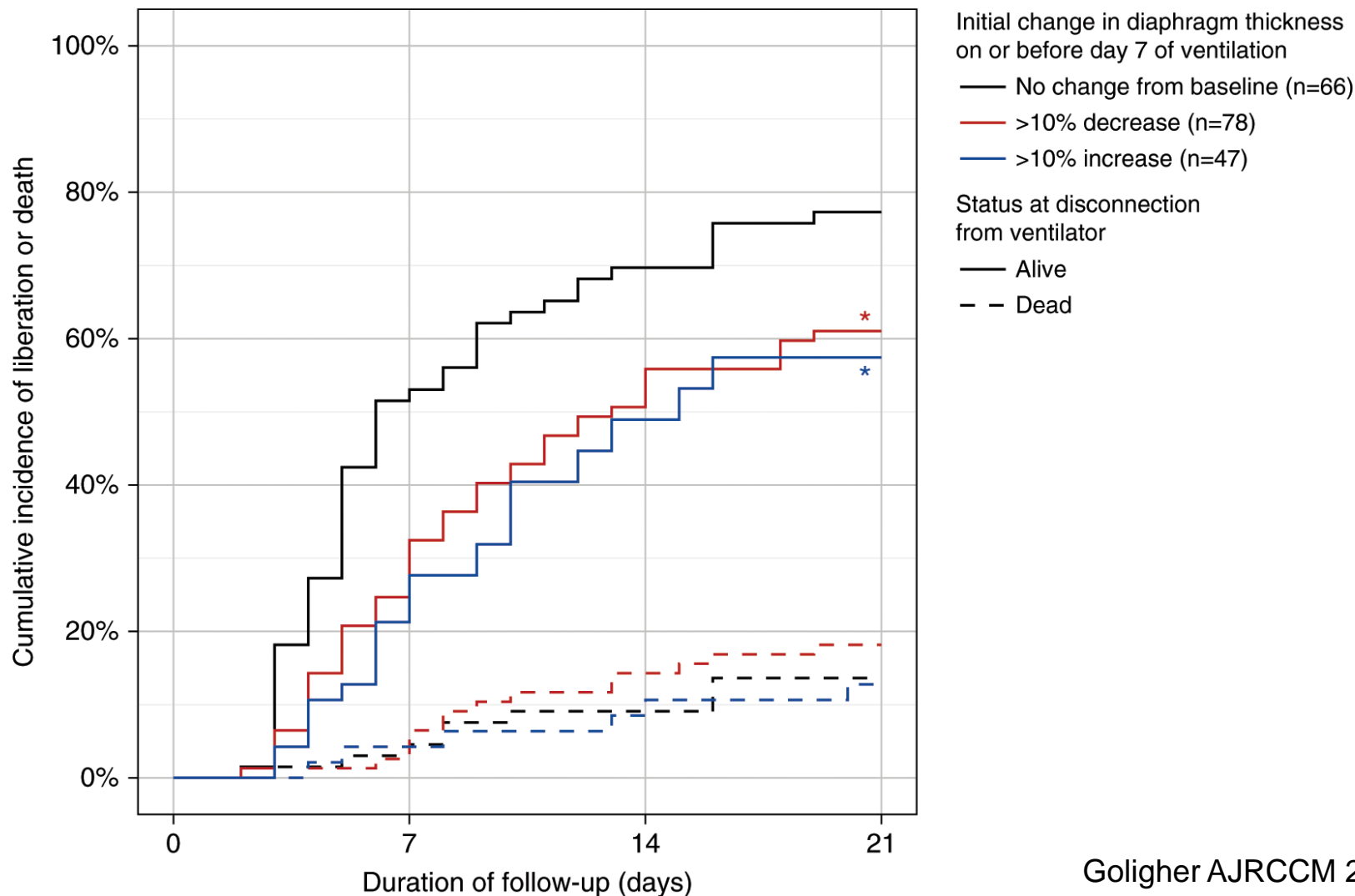
.... but could this also be harmful ?

