Biological mechanisms of muscle mass loss and cachexia in patients with COPD

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Presenter Disclosures

ESTHER BARREIRO

(1) The following relationships with commercial interests related to this presentation existed during the past 12 months:

“No relationships to disclose”

Chronic obstructive pulmonary disease (COPD)

&

Skeletal muscle dysfunction

&

Exercise intolerance

⇓

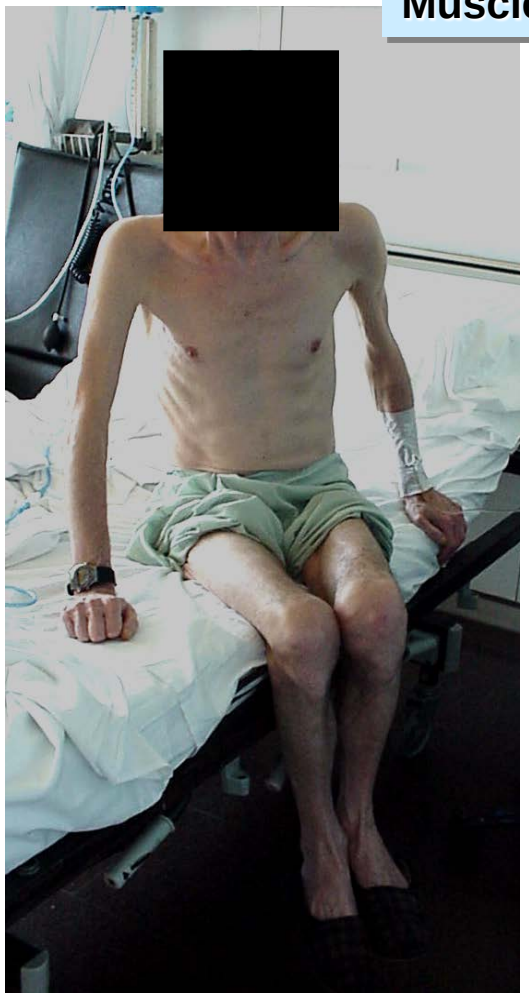
PROGNOSIS VALUE

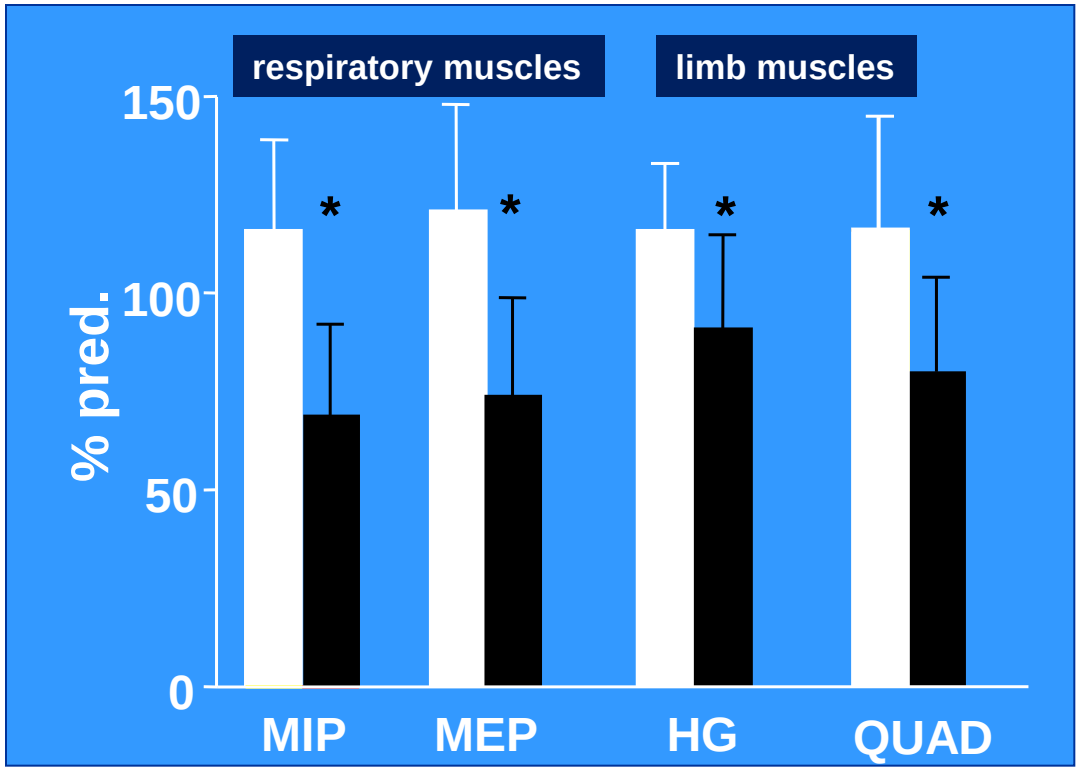
EVIDENCE OF MUSCLE DYSFUNCTION

Muscle dysfunction in COPD → **↓ Force & ↓ Endurance**

± Cachexia
Muscle loss

Exercise tolerance → QoL





Gosselink *et al.* AJRCCM 1996; 153. 976-80

PREVALENCE OF QUADRICEPS DYSFUNCTION IN COPD PATIENTS

TABLE 3 Prevalence of quadriceps weakness in chronic obstructive pulmonary disease (COPD)

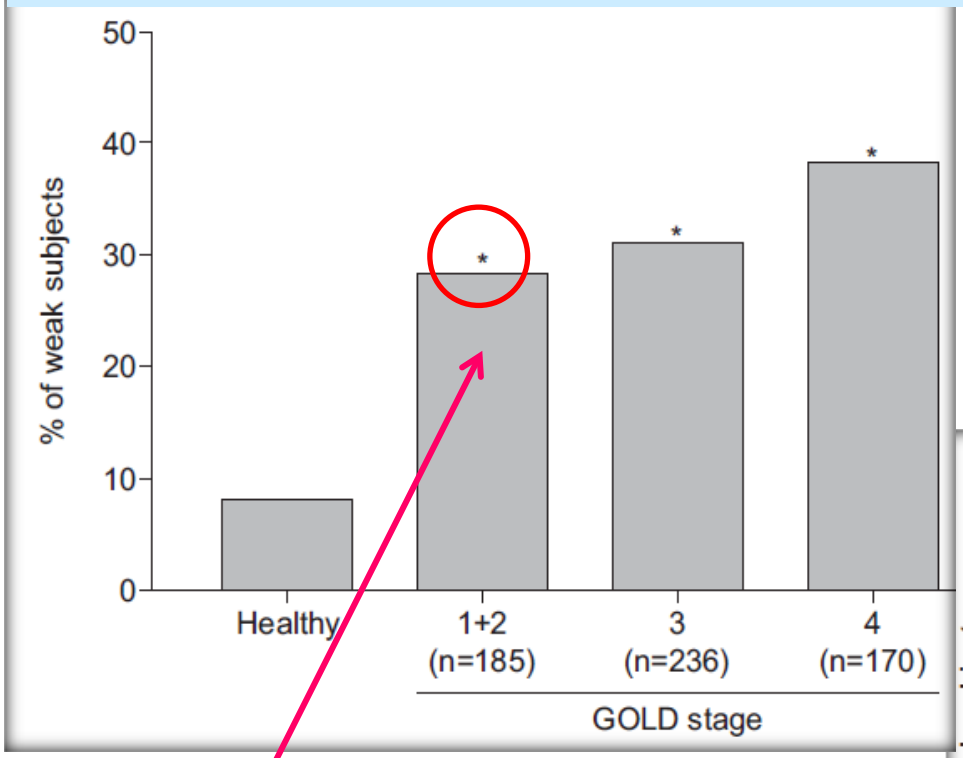
	UK Healthy	COPD		
		UK	the Netherlands	UK and the Netherlands
Male				
Subjects n	94	161	200	361
BMI kg·m^{-2}	26.1±3.3	24.4±4.8$^{\#}$	24.2±4.5$^{\#}$	24.6±4.4$^{\#}$
FFM index kg·m^{-2}	18.8±2.0	16.6±2.2$^{\#}$	16.6±2.0$^{\#}$	16.6±2.1$^{\#}$
QMVC kg	46.9±12.3	35.2±10.7$^{\#}$	33.9±10.6$^{\#}$	34.4±10.6$^{\#}$
COPD patients with weak QMVC n (%)		45 (28)	68 (34)	113 (31)$^{\#}$
Female				
Subjects n	118	79	151	230
BMI kg·m^{-2}	24.1±4.2¶	24.4±5.0	23.2±4.2¶	23.6±4.6$^{\#}$
FFM index kg·m^{-2}	15.2±1.2¶	15.4±1.9¶	14.6±1.5$^{\#,¶,+}$	14.9±1.9$^{\#,¶}$
QMVC kg	33.6±8.4¶	25.7±9.9$^{\#,¶}$	24.6±6.9$^{\#,¶}$	24.9±8.1$^{\#,¶}$
COPD patients with weak QMVC n (%)		31 (39)	47 (31)	78 (34)
Male and female				
Subjects n	212	240	351	591
BMI kg·m^{-2}	24.9±3.9	24.4±4.8	23.8±4.4$^{\#}$	24.0±4.6$^{\#}$
FFM index kg·m^{-2}	16.8±2.6	16.2±2.2$^{\#}$	15.7±2.1$^{\#,+}$	15.9±2.1$^{\#}$
QMVC kg	39.5±12.3	32.0±11.3$^{\#}$	29.9±10.4$^{\#,+}$	30.7±10.8$^{\#}$
COPD patients with weak QMVC n (%)		76 (32)	115 (33)	191 (32)

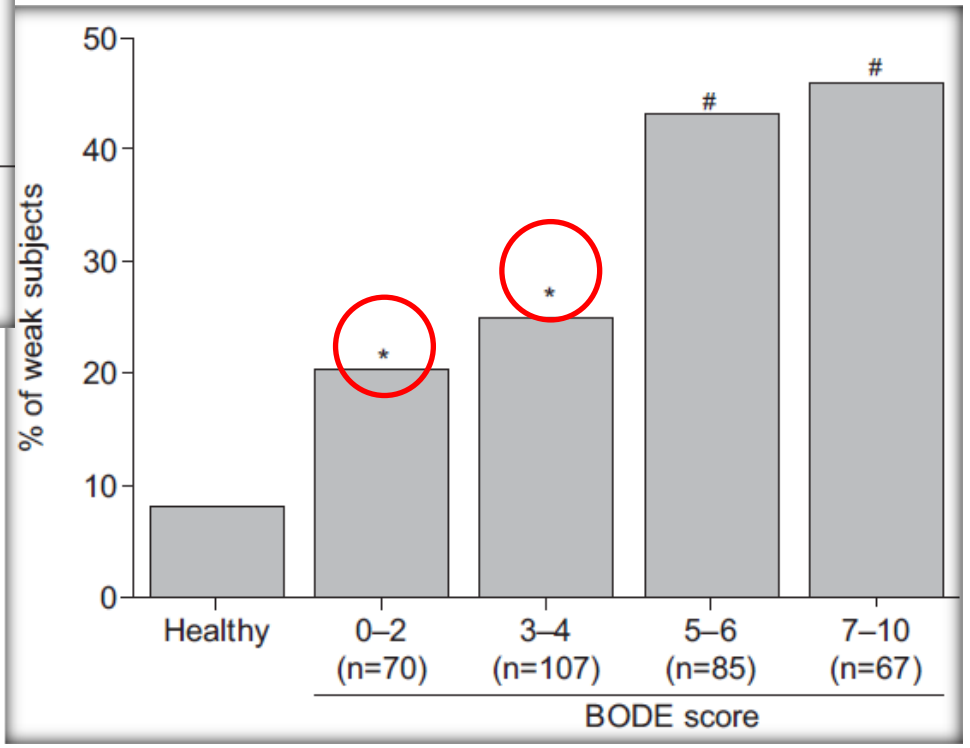
1/3 of the patients

Data are presented as mean±SD, unless otherwise stated, for patients diagnosed with quadriceps weakness, split by sex and disease cohort. Body mass index (BMI), fat-free mass (FFM) index and quadriceps maximum voluntary contraction strength (QMVC) in each group are shown for reference. $^{\#}$: $p<0.05$ compared with healthy subjects; ¶: $p<0.05$ between males and females; $^{+}$: $p<0.05$ between UK and Dutch COPD patients.

Seymour *et al. Eur Respir J* 2010; 36: 81-88

QUADRICEPS WEAKNESS & DISEASE SEVERITY IN COPD PATIENTS

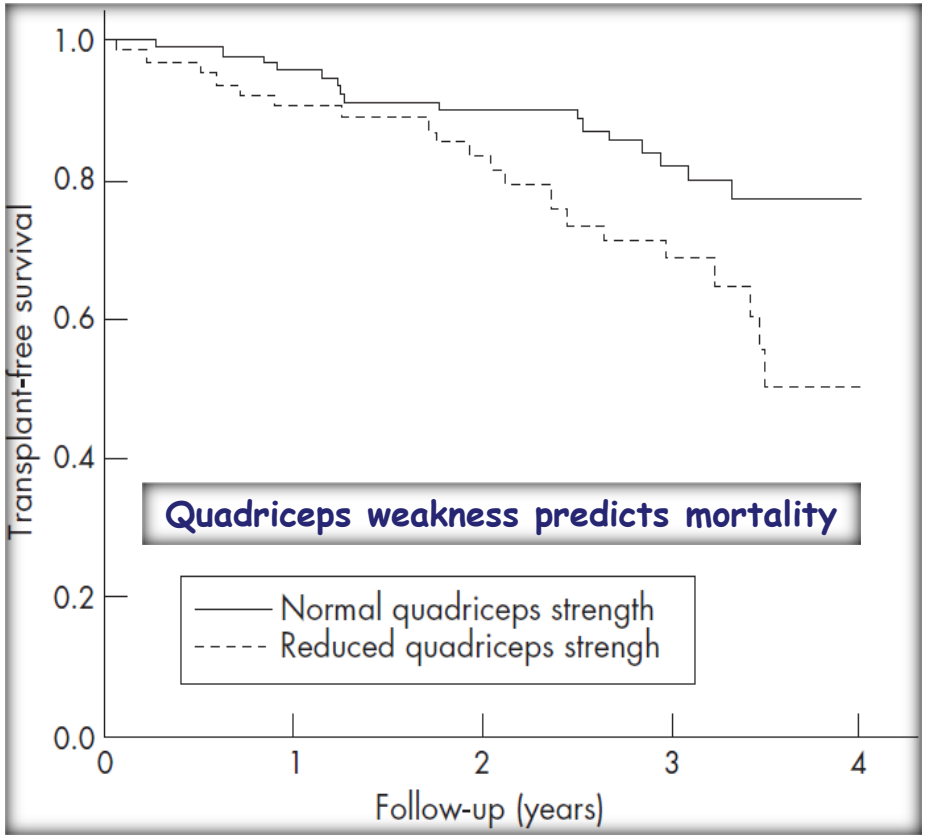


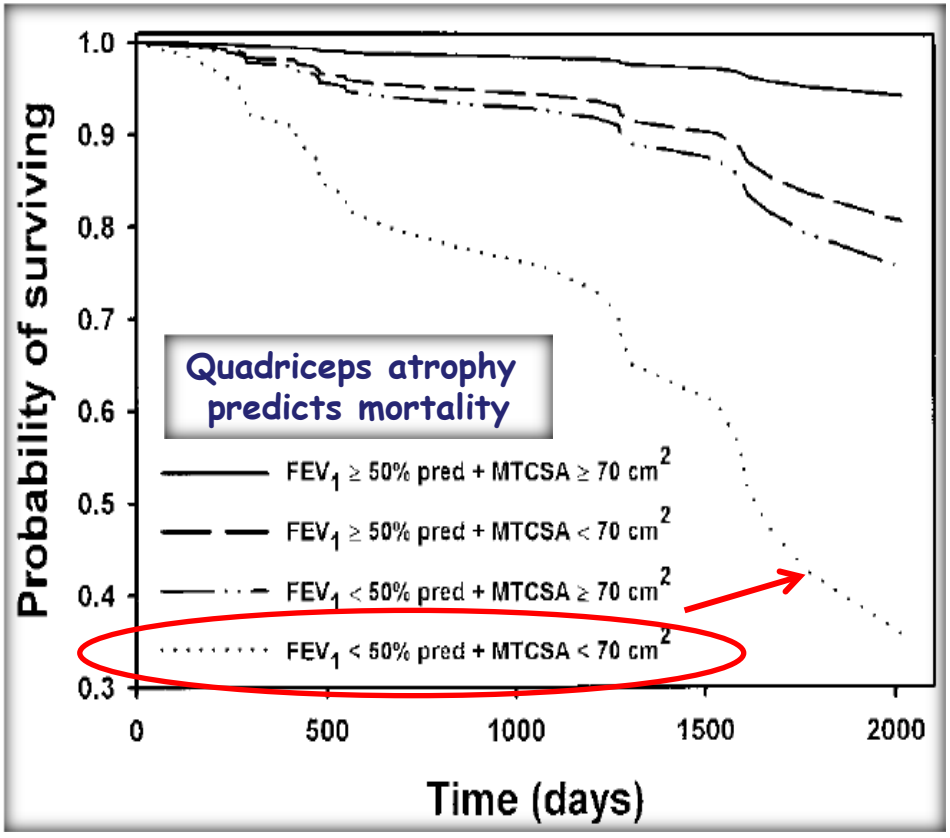


Quadriceps weakness exists in the absence of severe airflow obstruction!

Seymour *et al. Eur Respir J* 2010; 36: 81-88

QUADRICEPS WEAKNESS & ATROPHY PREDICT MORTALITY IN COPD PATIENTS





QMVC is simple and provides better prognostic information than other parameters (age, BMI, and FEV1) in COPD

Swallow *et al. Thorax* 2007; 62: 115-120.

Midthigh muscle cross sectional area is a better predictor of mortality than BMI in COPD patients

4 different phenoptyes of COPD patients

Marquis *et al. AJRCCM* 2002; 166: 809-813.