Mechanical Ventilation Protects against Diaphragm Injury in Sepsis

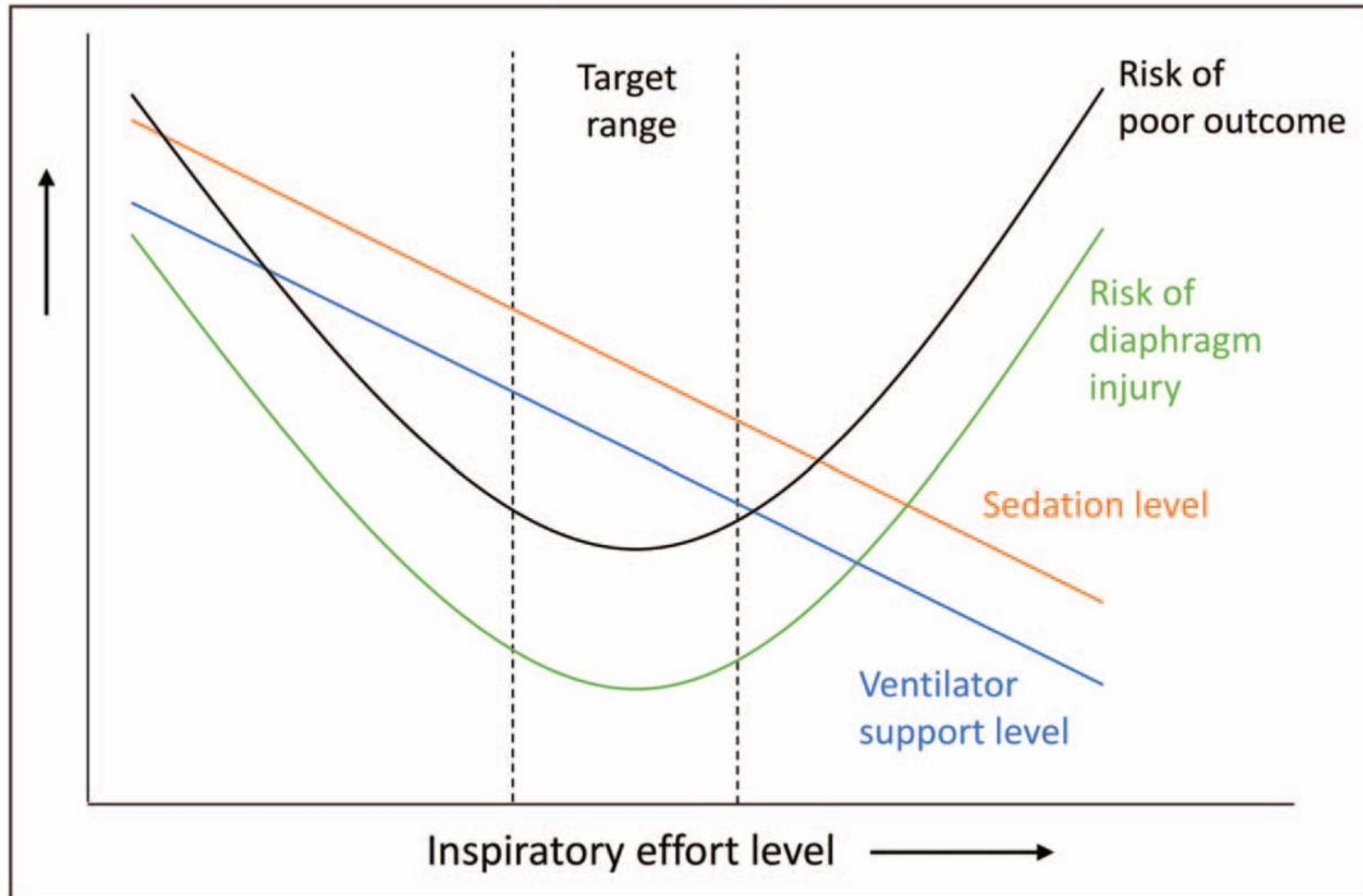
Interaction of Oxidative and Mechanical Stresses



Diaphragm thinning and thickening: Both = worse outcome



Concept of Diaphragm-Protective Ventilation



Summary of potential therapies

- **Optimize Diaphragm Activity**

Level

- Modify the level of ventilator support
- Transvenous phrenic nerve pacing
- Inspiratory muscle training

- **Metabolic Intervention**

- Nutritional
- Intensive insulin therapy

- **Drug Therapies**

Compound	Proposed Mechanism or Target	Preclinical Benefits Demonstrated in VIDD or SIDD?	Prior Use or Clinical Trials in Humans?
Oxidative stress <ul style="list-style-type: none"> • N-Acetylcysteine • Vitamin E • Curcumin • Superoxide dismutase • SS-31 • MitoQ 			
Inflammation signaling <ul style="list-style-type: none"> • R545, R546 • Ruxolitinib • SN50 • Edasason • Tocilizumab • Siltuximab • Eritoran • CD147 			
Proteolysis <ul style="list-style-type: none"> • Leupeptin • Calpain inhibitor • Eicosanoid • β-Hydroxy-methylglutaryl-CoA • Bortezomib 			
Contractile dysfunction <ul style="list-style-type: none"> • Rycal • BGP-15 			
• CK-2066260	• Troponin (thin filament) calcium insensitivity	• VIDD (human diaphragm biopsies)	• Yes (for analog drug tirasemtiv)





QUESTIONS