BODY COMPOSITION & MORTALITY IN COPD

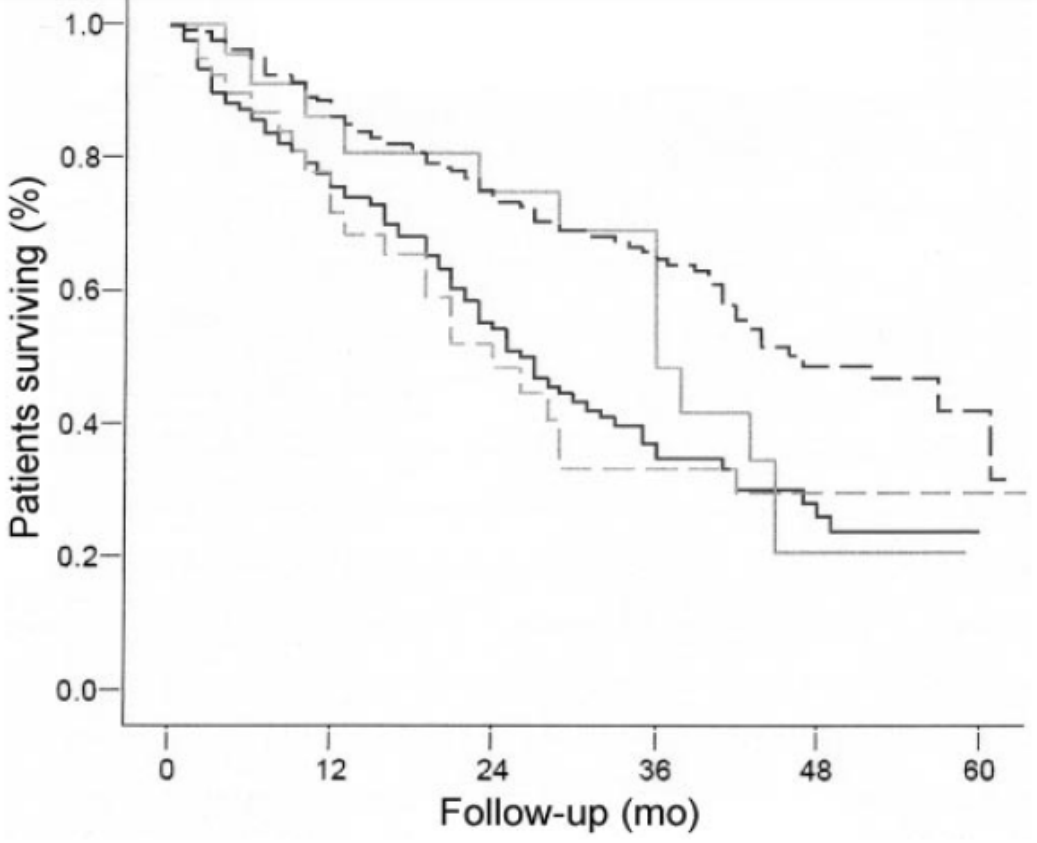
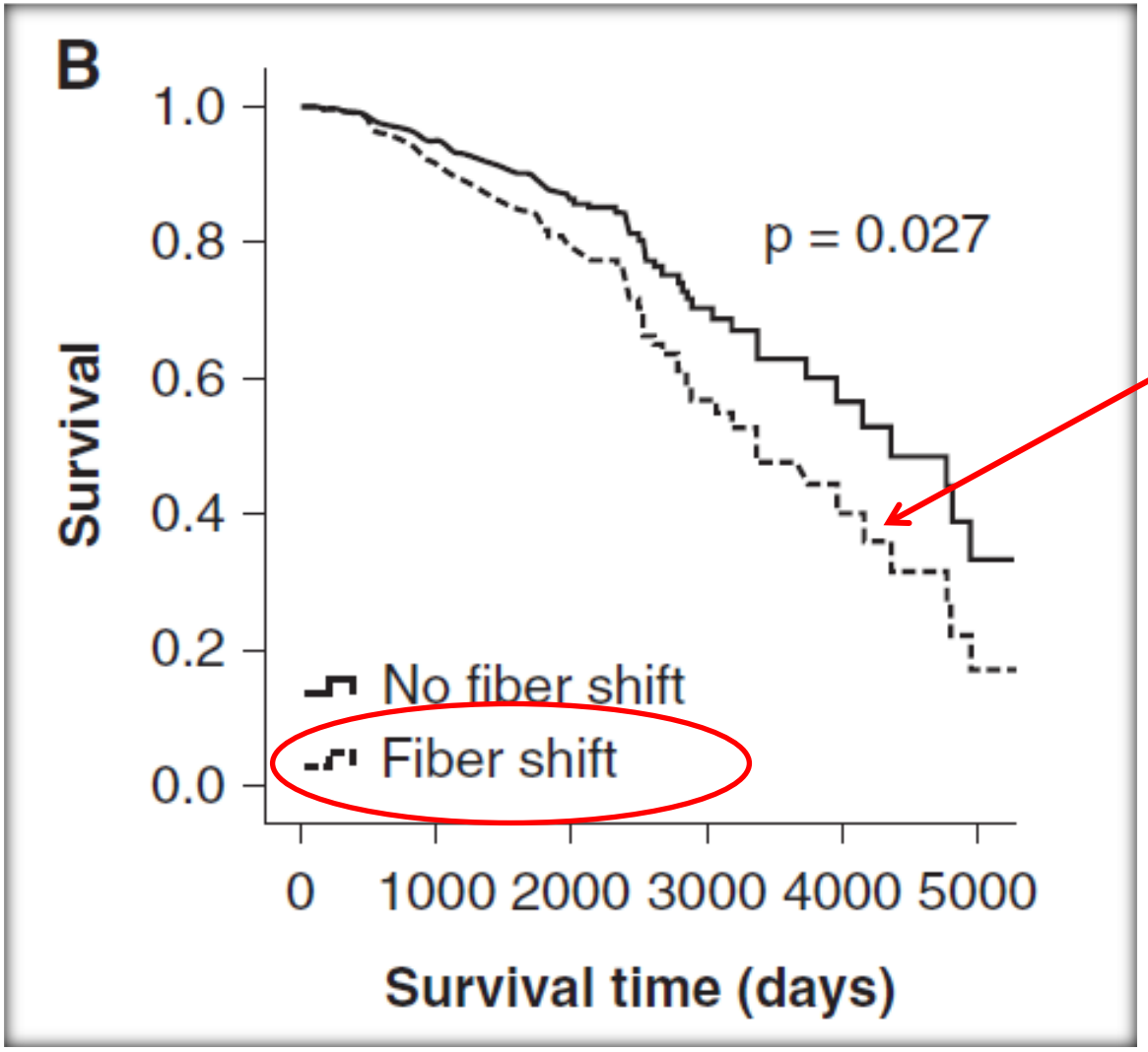


FIGURE 2. Kaplan-Meier plot of survival in different body-composition categories. Category 1 (cachexia; $n = 117$), solid black line; category 2 (semistarvation; $n = 23$), solid gray line; category 3 (muscle atrophy; $n = 40$), dashed gray line; category 4 (no impairment; $n = 232$), dashed black line. Median (95% CI) survival was significantly ($P < 0.001$) less in patients with cachexia (26 mo; 21, 31 mo) and muscle atrophy (24 mo; 15, 33 mo) than in patients with semistarvation (36 mo; 28, 44 mo) or no impairment (47 mo; 37, 57 mo). The survival plot of the semistarvation category did not differ significantly from that of the no-impairment category during the first 3 y.

AMWJ Schols et al. *Am J Clin Nutr* 2005; 82: 53-9

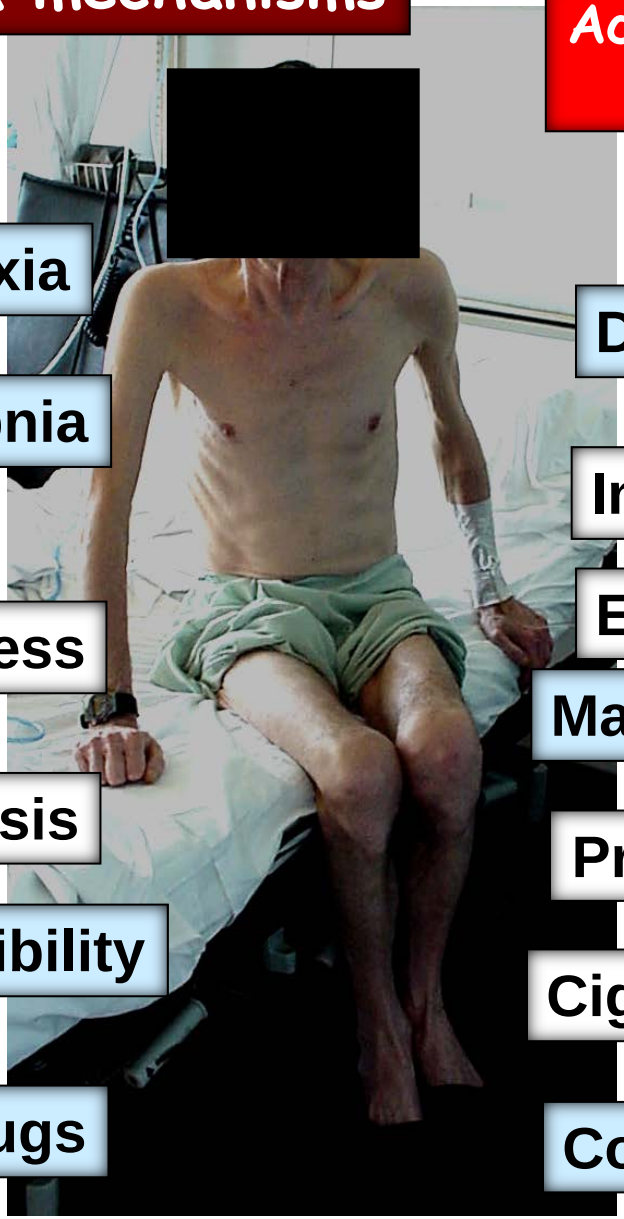
FIBER TYPE SHIFT & MORTALITY IN COPD



Patel et al. *Am J Respir Crit Care Med* 2014; 190: 350-51

Skeletal muscle dysfunction in COPD patients: Mechanisms

MULTIFACTORIAL ETIOLOGY OF MUSCLE DYSFUNCTION IN COPD



Factors & mechanisms

Activity & type of muscle !

- Hypoxia
- Hypercapnia
- Oxidative stress
- Apoptosis
- Genetic susceptibility
- Drugs
- Deconditioning
- Inflammation
- Epigenetics
- Malnutrition
- Proteolysis
- Cigarette smoking
- Comorbidities

OCCASIONAL ESSAY

Muscle Dysfunction in Patients with Lung Diseases

A Growing Epidemic

Esther Barreiro[1,2], Jacob I. Sznajder[3], Gustavo A. Nader[4,5], and G. R. Scott Budinger[3]

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J Appl Physiol 114: 1220–1221, 2013;
doi:10.1152/japplphysiol.00162.2013.

HIGHLIGHTED TOPIC | *Muscle Dysfunction in COPD*

Muscle dysfunction in COPD

Esther Barreiro[1,2] and Gary Sieck[3]

1.- Pathophysiology of muscle dysfunction in COPD.

2.- Motor control in muscle dysfunction in COPD.

3.- Muscle remodeling in COPD.

4.- Role of cachexia in COPD muscle dysfunction.

5.- Role of epigenetics in COPD muscle dysfunction.

6.- Role of autophagy in COPD muscle dysfunction.

7.- Metabolic derangements in COPD muscle dysfunction.

8.- Mechanisms of muscle dysfunction during acute exacerbations in COPD.

9.- Should all COPD patients be trained? Who, when, and how? Pros and cons.

ERS EUROPEAN RESPIRATORY SOCIETY
every breath counts

AMERICAN THORACIC SOCIETY 1905 ATS

AMERICAN THORACIC SOCIETY DOCUMENTS

An Official American Thoracic Society/European Respiratory Society Statement: Update on Limb Muscle Dysfunction in Chronic Obstructive Pulmonary Disease

Executive Summary

François Maltais, Marc Decramer, Richard Casaburi, Esther Barreiro, Yan Burelle, Richard Debigaré, P. N. Richard Dekhuijzen, Frits Franssen, Ghislaine Gayan-Ramirez, Joaquim Gea, Harry R. Gosker, Rik Gosselink, Maurice Hayot, Sabah N. A. Hussain, Wim Janssens, Michael I. Polkey, Josep Roca, Didier Saey, Annemie M. W. J. Schols, Martijn A. Spruit, Michael Steiner, Tanja Taivassalo, Thierry Troosters, Ioannis Vogiatzis, and Peter D. Wagner; on behalf of the ATS/ERS Ad Hoc Committee on Limb Muscle Dysfunction in COPD

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) AND THE EUROPEAN RESPIRATORY SOCIETY (ERS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, NOVEMBER 2013, AND BY THE ERS EXECUTIVE COMMITTEE, SEPTEMBER 2013

Maltais F et al. Am J Respir Crit Care Med 2014; 189: e15-62.

SPANISH GUIDELINES ON MUSCLE DYSFUNCTION IN COPD

Arch Bronconeumol. 2015;51(8):384–395

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Recommendations of SEPAR

Guidelines for the Evaluation and Treatment of Muscle Dysfunction in Patients With Chronic Obstructive Pulmonary Disease☆

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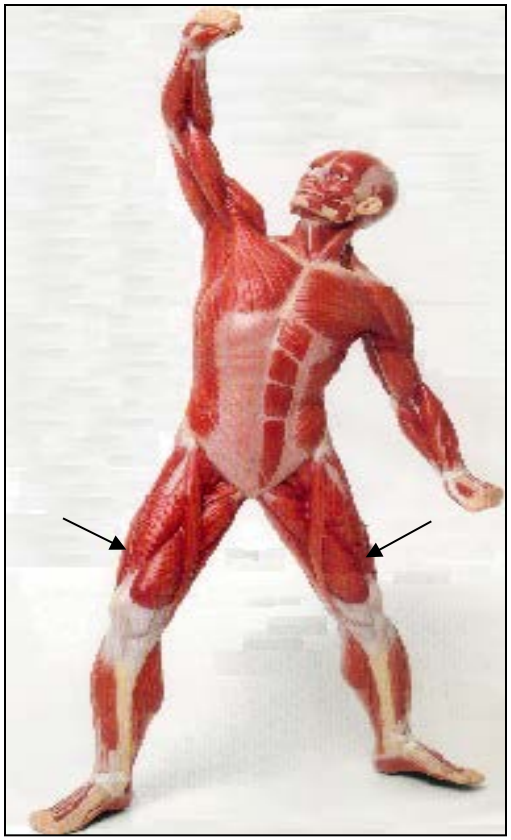
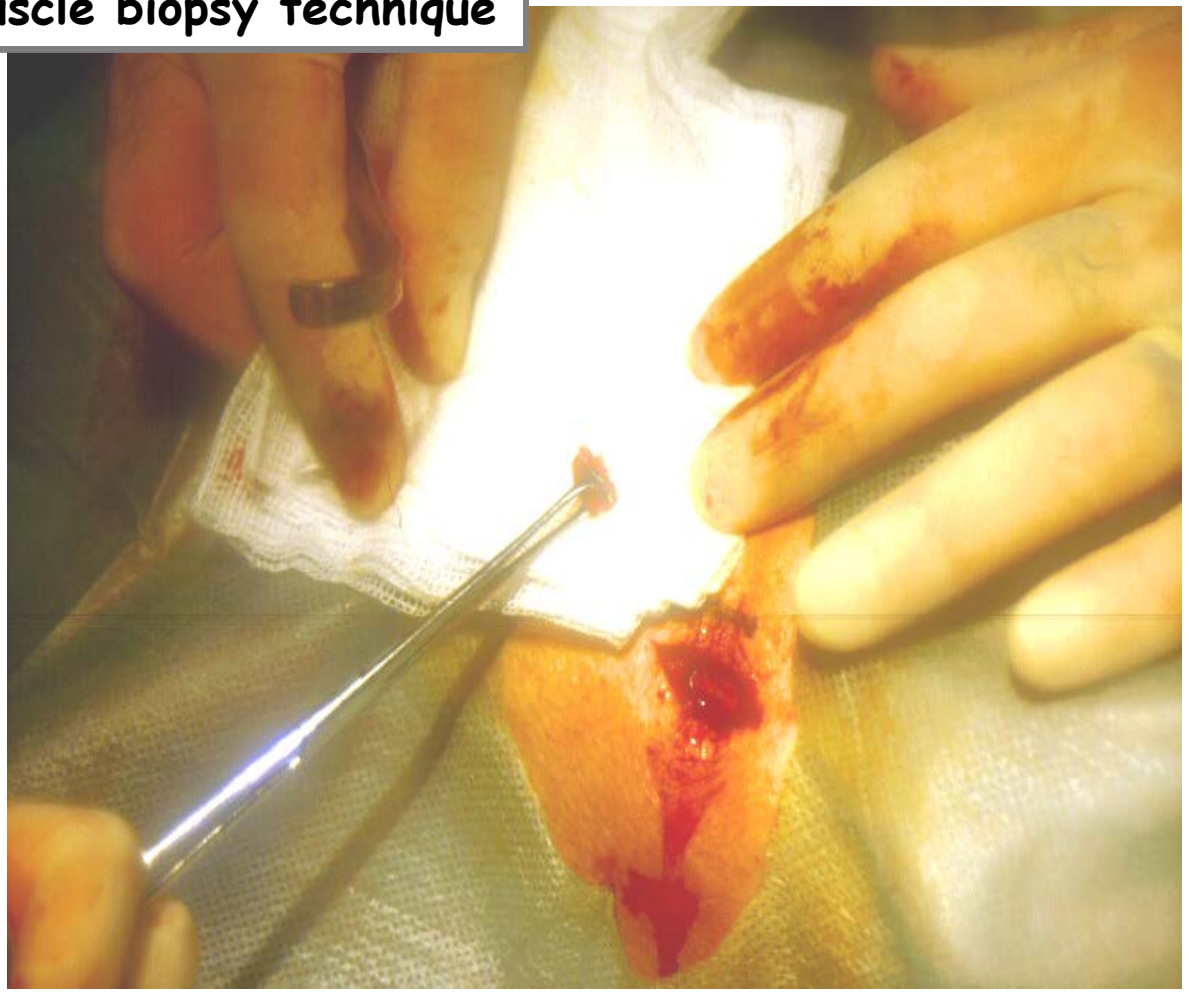
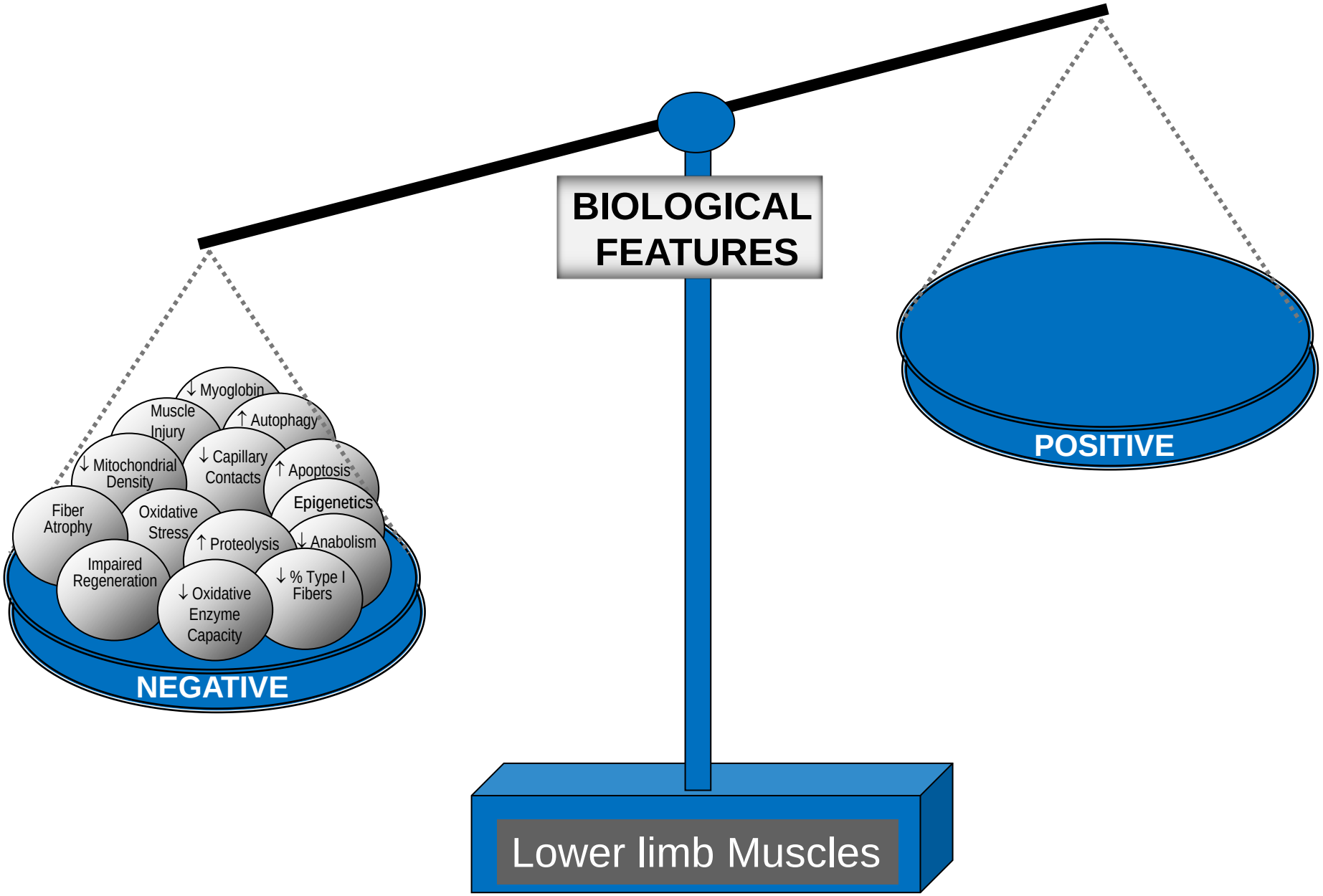
LIMB MUSCLES: VASTUS LATERALIS

Open muscle biopsy technique

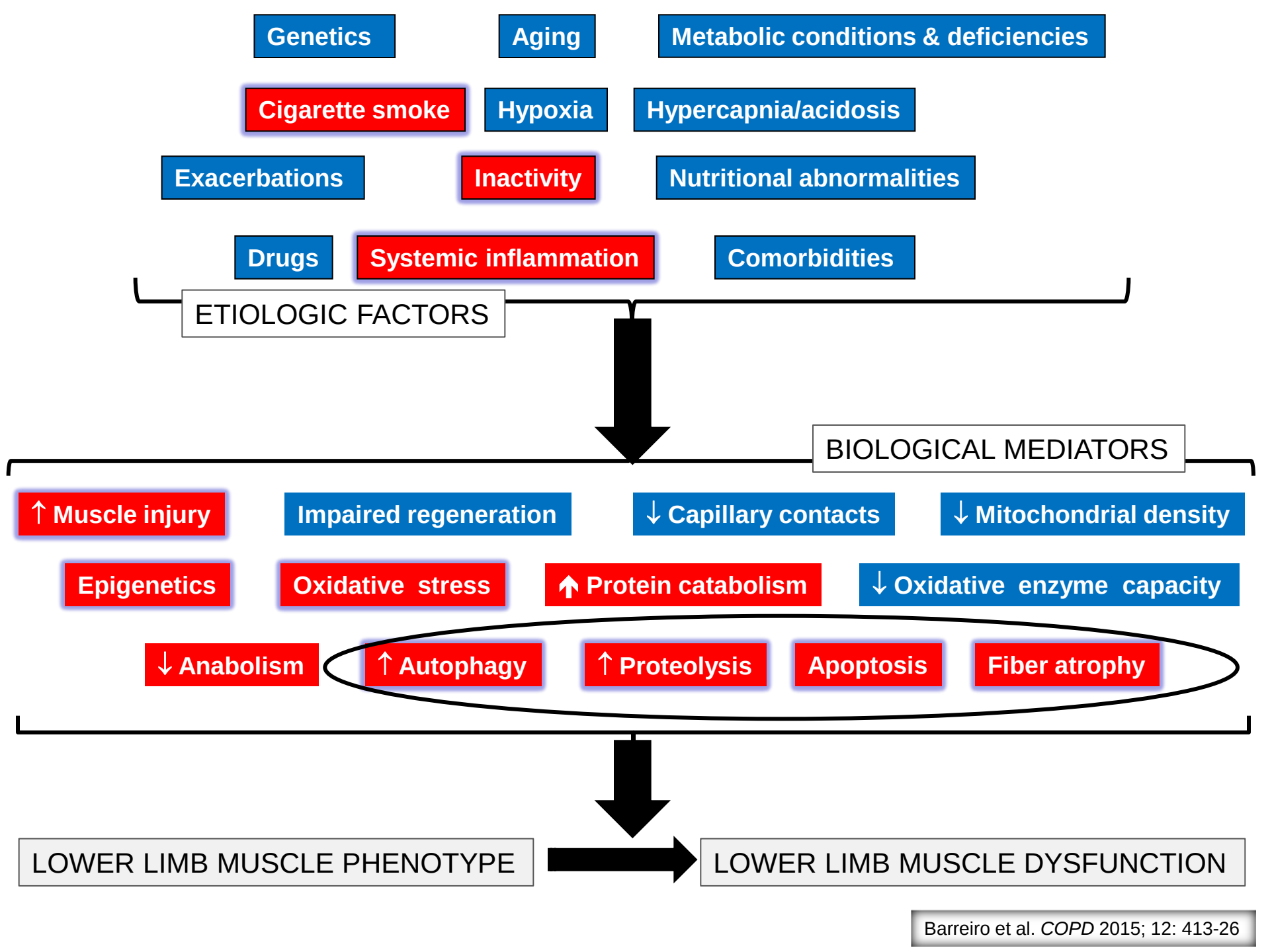




BIOLOGICAL MECHANISMS OF MUSCLE DYSFUNCTION IN COPD



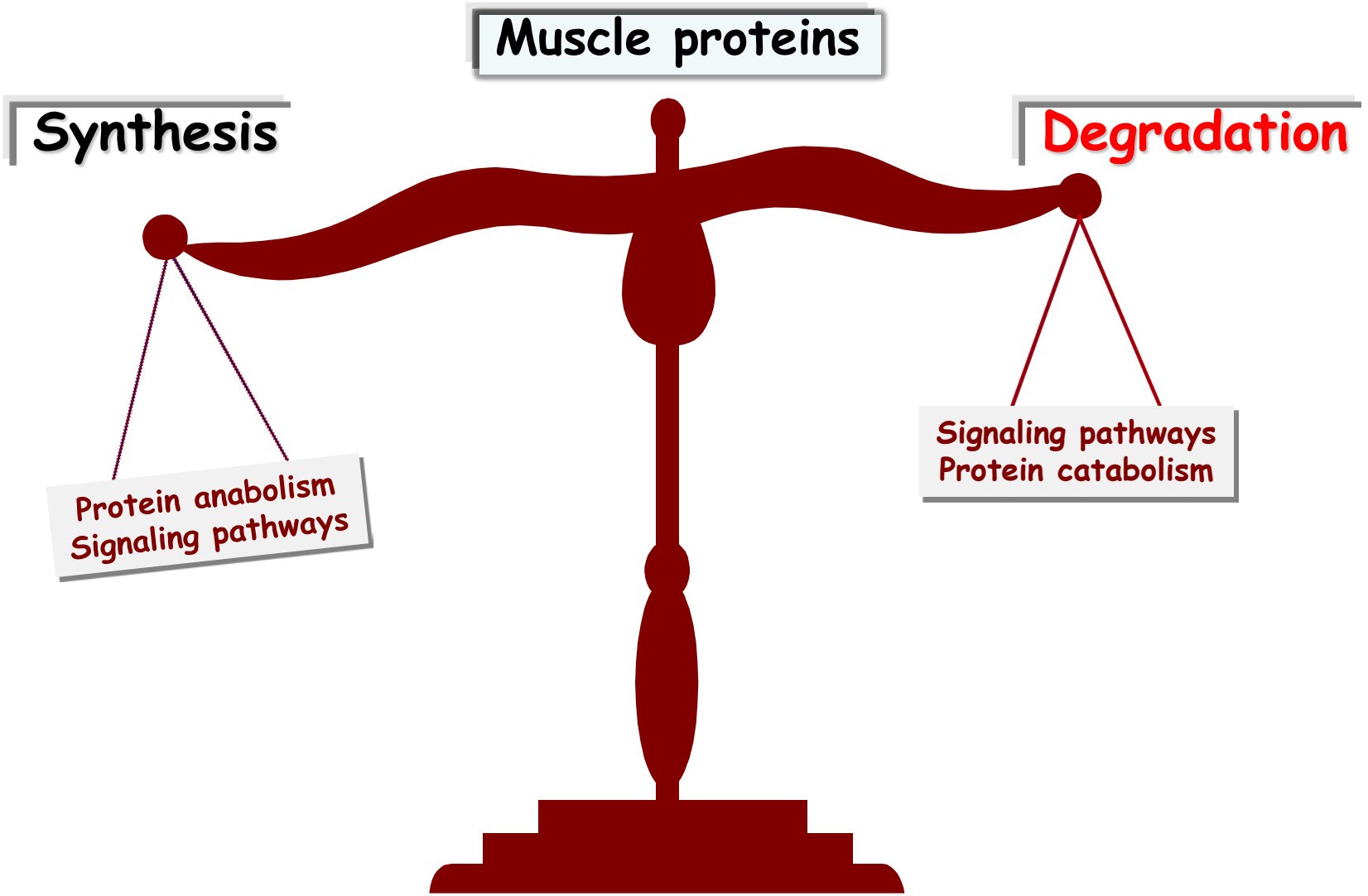
Barreiro et al. *COPD* 2015; 12: 413-26



Barreiro et al. *COPD* 2015; 12: 413-26

MUSCLE MASS LOSS ⇒ ATROPHY

IMBALANCE BETWEEN PROTEIN SYNTHESIS & DEGRADATION



MUSCLE FIBER ATROPHY

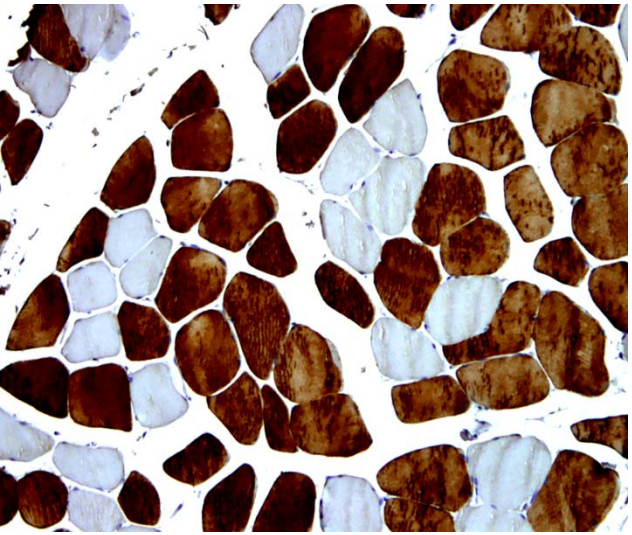
Table 3. Structural characteristics of the *vastus lateralis* muscle in severe COPD patients and healthy controls

	Control subjects	Non-wasted severe COPD patients	Muscle-wasted severe COPD patients
VASTUS LATERALIS			
Type I fibers, %	30 (5)	29 (7)	23 (6) *, †
Type II fibers, %	70 (5)	71 (7)	77 (6) *, †
Cross sectional area, type I fibers, μm^2	2581(278)	2452 (425)	2243 (514)
Cross sectional area, type II fibers, μm^2	2909 (540)	2880 (361)	2306 (533) *, †
Normal muscle, %	98.5 (0.4)	97.5 (0.7) **	97.5 (0.9) *
Abnormal muscle, %	1.5 (0.4)	2.5 (0.7) **	2.5 (0.9) *

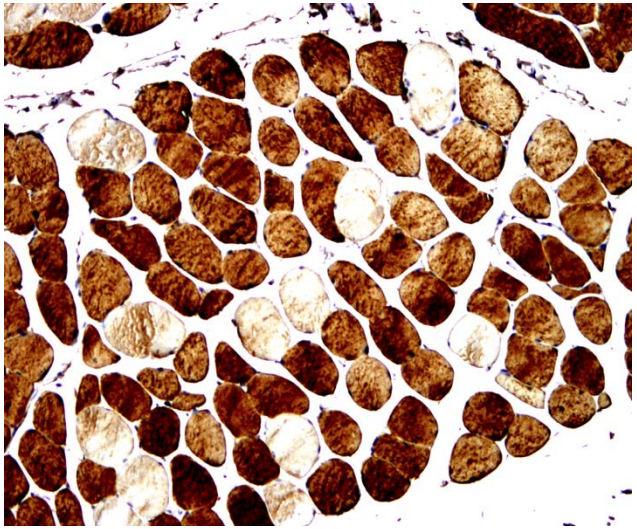
Fermoselle *et al.* *Eur Respir J* 2012, 40: 851-62

MUSCLE FIBER SIZES

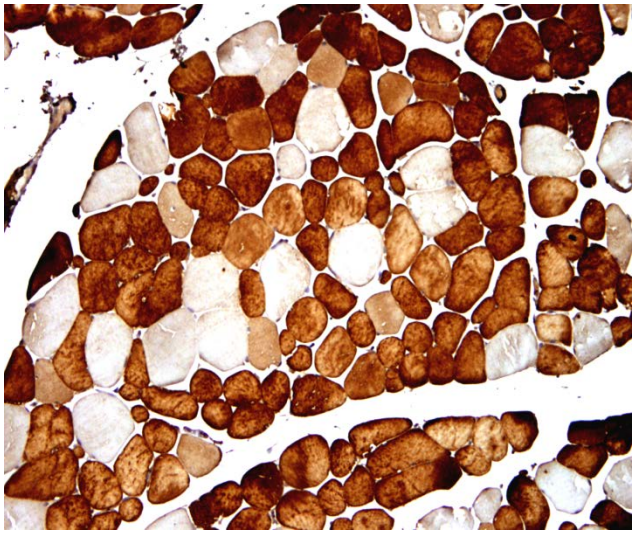
Cross-sections of muscle fibers, VL



Healthy control



LC Cachexia



COPD Cachexia

Respiratory cachexia

Puig-Vilanova *et al. Free Radic Biol Med* 2015: 79: 91-108

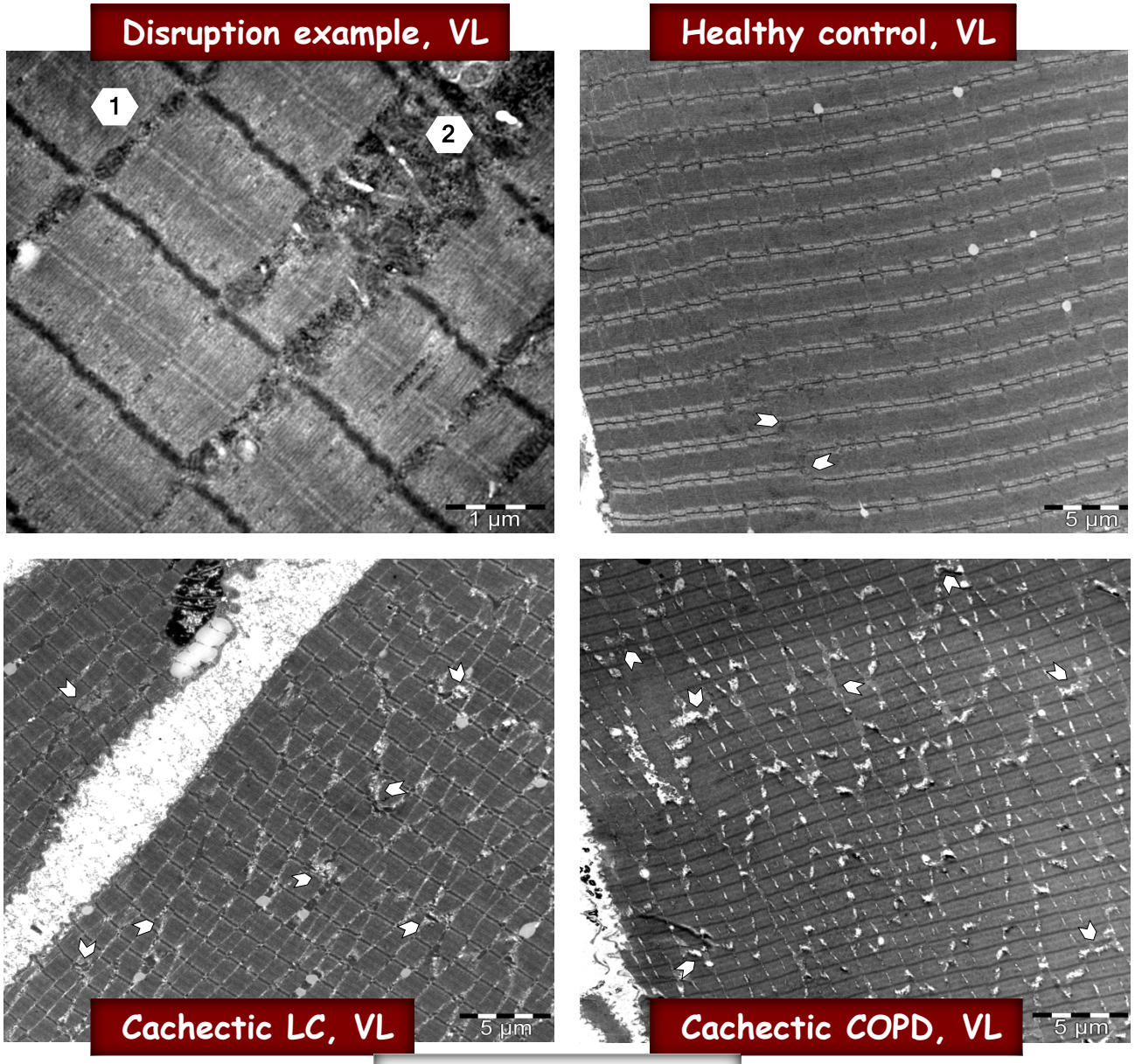
MUSCLE FIBER SIZES

Cross-sections of muscle fibers, VL — **Respiratory cachexia**

	Controls N= 10	LC Cachexia N= 10	COPD Cachexia N= 10
Muscle fiber type composition			
Type I fibers, percentages	31 (4)	28 (4)	23 (6) **
Type II fibers, percentages	69 (4)	72 (4)	77 (6) **
Type I fibers, CSA (μm^2)	2920 (458)	2639 (172)	2582 (214)
Type II fibers, CSA (μm^2)	3279 (452)	2499 (594) *	2109 (416) **
Muscle structure			
Percentage of total abnormal fraction area	1.49 (0.4)	2.39 (0.4) **	2.5 (0.9) **
Percentage of internal nuclei	0.59 (0.4)	0.67 (0.3)	0.47 (0.3)
Percentage of inflammatory cells	0.79 (0.3)	1.25 (0.5) *	1.34 (0.5) *
Percentage of other items (§)	0.11 (0.1)	0.46 (0.2) **	0.68 (0.8) *

Puig-Vilanova *et al. Free Radic Biol Med* 2015: 79: 91-108

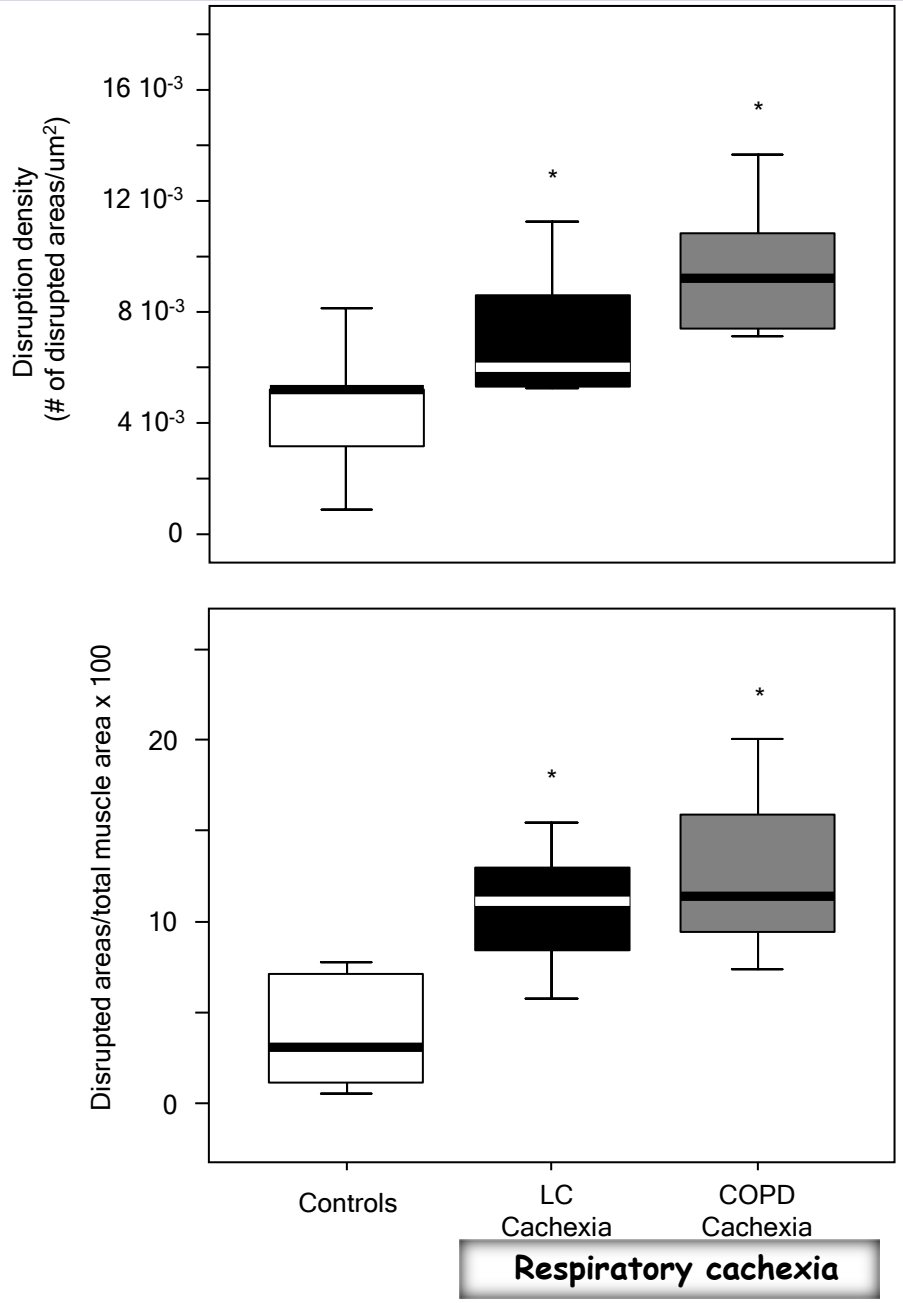
SKELETAL MUSCLE DISRUPTIONS



Respiratory cachexia

Puig-Vilanova *et al.*
Free Radic Biol Med 2015: 79: 91-108

SKELETAL MUSCLE DISRUPTIONS

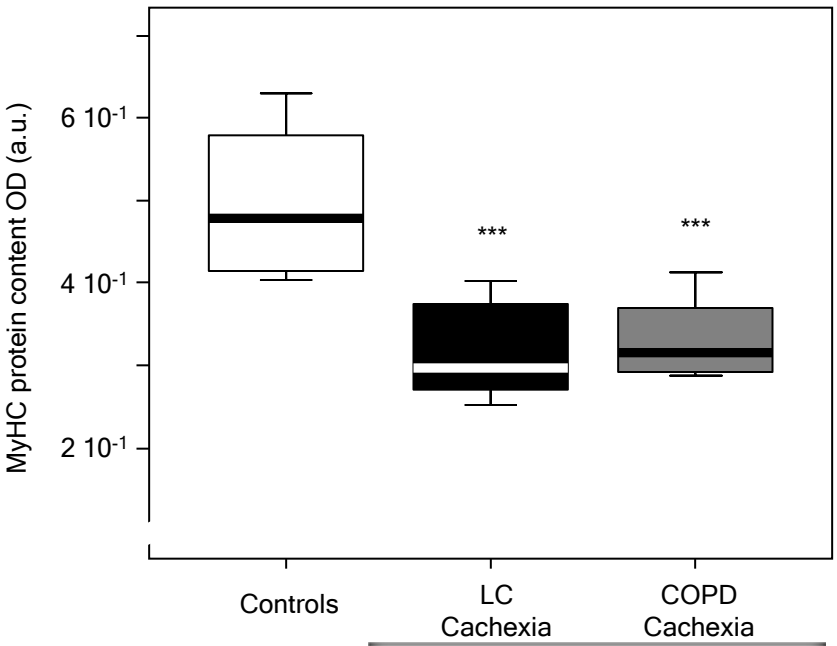


Puig-Vilanova *et al. Free Radic Biol Med* 2015: 79: 91-108

LEVELS OF SPECIFIC MUSCLE PROTEINS

Structural proteins

Myosin heavy chain, VL



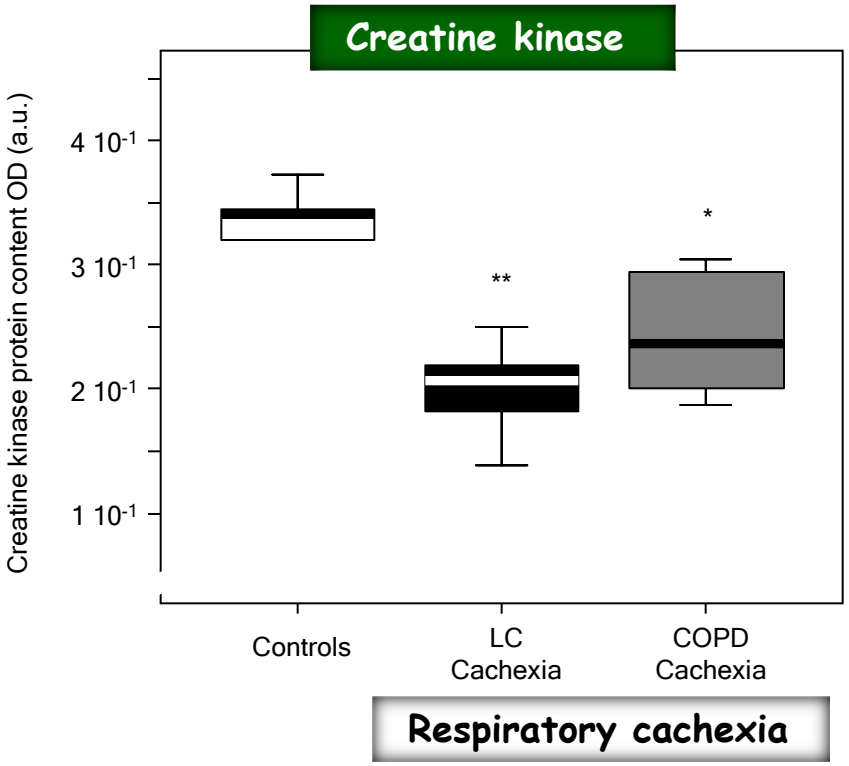
Respiratory cachexia

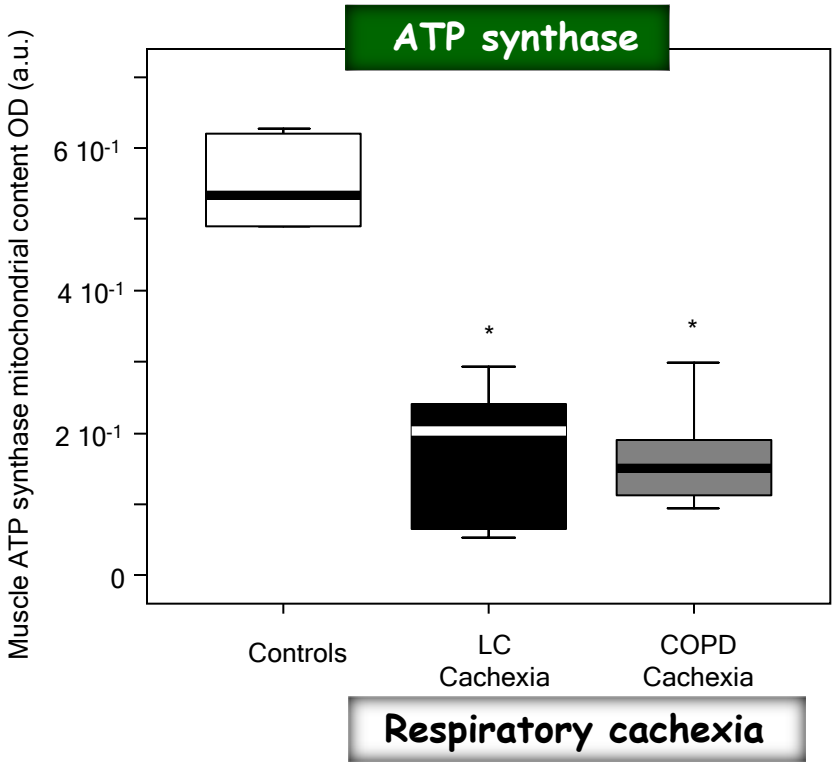
Inverse correlation between sarcomere disruptions & MyHC
r=-0.648
p=0.043

Puig-Vilanova *et al. Free Radic Biol Med* 2015: 79: 91-108

LEVELS OF MUSCLE PROTEINS

Muscle metabolic enzymes, VL

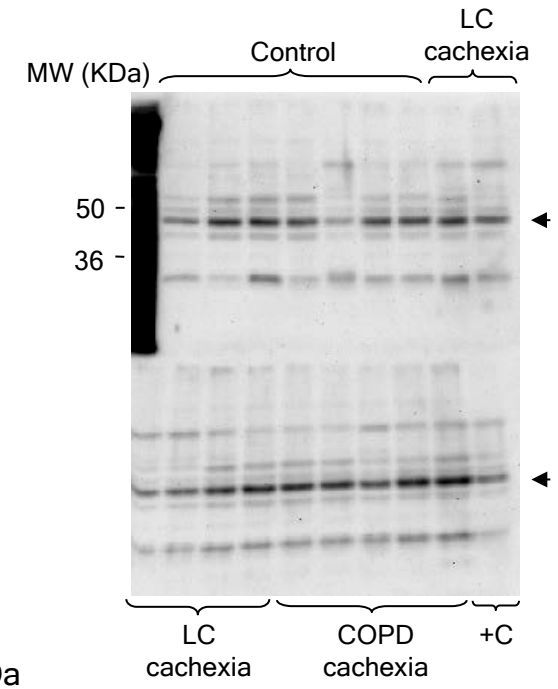




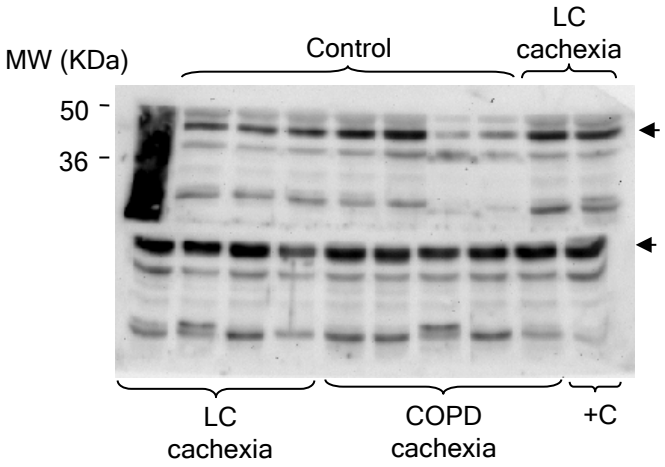
Puig-Vilanova *et al. Free Radic Biol Med* 2015: 79: 91-108

SIGNALING PATHWAYS OF MUSCLE ATROPHY

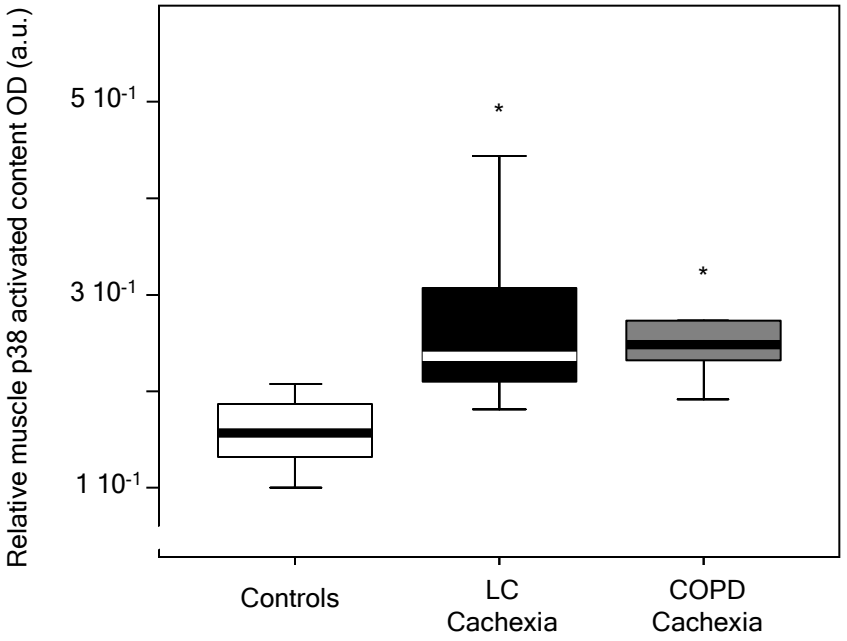
p38, 38 kDa



p-p38, 38 kDa



MAPK, P38



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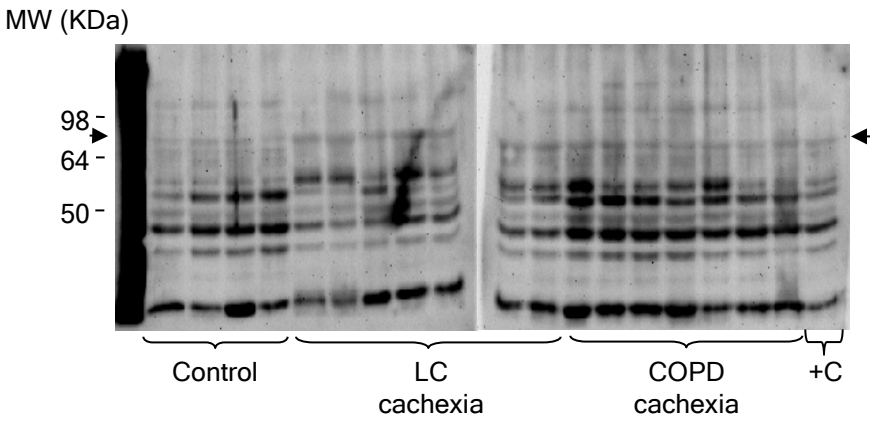
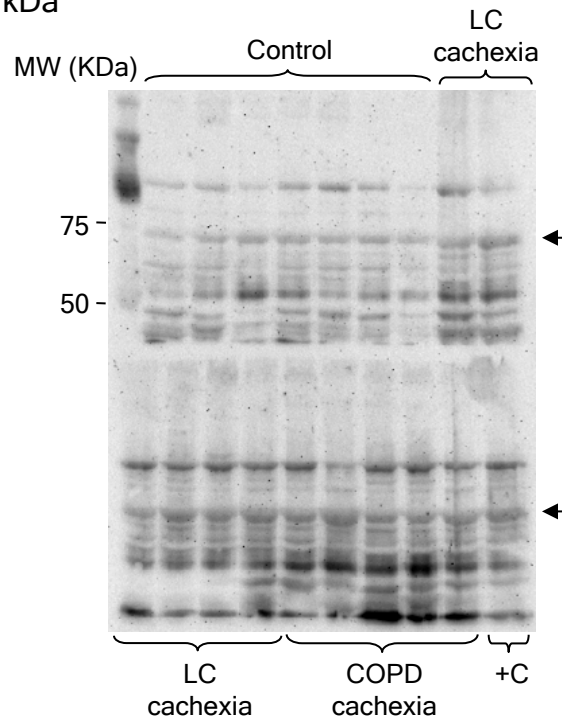
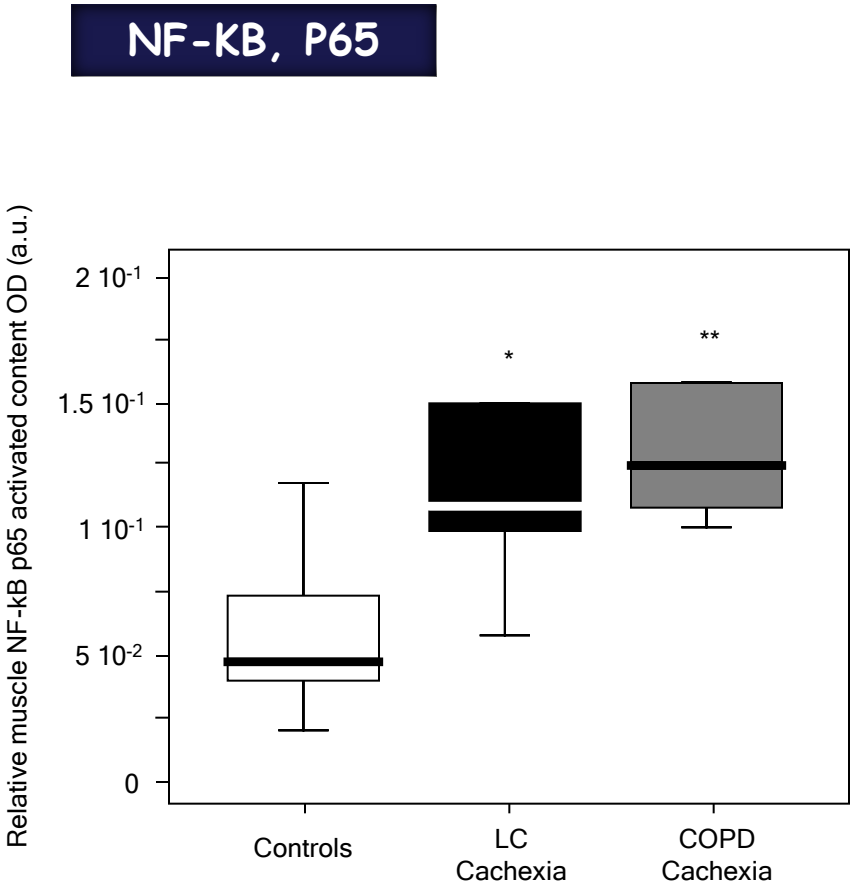
SIGNALING PATHWAYS OF MUSCLE ATROPHY

NF-kB p65, 65 kDa



p-NF-kB p65, 65 kDa

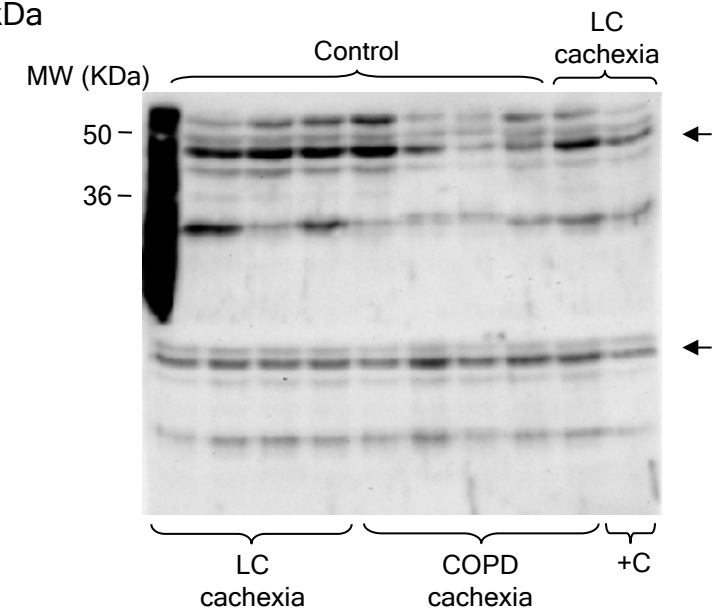




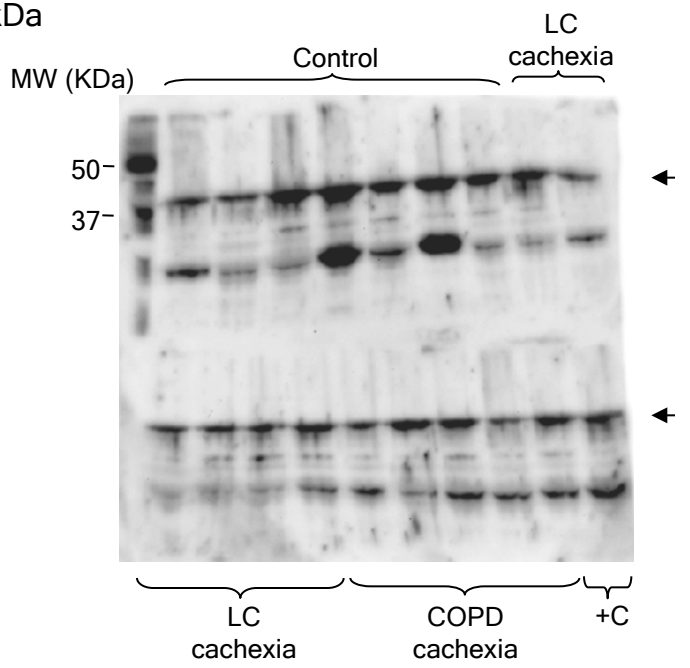
Puig-Vilanova *et al. Free Radic Biol Med* 2015: 79: 91-108

SIGNALING PATHWAYS OF MUSCLE ATROPHY

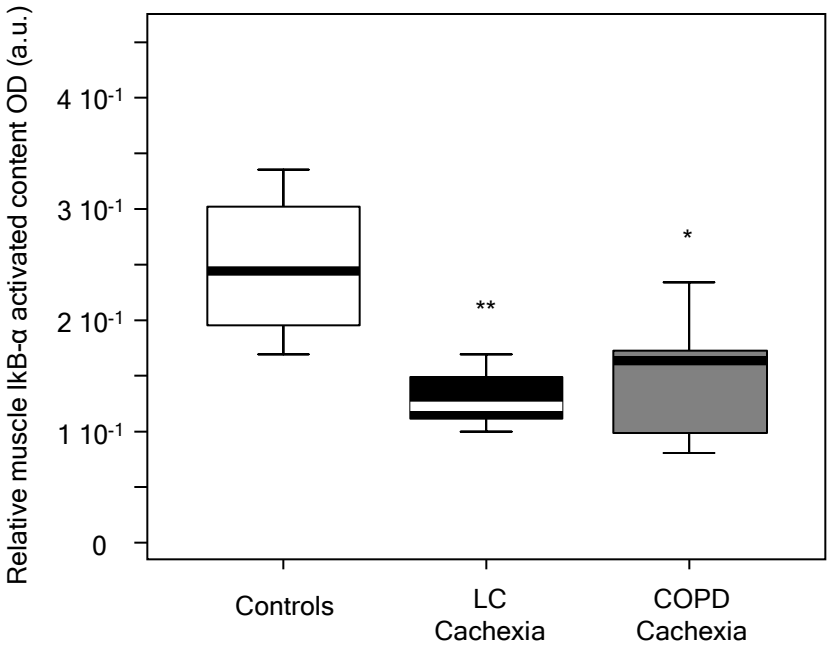
IkB-α, 37 kDa



p-IkB-α, 41 kDa



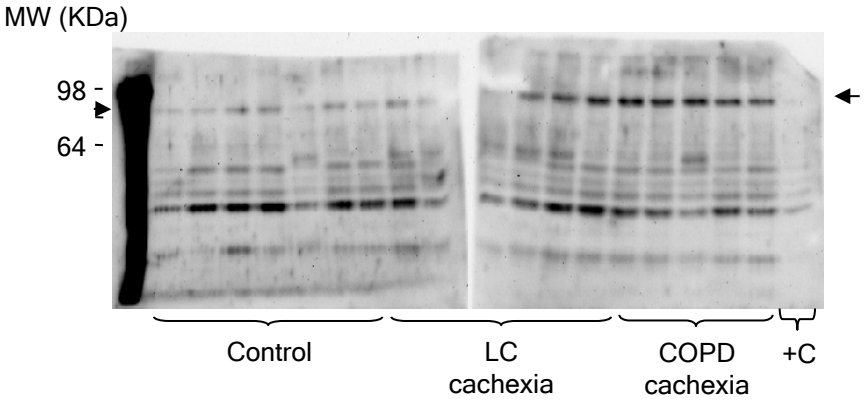
NF-KB, IkB-α



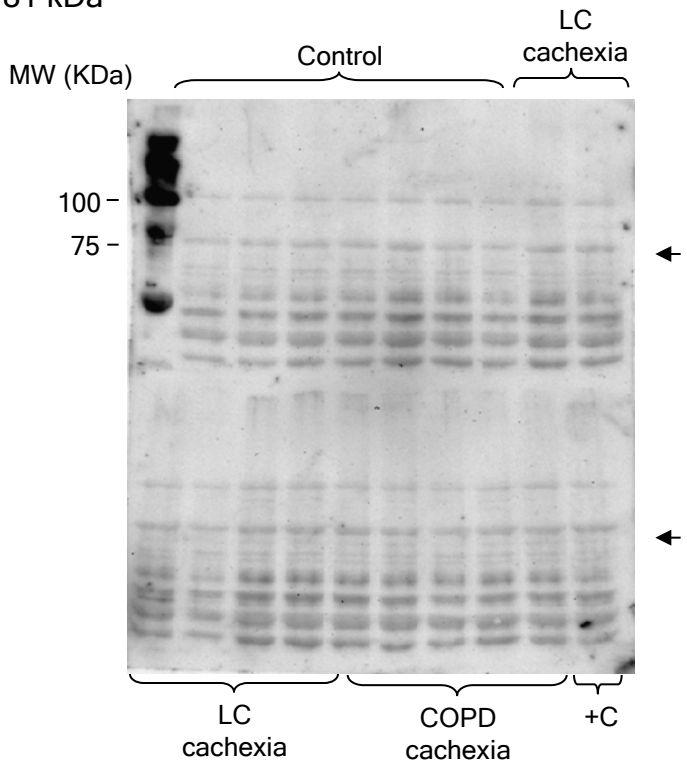
Puig-Vilanova *et al. Free Radic Biol Med* 2015: 79: 91-108

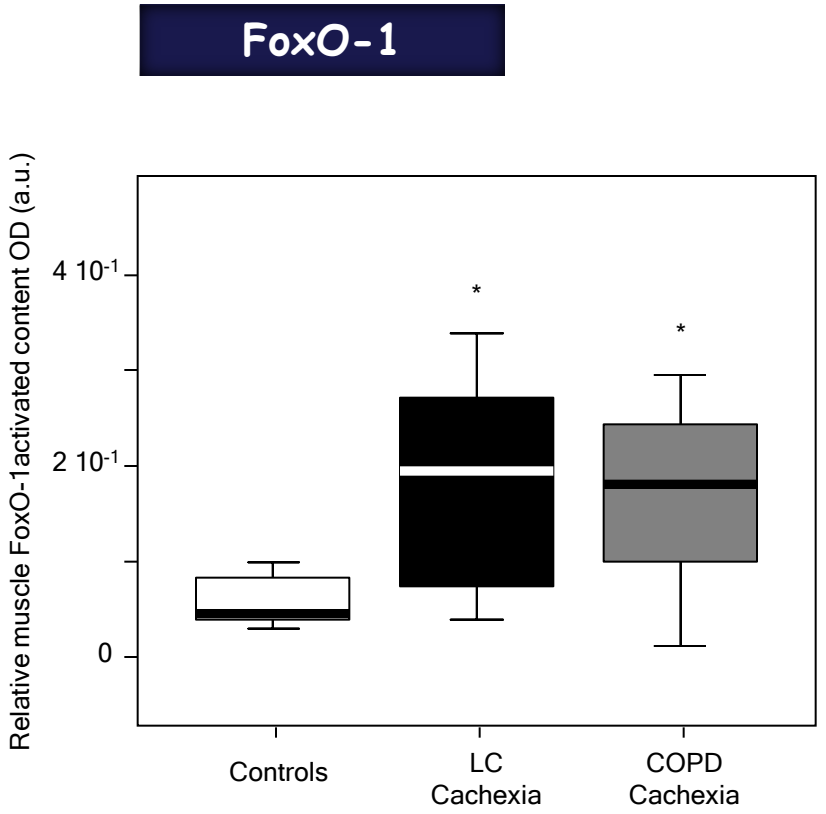
SIGNALING PATHWAYS OF MUSCLE ATROPHY

FoxO-1, 80 kDa



p-FoxO-1, 81 kDa





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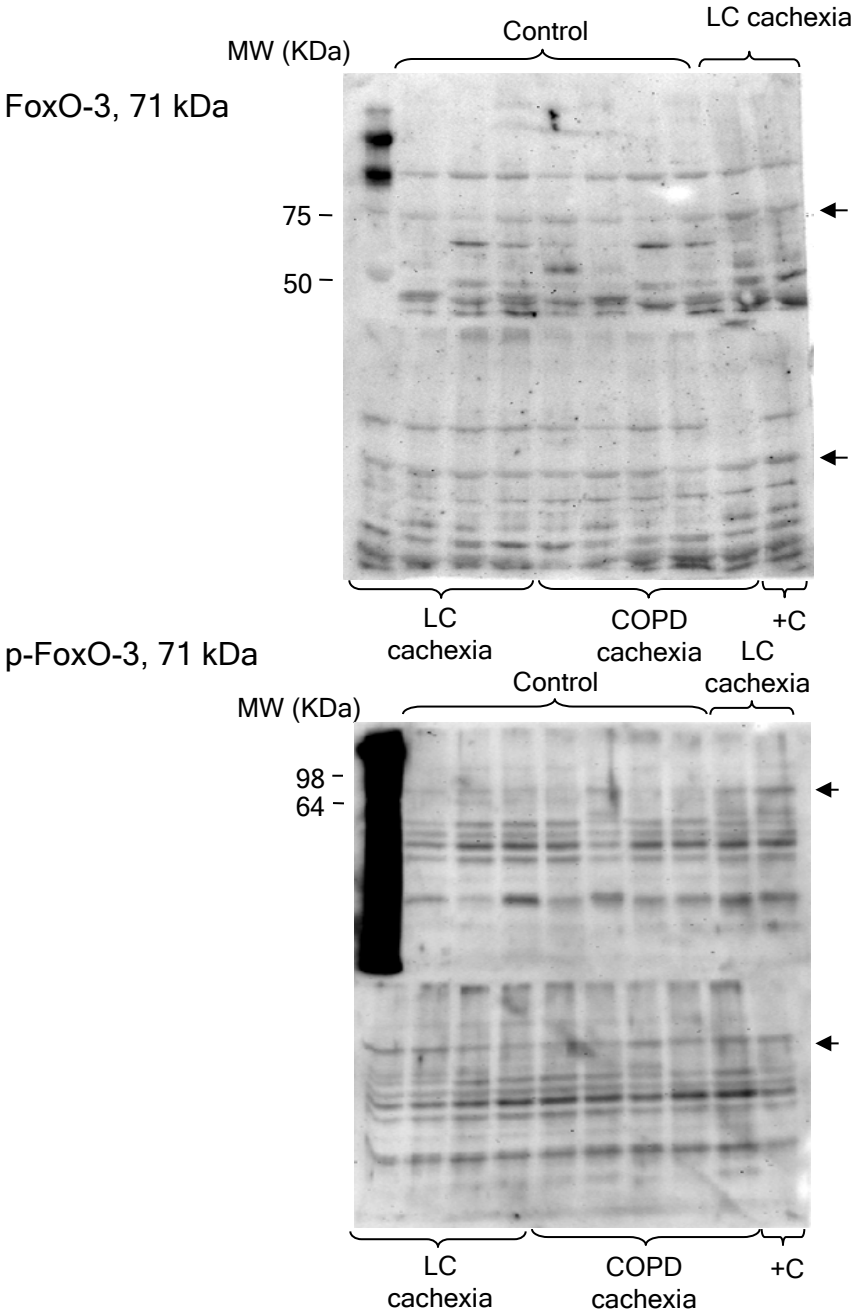
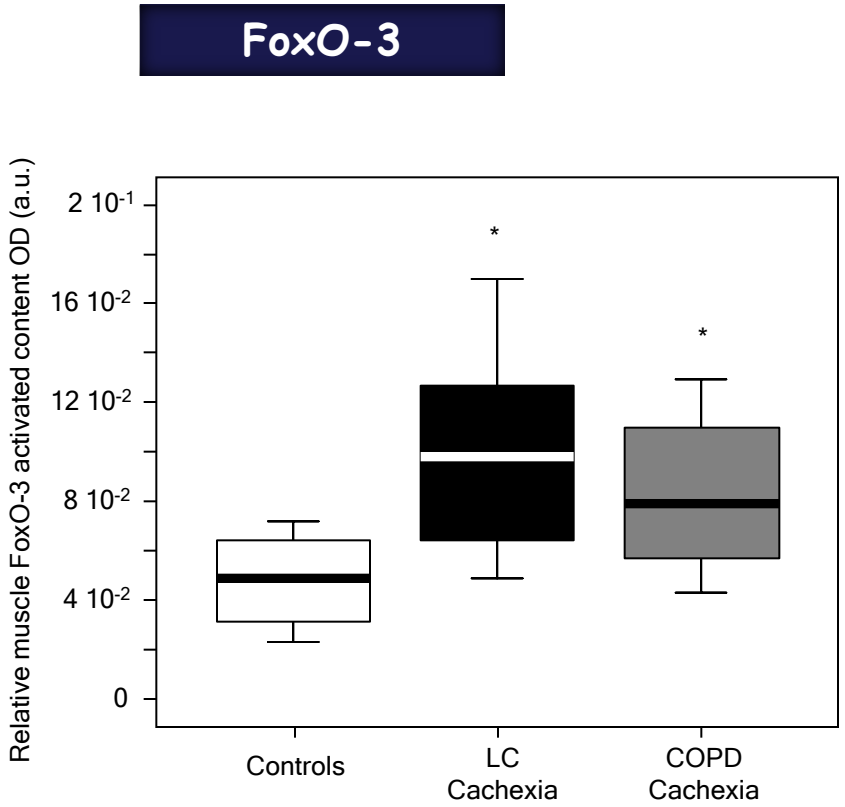
SIGNALING PATHWAYS OF MUSCLE ATROPHY





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Enhanced muscle proteolysis

Vastus lateralis, stable COPD patients:

Doucet *et al*. *Am J Respir Crit Care Med* 2007

Plant *et al*. *Am J Respir Cell Mol Biol* 2010

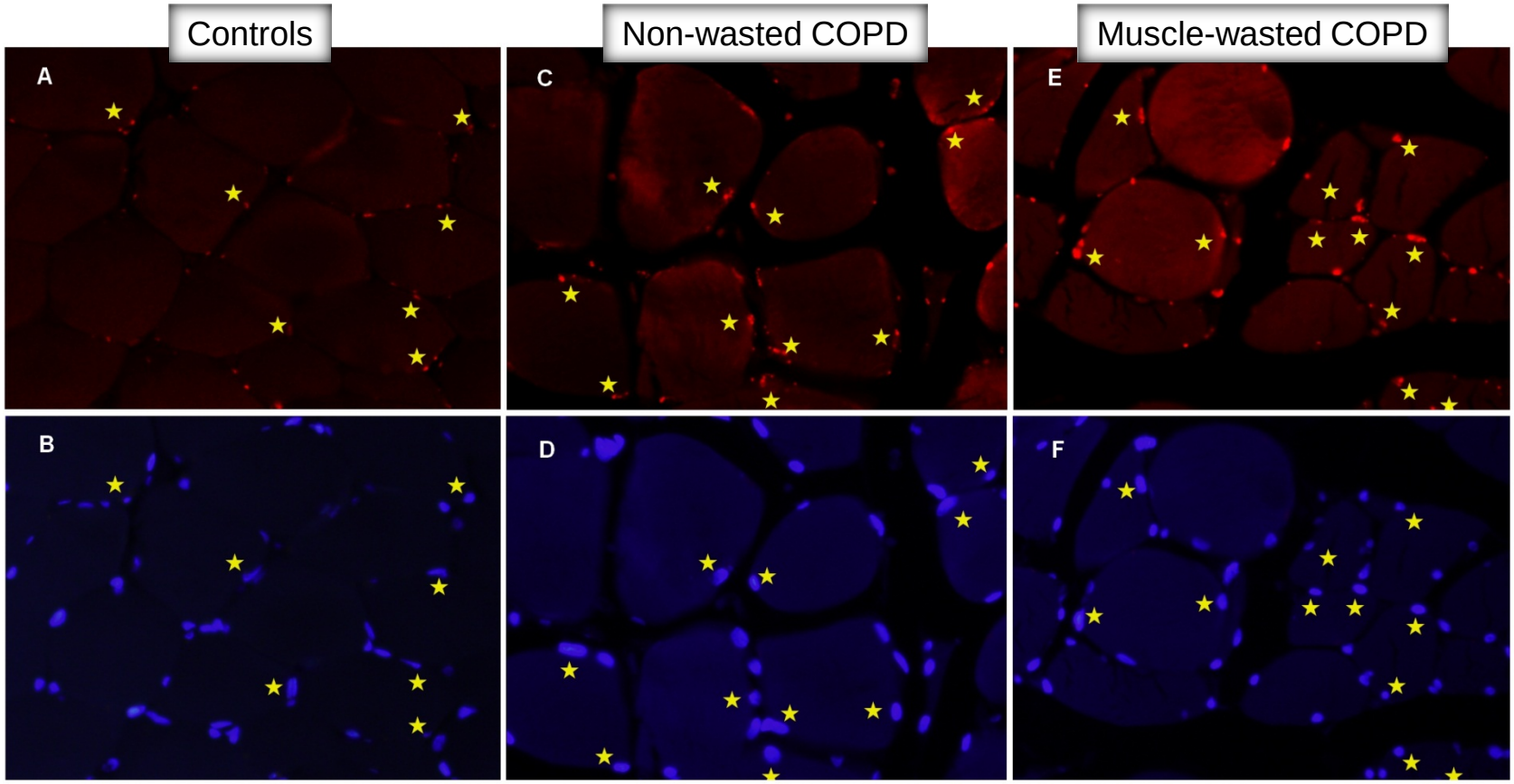
Fermoselle *et al. Eur Respir J* 2012, 40: 851-62

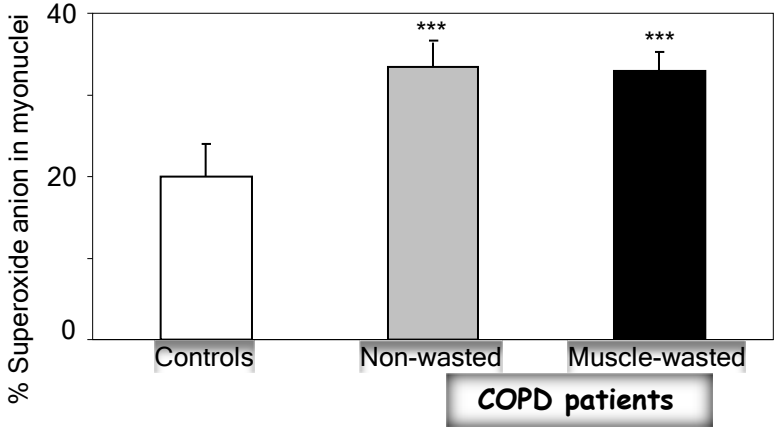
Several proteolytic mechanisms, VL

Vastus lateralis, COPD patients during exacerbations:

Crul *et al*. *Cell Physiol Biochem* 2010

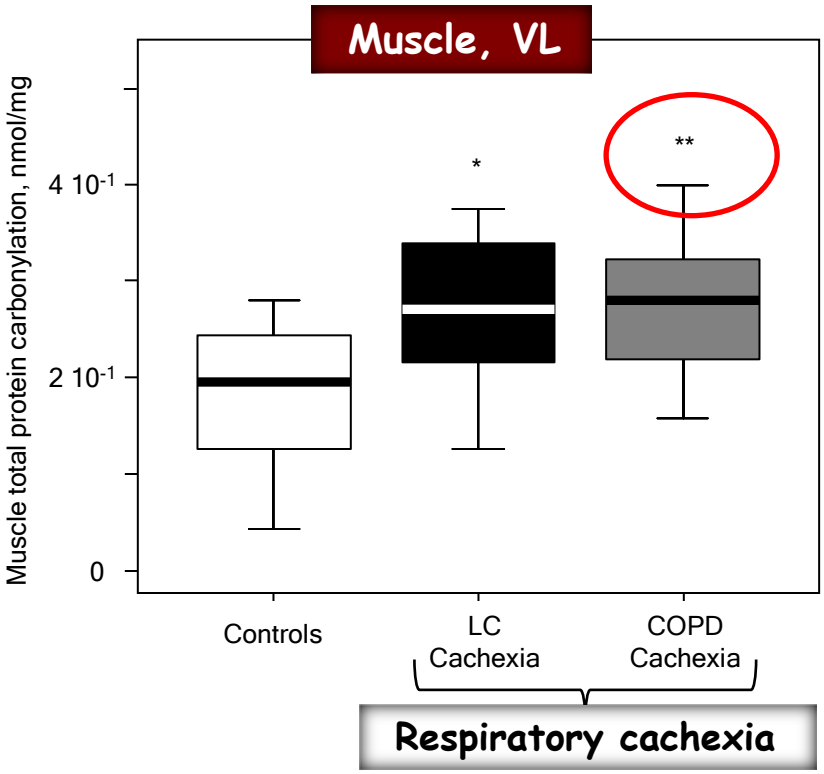
SUPEROXIDE ANION IN THE MYONUCLEI

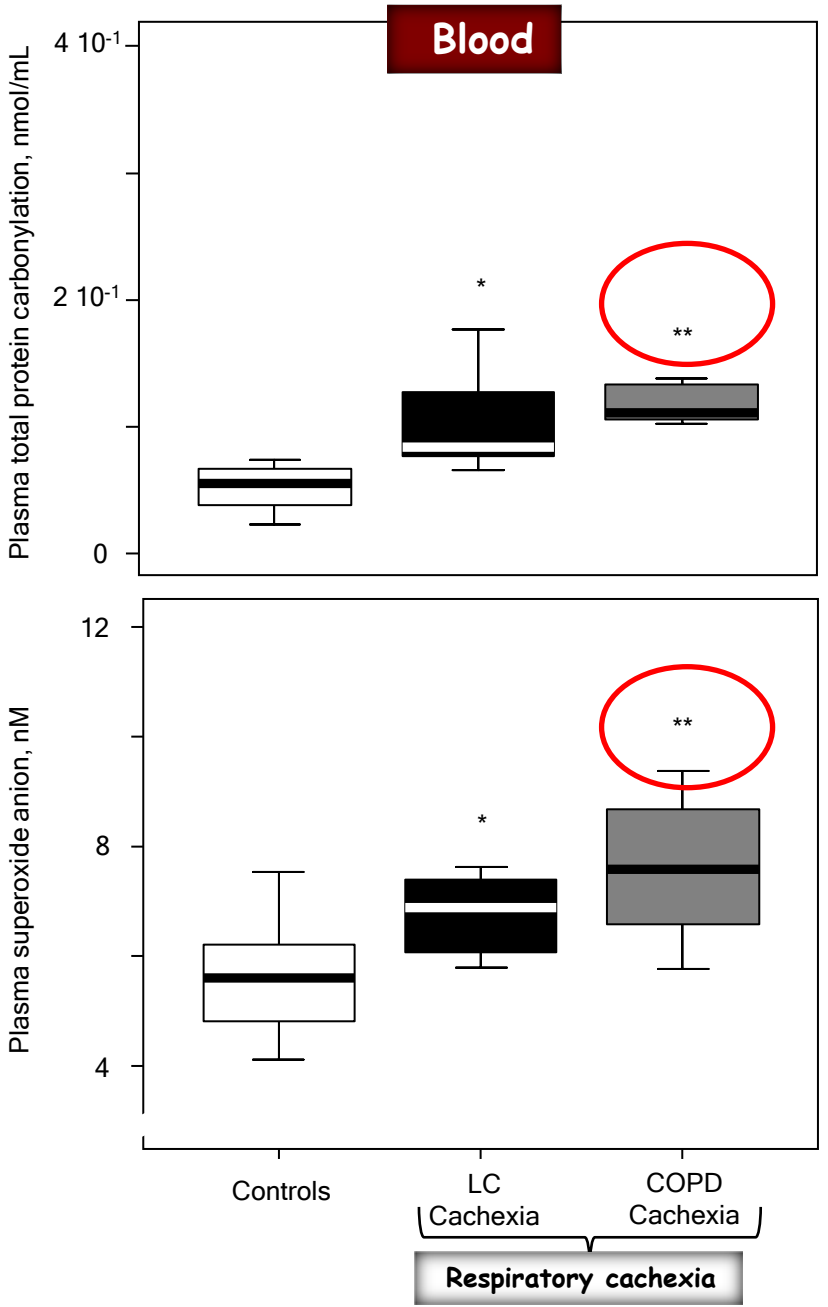




Fermoselle *et al. Eur Respir J* 2012, 40: 851-62

OXIDATIVE STRESS: MUSCLE & BLOOD

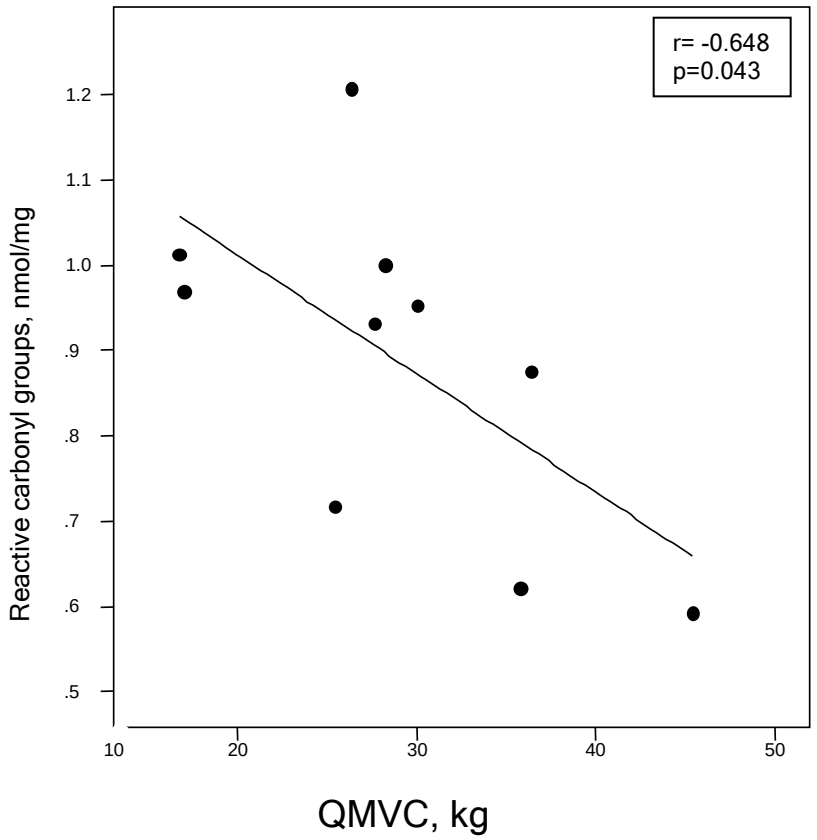


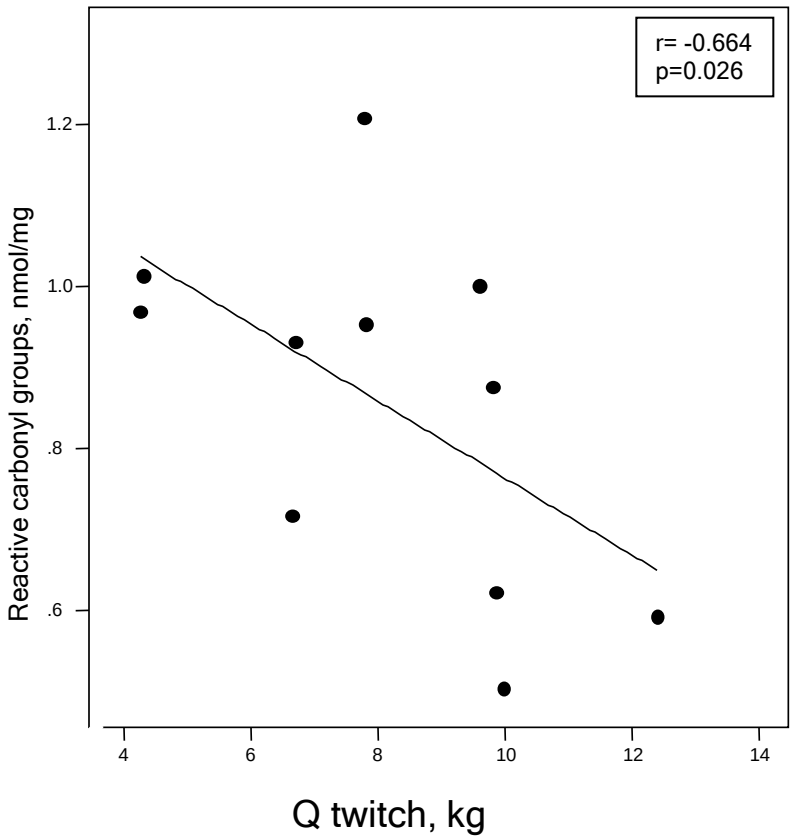


Puig-Vilanova *et al. Free Radic Biol Med* 2015: 79: 91-108

OXIDATIVE STRESS: CLINICAL IMPLICATIONS

Muscle protein oxidation – Quadriceps muscle force



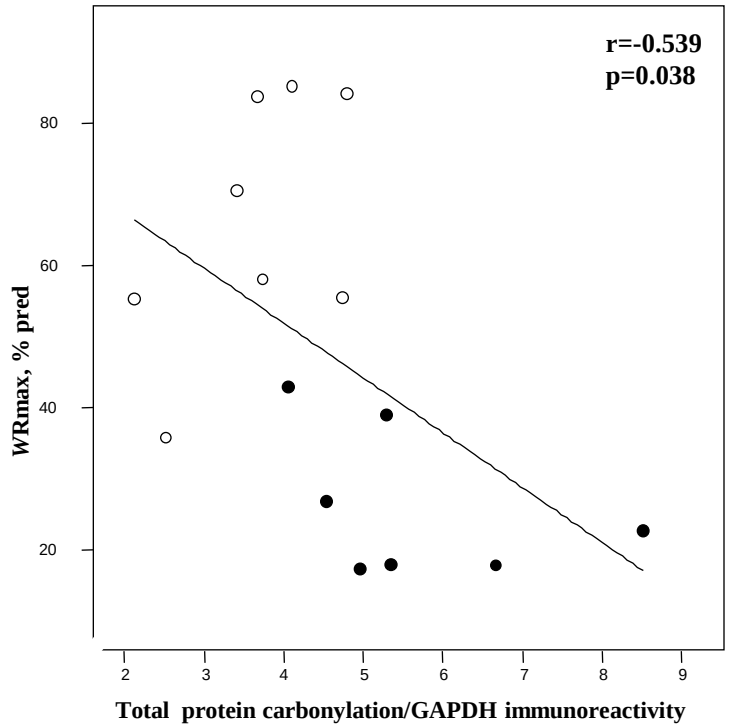


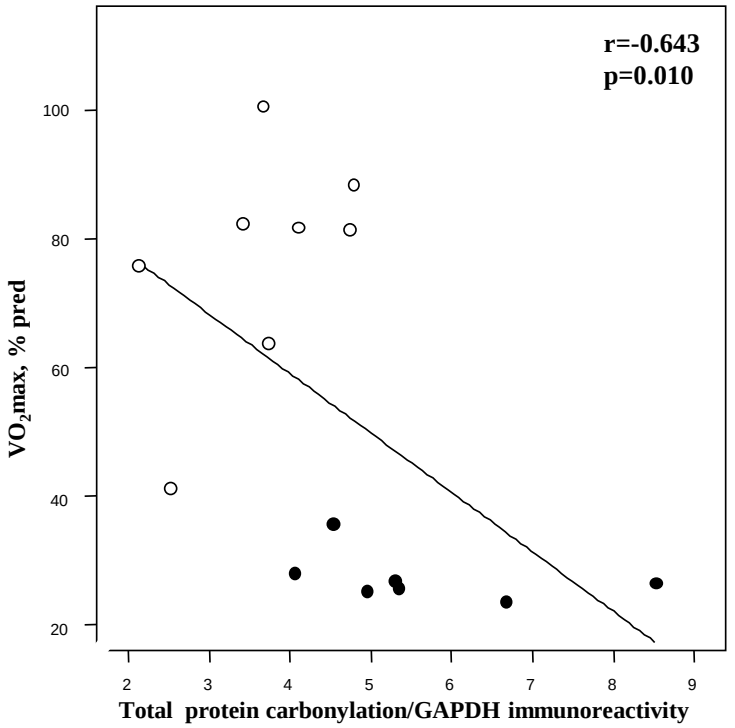
Quadriceps strength: voluntary & involuntary maneuvers

E. Barreiro *et al. Thorax* 2008; 63: 100-107

OXIDATIVE STRESS: CLINICAL IMPLICATIONS

Muscle protein oxidation – Exercise capacity





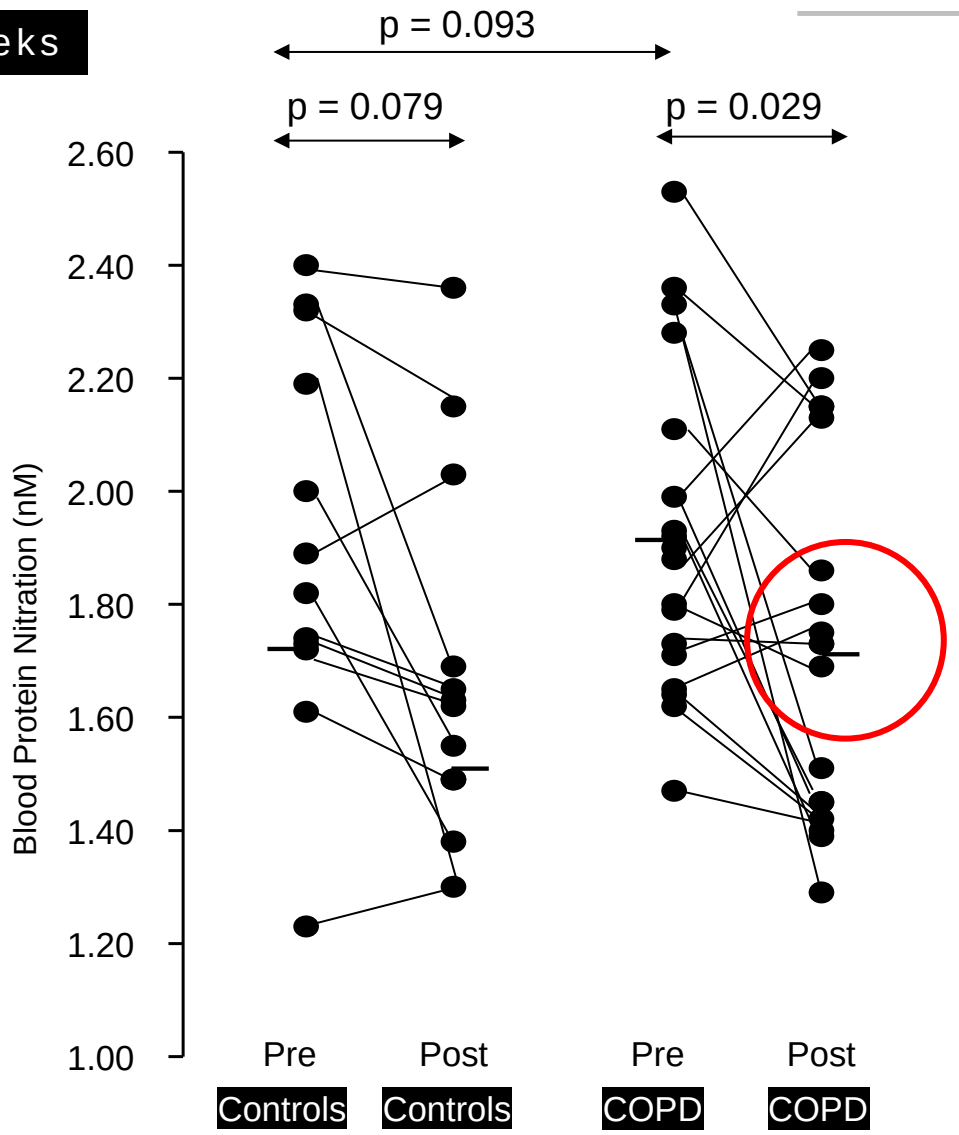
Cycloergometry

E. Barreiro *et al. Thorax* 2009; 64: 13-19

Endurance Exercise Training
Protein tyrosine nitration

Blood, COPD patients

After exercise training, 8 weeks

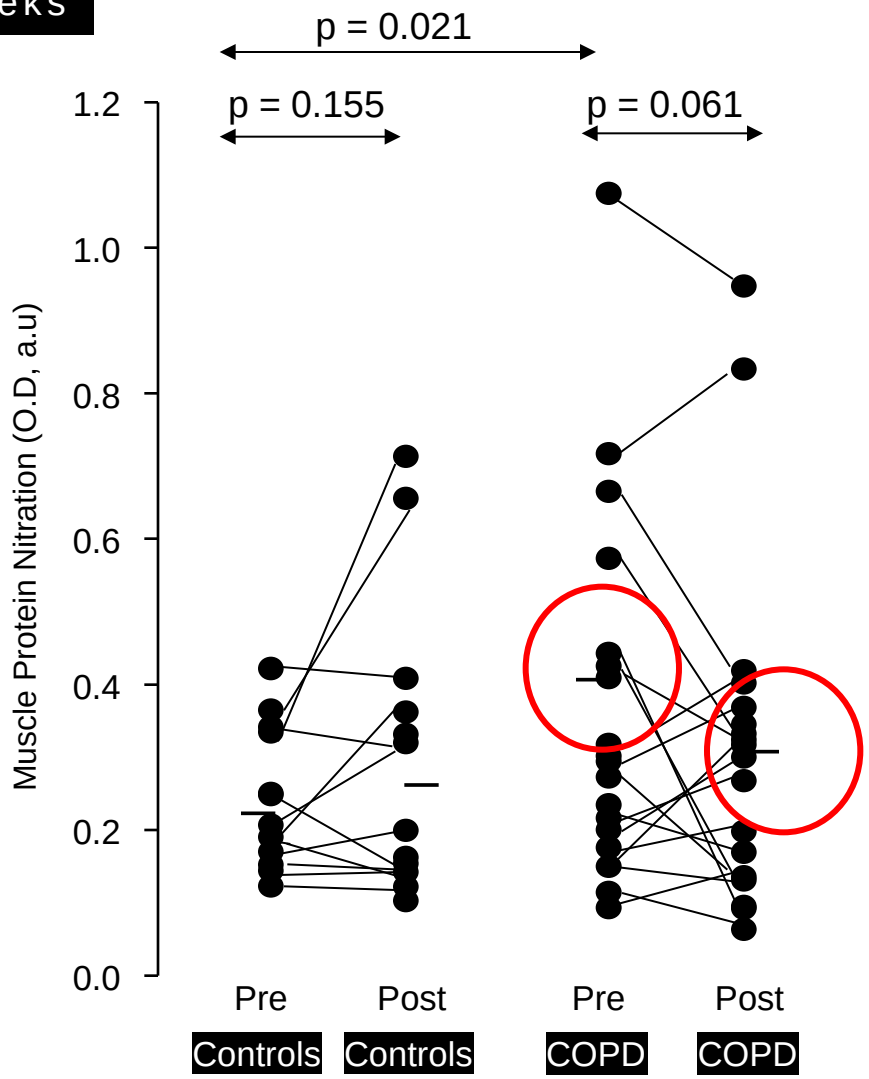


Rodriguez *et al. Free Radic Biol Med* 2012; 52: 88-94.

Endurance Exercise Training
Muscle protein tyrosine nitration

VL, COPD patients

After exercise training, 8 weeks

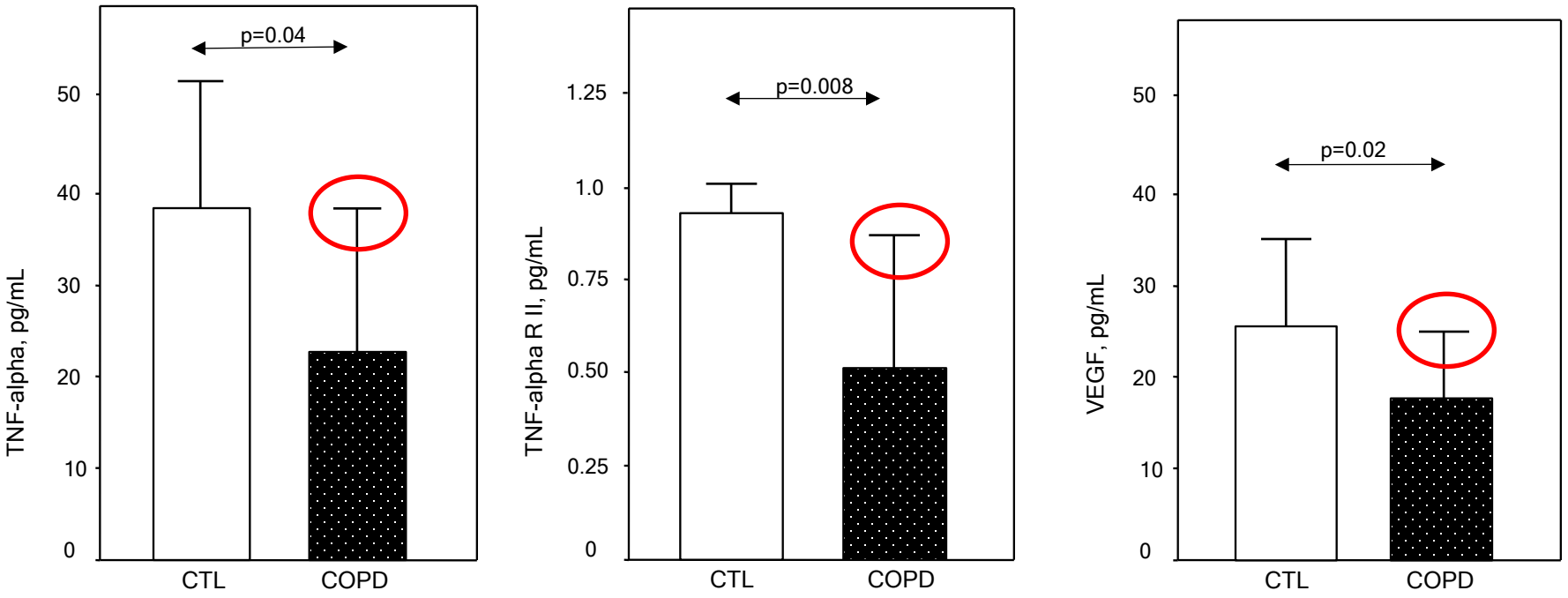


Rodriguez *et al. Free Radic Biol Med* 2012; 52: 88-94.

Role of local inflammation in COPD ?

⇓ Cytokines in the *vastus lateralis* of severe COPD patients at baseline

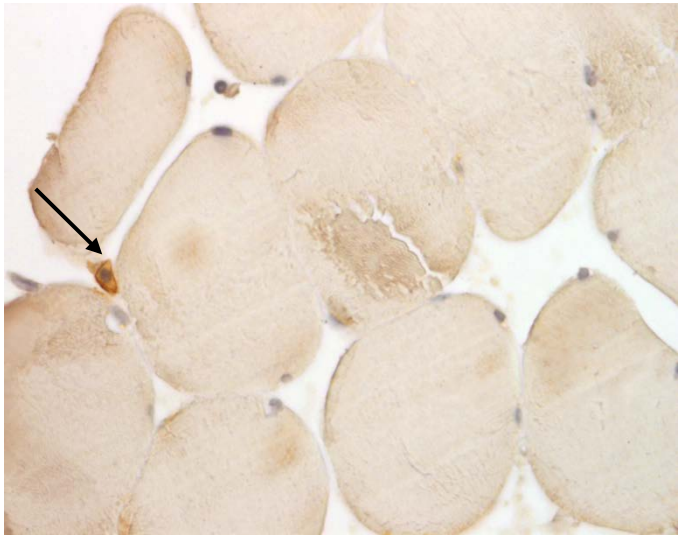
Vastus lateralis



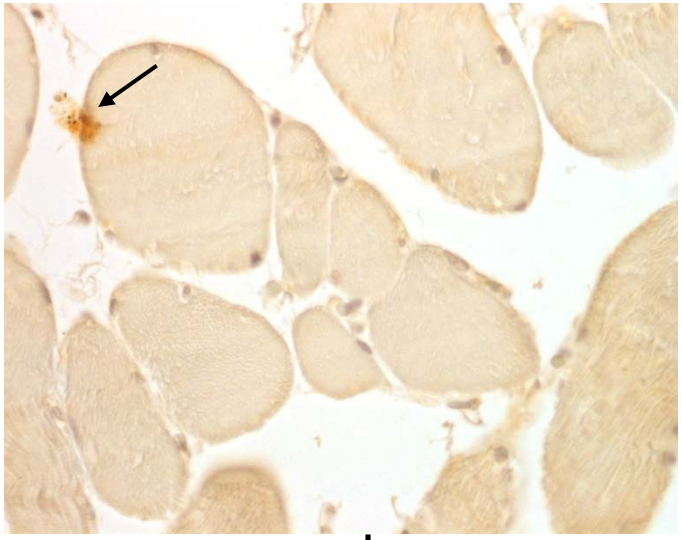
E. Barreiro *et al. Thorax* 2008; 63: 100-107

Cellular inflammation

Patients with COPD, Vastus lateralis



leucocyte



macrophage

Barreiro *et al. J Appl Physiol* 2011; 111: 808-817

Cellular inflammation

Patients with COPD, Vastus lateralis

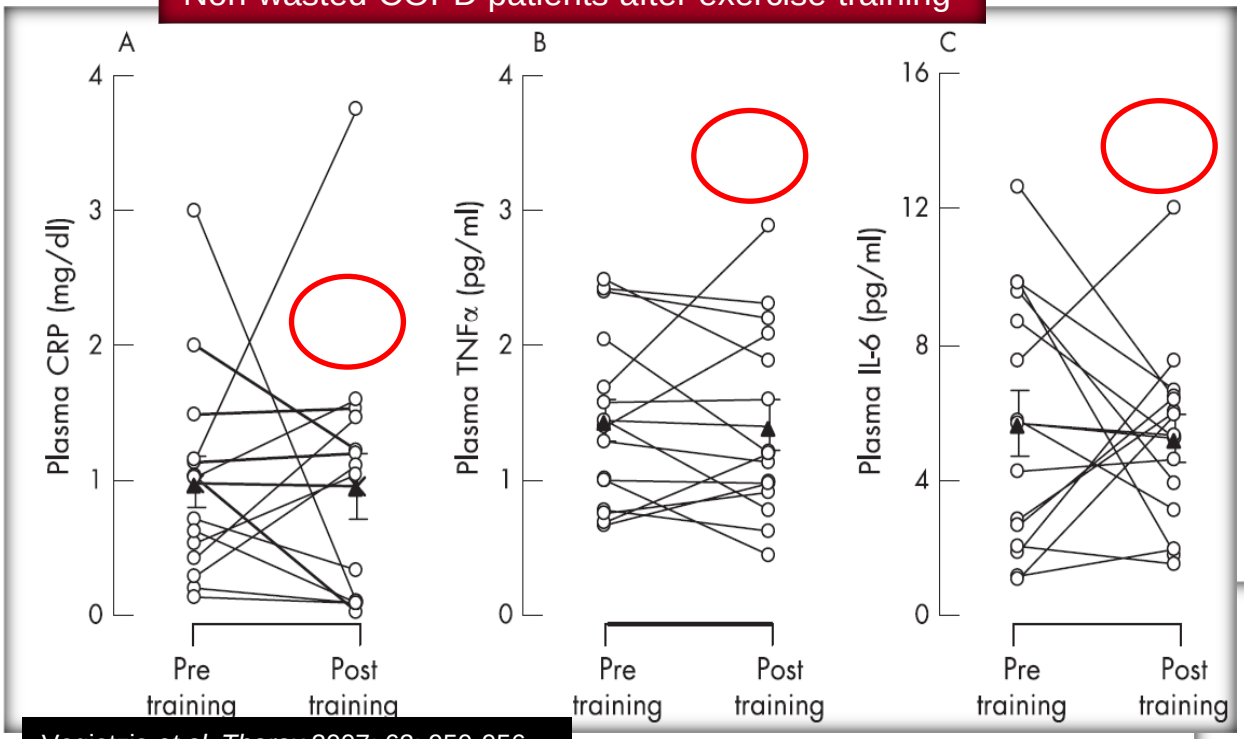
Table 4. Muscle inflammation in the human study subjects

	Control subjects n=10	Smokers n=9	COPD n=10
IL-6, pg/ml	0.29 (0.19)	0.23 (0.12)	0.32 (0.30)
TNF-alpha, pg/ml	1.64 (0.37)	1.72 (0.33)	1.64 (0.24)
Total inflammatory cells, cells/mm^2	0.99 (0.60)	0.88 (0.51)	2.57 (1.70) *, †

Barreiro *et al*. *Am J Respir Crit Care Med* 2010; 182: 477-488.

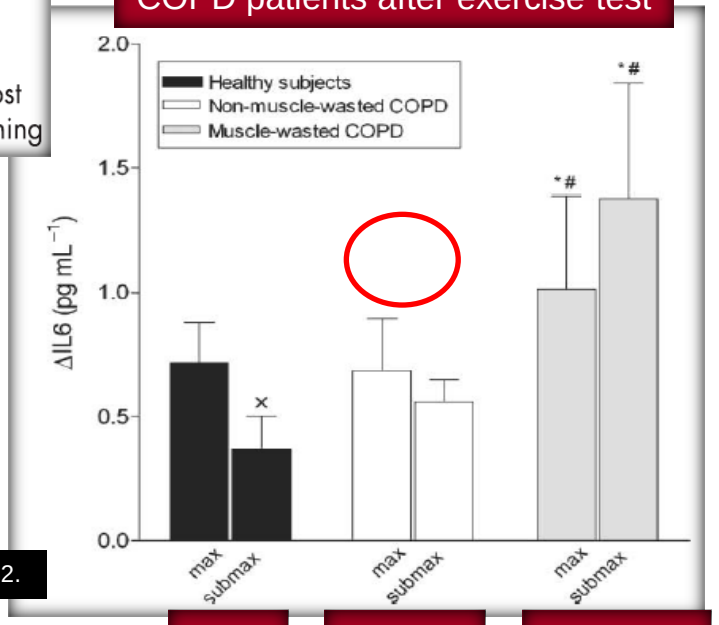
Systemic inflammation in COPD patients & muscle mass

Non-wasted COPD patients after exercise training



Vogiatzis *et al*. *Thorax* 2007; 62: 950-956.

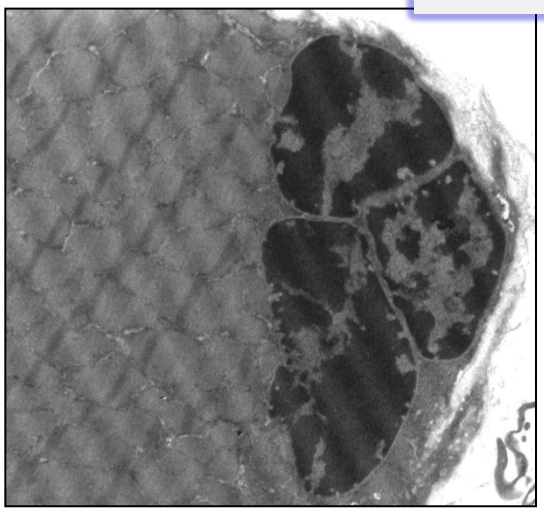
COPD patients after exercise test



Van Helvoort *et al*. Med Sci Sports Exerc 2006; 38: 1543-52.

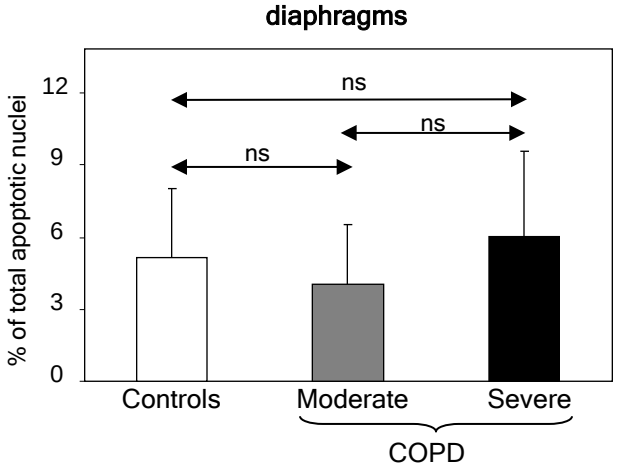
APOPTOSIS, ELECTRON MICROSCOPY

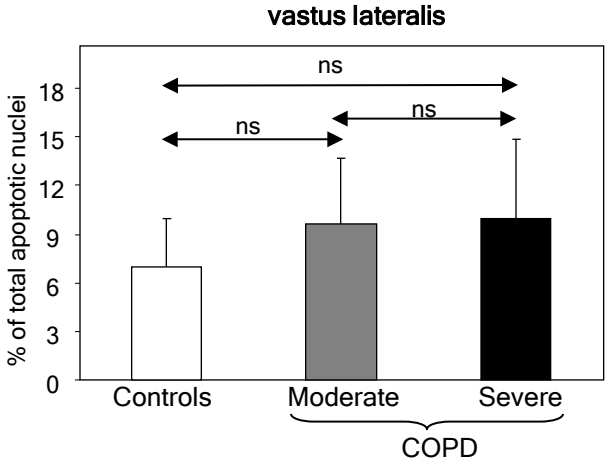
Severe COPD patient



Early apoptosis

Late apoptosis

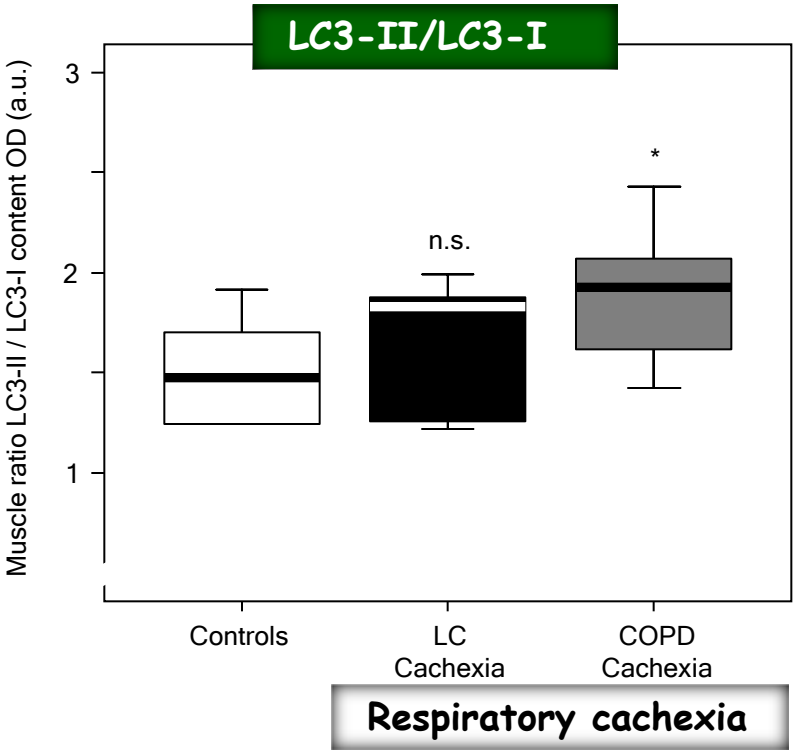


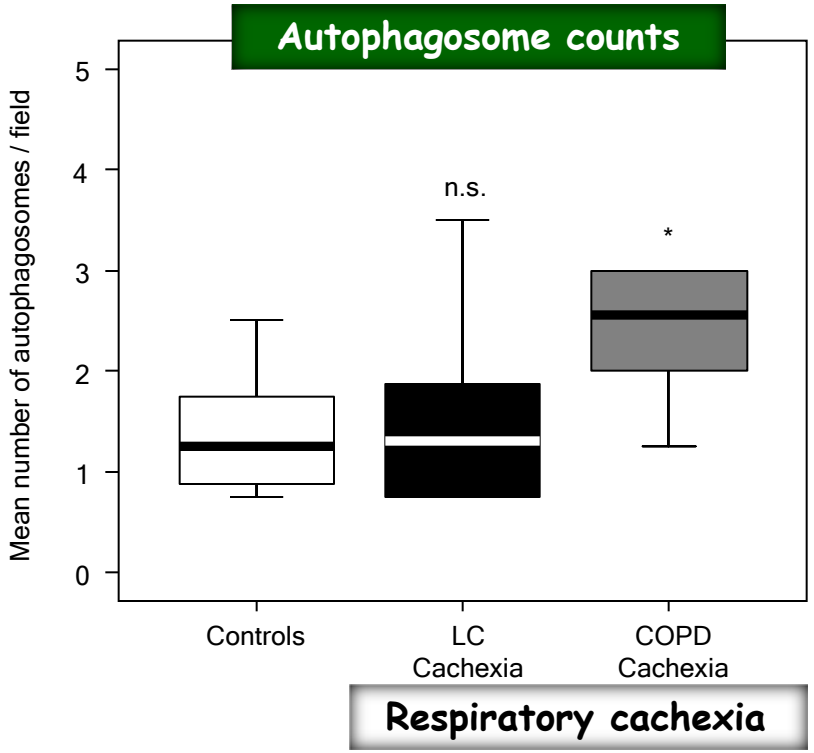


Barreiro *et al. J Appl Phisiol 2011; 111: 808-817.*

AUTOPHAGY IN MUSCLES

Autophagy markers, VL

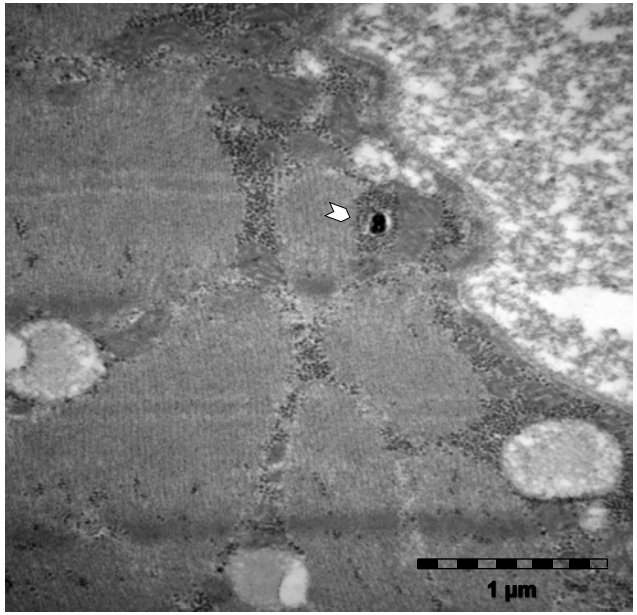




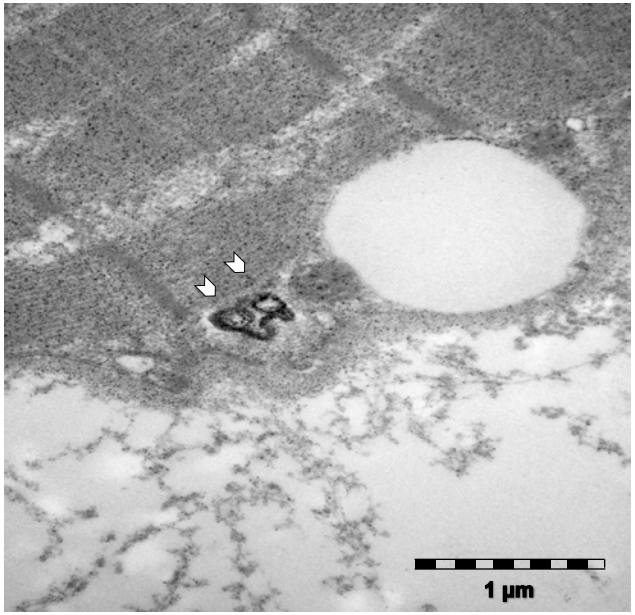
Puig-Vilanova *et al. Free Radic Biol Med* 2015: 79: 91-108

AUTOPHAGY IN MUSCLES

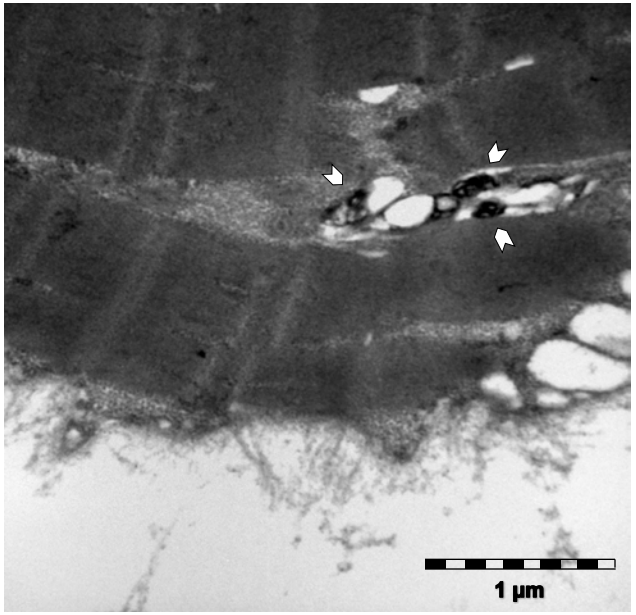
Autophagosomes, VL



Healthy control



LC Cachexia



COPD Cachexia

Respiratory cachexia

Puig-Vilanova *et al. Free Radic Biol Med* 2015: 79: 91-108

EPIGENETIC MECHANISMS IN CELLS

Table I. Epigenetic mechanisms in cells

DNA methylation	Histone acetylation	Histone methylation	MicroRNAs
Addition of a methyl group to 5′-cytosine before guanine in the same chain (CpG islands)	Acetylation: acetyl group from acetyl-CoA transferred to lysine residues ⇒ euchromatin ⇒ favors transcription Deacetylation: reverses acetylation ⇒ heterochromatin ⇒ blocks transcription	Addition of methyl groups to lysine (×3) & arginine (×2) residues ⇒ may favor or block transcription	Noncoding single-stranded RNA molecules ⇒ post-transcriptional regulation of gene expression Base pairing with complementary sequences in mRNA molecules ⇒ gene silencing (translational repression or target degradation)

Histone acetylation ➔ role in atrophy?

Abbreviations: DNA, deoxyribonucleic acid; RNA, ribonucleic acid.

Barreiro et al. *Trans Res* 2015; 165: 61-73.

AND IN MUSCLES...

Table 1. *Regulation of muscle development by miRNAs: function and target molecules*

	Action	Target Pathways
MyomiRs		
miR-1	Promotes myotube formation Innervation process	HDAC4 (23, 56) Connexin 43-dependent gap junctional communication (5) IGF-1 signal transduction cascade (33, 56)
miR-206	Promotes myotube formation Commitment to terminal cell differentiation Innervation process	Subunit p180 of DNA polymerase alpha (30, 71) Inhibition of DNA synthesis & Cell cycle withdrawal (30, 71) Connexin 43-dependent gap junctional communication (5)
miR-133	Induces myoblast proliferation	Inhibition of myotube formation (23) Repression of SFR (23)
Other miRNAs		
miR-27	Entry of satellite cells into myogenic differentiation program	Pax3 mRNA, Satellite cells & embryonic myotomes (27)
miR-181	MyoD induction	Repressor of myoblast terminal differentiation Hox-A11 (70)
miR-29	Promotes myogenesis	Inhibition of Ying Yang 1 (92)

MyomiRs, muscle-specific miRNAs; HDAC4, histone deacetylase 4; IGF-1, insulin-like growth factor; SFR, serum response factor.

J Appl Physiol • doi:10.1152/japplphysiol.01027.2012 • www.

Barreiro et al. *J Appl Physiol* 2013; 114: 1263-1272.

PATIENT CHARACTERISTICS

+/-Quadriceps weakness

	Controls $N = 19$	All COPD patients $N = 41$	Non-muscle weakness $N = 16$	Muscle weakness $N = 25$
Anthropometry				
Age (years)	65 (8)	68 (6)	68 (6)	68 (5)
BMI (kg/m^2)	26 (3)	24 (5)*	26 (4)	22 (4)§§¶¶
FFMI (kg/m^2)	19 (2)	16 (2)***	18 (2)	16 (2)§§§¶
Body weight (kg)	73 (8)	69 (13)	76 (12)	66 (13)§§§
Body weight change (kg/year)	0 (0)	−1.8 (2.4)***	−0.3 (2.5)	−2.8 (1.7)§§§¶¶¶
Smoking history				
Active, *N* (%)	6, 32	16, 39	10, 63	6, 24¶
Ex-smoker, *N* (%)	8, 42	25, 61	6, 37	19, 76¶
Never smoker, *N* (%)	5, 26	0, 0	0, 0	0, 0
Packs-year	54 (20)	61 (24)	59 (28)	62 (22)
Lung function				
FEV_1 (% pred)	93 (12)	34 (15)***	51 (6)§§§	23 (5)§§§¶¶¶
FVC (% pred)	88 (9)	58 (18)***	76 (16)	50 (12)§§§¶¶¶
FEV_1/FVC (%)	73 (4)	44 (11)***	53 (9)§§§	38 (9)§§§¶¶¶
RV (% pred)	105 (18)	198 (69)***	139 (44)	220 (63)§§§¶¶
TLC (% pred)	101 (12)	109 (16)	105 (18)	111 (15)
RV/TLC	49 (23)	64 (11)***	54 (7)	70 (7)§§§¶¶
DLco (% pred)	89 (14)	52 (26)***	71 (21)§	38 (21)§§§¶¶¶
K_{CO} (% pred)	87 (16)	63 (20)***	71 (19)	59 (20)§§§
PaO_2 (kPa)	11.6 (1.1)	9.2 (1.2)***	9.5 (1.3)§§	9.0 (1)§§§
$PaCO_2$ (kPa)	5.2 (0.5)	5.6 (0.7)*	5.4 (0.8)	5.8 (0.5)
Exercise capacity and muscle function				
VO_2 peak (% pred)	87 (10)	48 (23)***	67 (16)§	31 (10)§§§¶¶¶
WR peak (% pred)	81 (21)	48 (26)***	64 (26)§	31 (12)§§§¶
6-min walking test (m)	508 (71)	412 (92)***	459 (69)	380 (93)§§§¶
QMVC (kg)	39 (2)	29 (3)***	32 (1)§§§	27 (1)§§§¶¶¶
Blood parameters				
Albumin (g/dl)	4.3 (0.4)	4.4 (0.4)	4.3 (0.3)	4.4 (0.5)
Total proteins (g/dl)	7.2 (0.5)	7.3 (0.5)	7.1 (0.6)	7.3 (0.5)
CRP (mg/dl)	0.3 (0.2)	1.5 (2.2)**	0.5 (0.4)	2.5 (2.7)§§¶¶
Fibrinogen (mg/dl)	311 (35)	412 (75)***	363 (53)	434 (74)§§§¶
GSV (mm/h)	6 (4)	28 (19)***	20 (11)§	32 (22)§§§¶

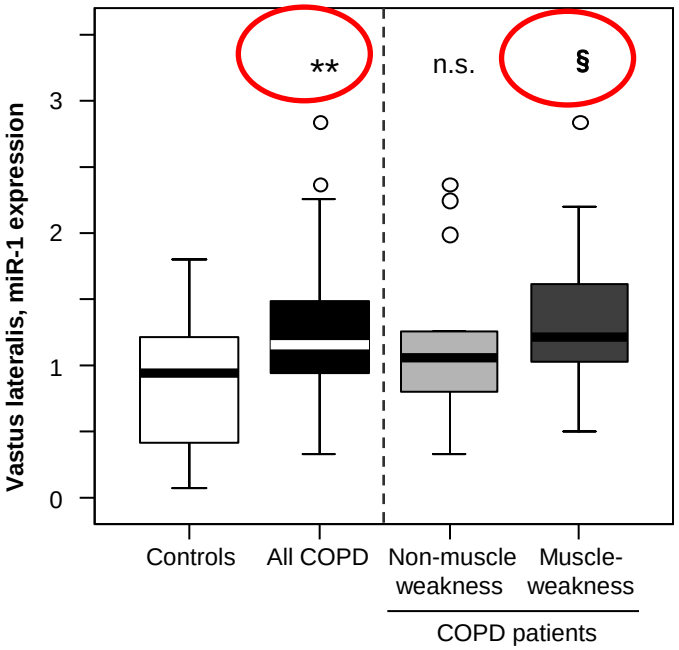
Puig-Vilanova *et al. Clin Sci* 2015; 128: 905-921.

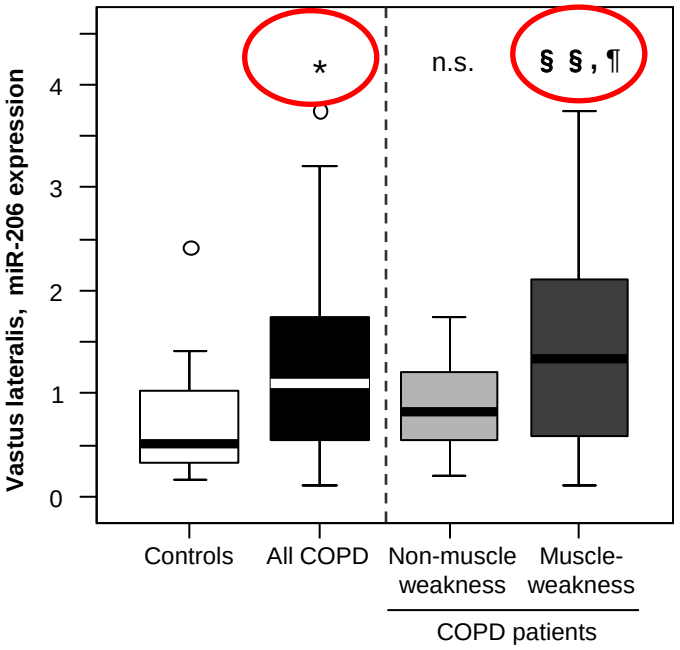
MUSCLE FIBER TYPE CHARACTERISTICS

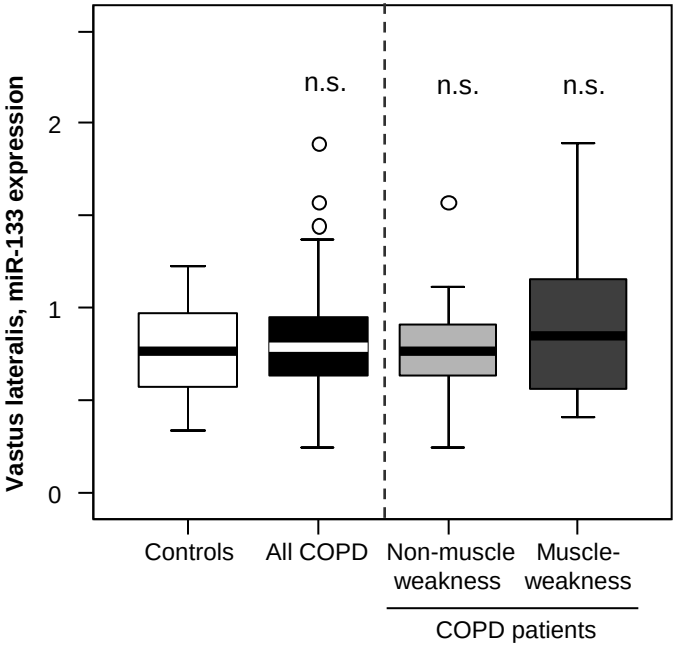
			COPD patients	
	Controls	All COPD patients	Non-muscle weakness	Muscle weakness
	N = 19	*N* = 41	*N* = 16	*N* = 25
Muscle fibre type composition				
Type I fibres, percentages	39 (6)	27 (10)***	31 (10)§	26 (9)§§
Type II fibres, percentages	61 (6)	73 (10)***	69 (10)§	74 (9)§§
Type I fibres, CSA (μm^2)	2698 (894)	2496 (855)	2618 (960)	2438 (817)
Type II fibres, CSA (μm^2)	2915 (755)	2436 (847)*	2807 (910)	2188 (718)§¶

Puig-Vilanova *et al. Clin Sci* 2015; 128: 905-921.

MicroRNAs, VL





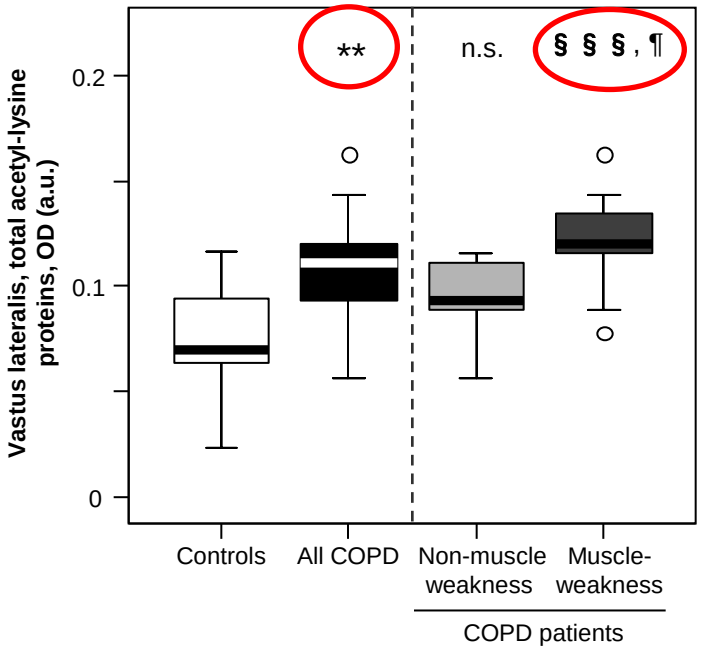


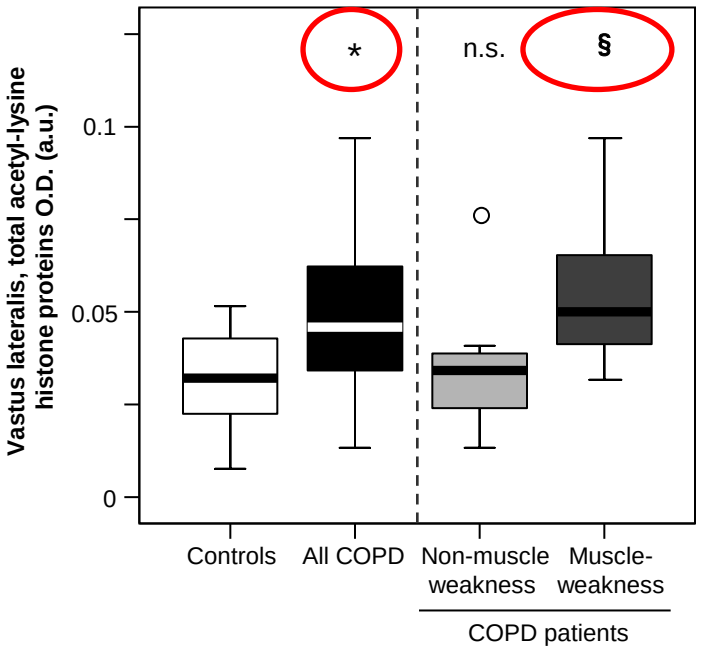
In all COPD & muscle weakness COPD:
↑ miR-1 & miR-206 ➔+ differentiation
miR-133 ➔ ⊘

Correlation between QMVC & miR-206

Puig-Vilanova *et al. Clin Sci* 2015; 128: 905-921.

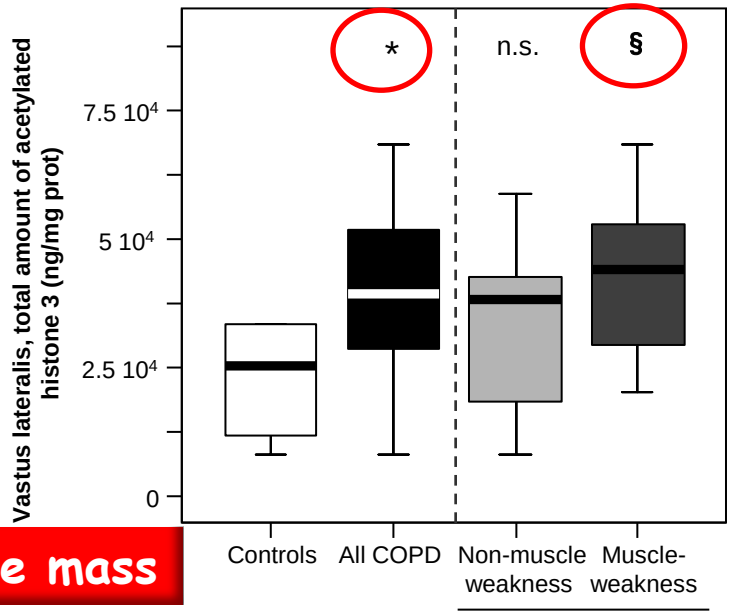
Total protein and histone acetylation, VL





In all COPD & muscle weakness COPD:
- ↑ Total protein acetylation
- ↑ Histone acetylation
- ↑ Acetylated Histone 3
- Acetylated Histone 4 → ⊘
- Histone acetyl transferases → ⊘

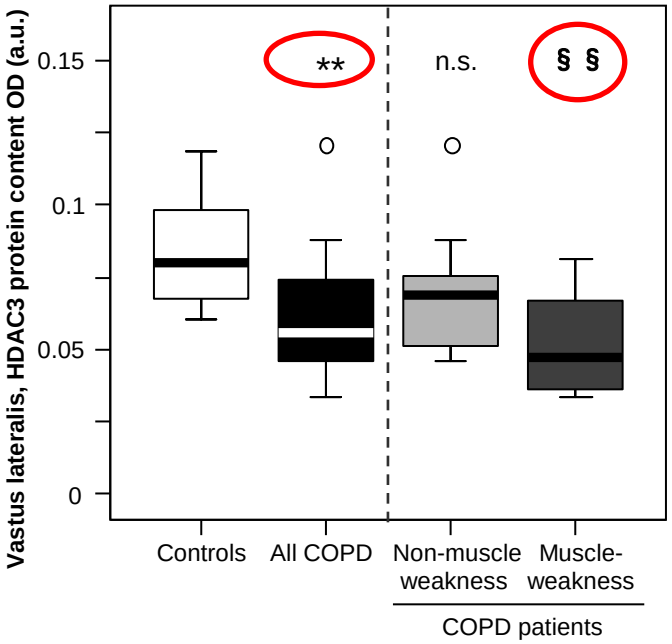
Correlation between acetylated H3 & FFMI

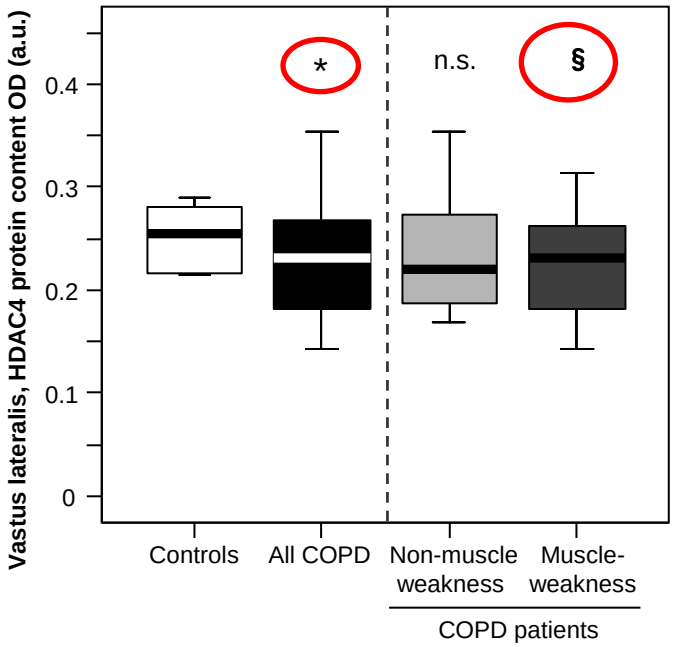


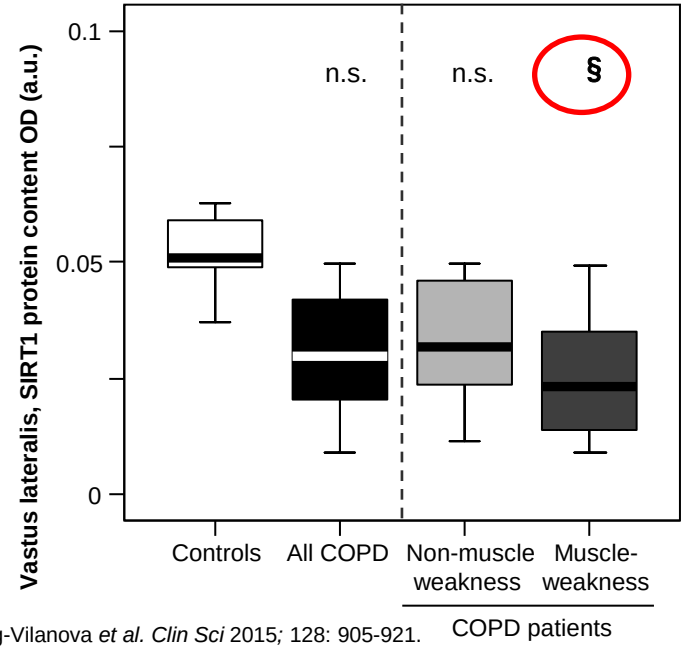
Protein & histone acetylation → ↓ muscle mass

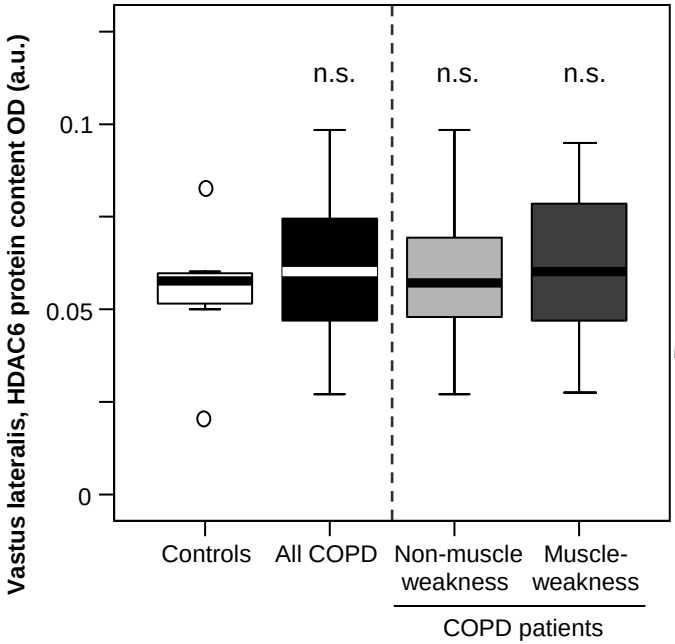
Puig-Vilanova *et al. Clin Sci* 2015; 128: 905-921.

Histone deacetylases, VL









In all COPD & muscle weakness COPD:
↓ HDAC3 & HDAC4

Only in muscle weakness COPD:
↓ SIRT-1

Correlations:
SIRT-1 & FFMI
SIRT-1 & total protein acetylation

Puig-Vilanova *et al. Clin Sci* 2015; 128: 905-921.

COPD muscle dysfunction & wasting: Present & Future

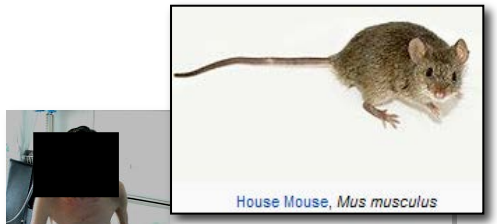
Targets

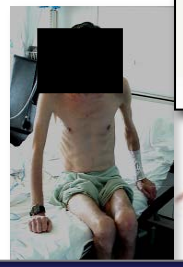
Environment, Triggers, Signaling pathways

Targets

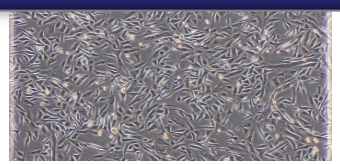
Proteolysis | Epigenetics | Apoptosis | Autophagy | Senescence | Protein misfolding

Muscle loss & dysfunction



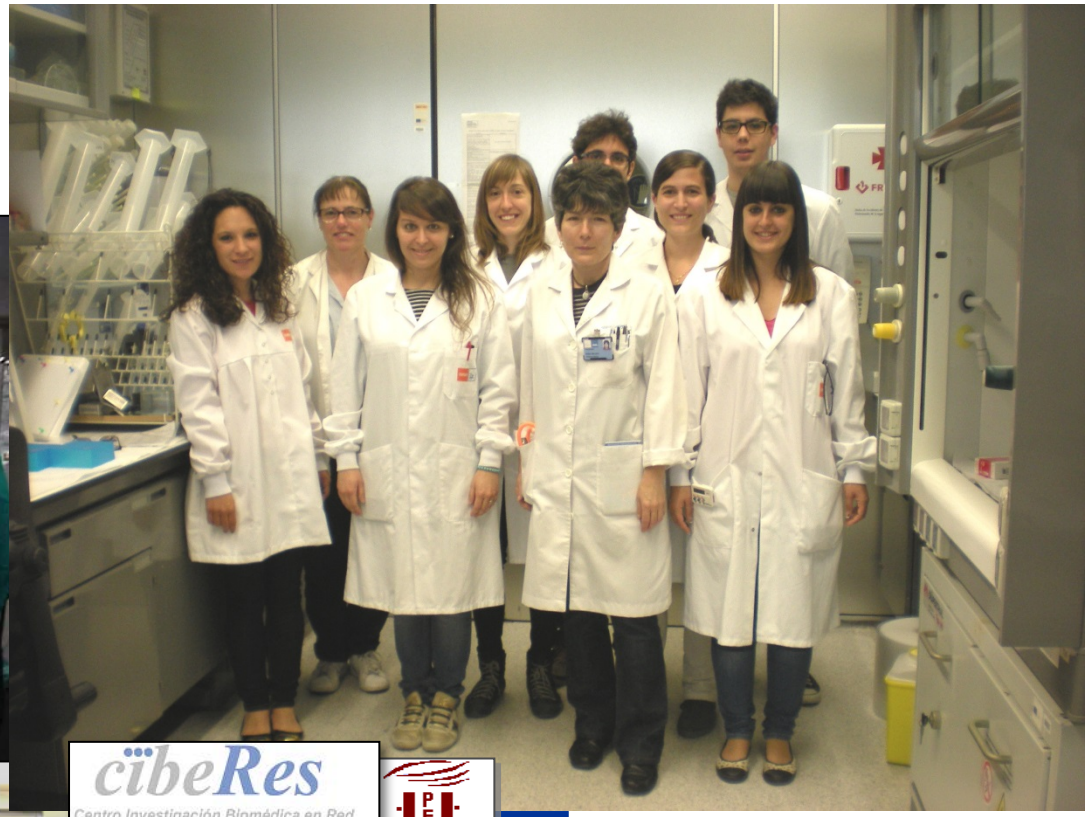


Different Experimental Models



Locomotor dysfunction ⇒ ↓ QoL ⇒ ↑ mortality

ACKNOWLEDGMENTS



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Chronic Obstructive Pulmonary Disease
July 11-12, 2016 Brisbane, Australia

THANK YOU FOR YOUR ATTENTION!