

# Le Diaphragme dans la BPCO

**Dr Bernard Wuyam,**  
CHU Grenoble-Alpes

12<sup>es</sup>

Journées

Francophones  
Alvéole

15 & 16  
mars  
2018

Cité des Congrès de Nantes

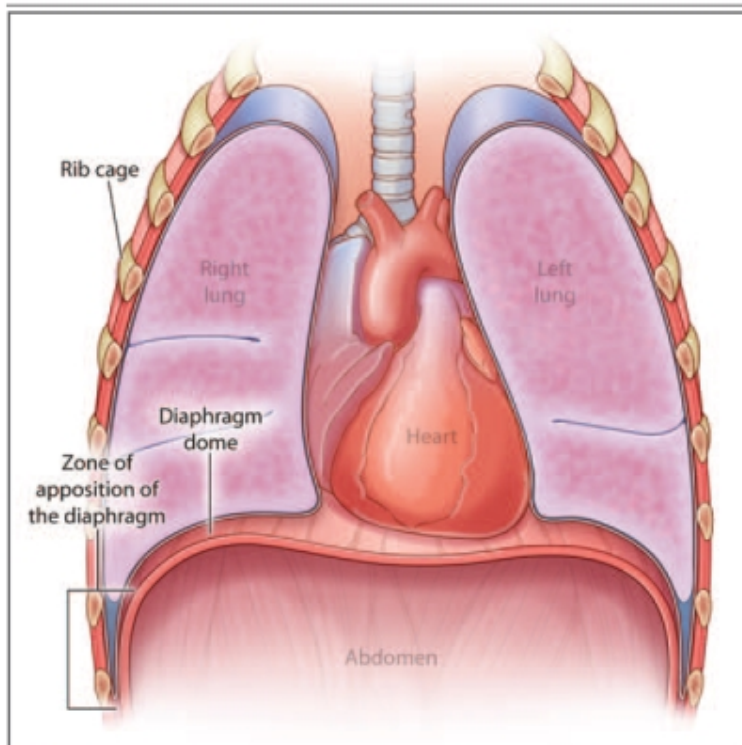
# Liens d'intérêt en lien avec cette présentation

**Aucun lien direct**

# Le diaphragme dans la BPCO.

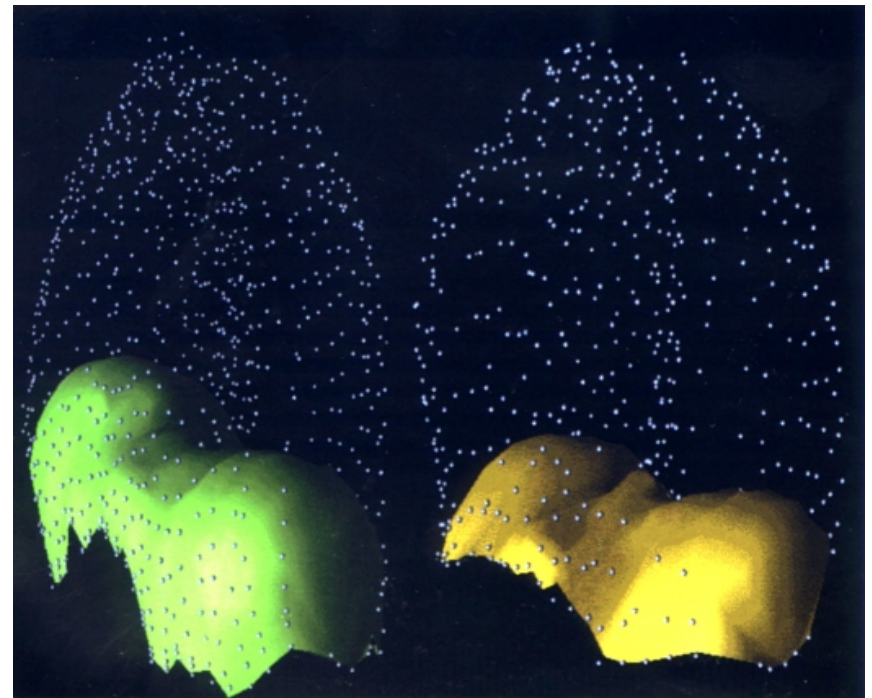
- Anatomie fonctionnelle. Action du diaphragme
- Effets de la distension sur la fonction du diaphragme
- Modifications des fibres diaphragmatiques dans la BPCO
  - Typologie du diaphragme
  - Effets du catabolisme protéique et de modifications de protéines de structures.
- Modifications de la **force** et de l'**endurance** du diaphragme (et des muscles respiratoires).
- **Fatigue** du diaphragme.
  
- Et non
  - **Evaluation** de la fonction du diaphragme
  - **Entraînement** des muscles respiratoires.

# Anatomie fonctionnelle du diaphragme



**Figure 1. Anatomical Arrangement of the Diaphragm with the Rib Cage and Abdomen.**

The cylindrical region of the diaphragm that apposes the lower rib cage is referred to as the zone of apposition of the diaphragm.



Cluzel P , Similowski T et al.  
Radiology. 2000 May;215(2):574-83

# Fonction ventilatoire du diaphragme

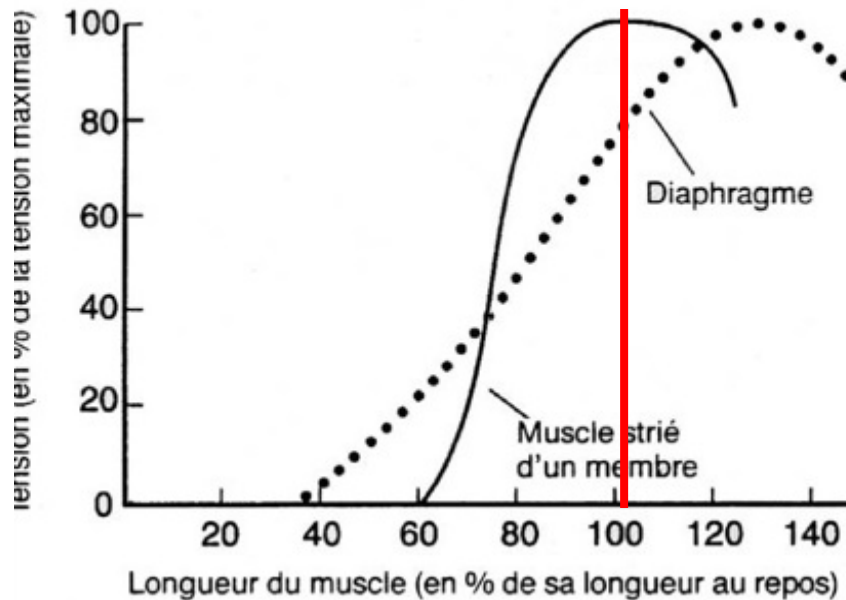
- Abaissement inspiratoire du **dôme**
- **Zone d'apposition** :
  - **Élévation** des côtes inférieures
    - Orientation axe K : BS-DD-AV
    - élévation K = mouvement vers l'extérieur.
    - Augmente dimensions latérales du thorax inférieur
  - **Transmission de la pression abdominale**
    - à la partie basse de la cage thoracique : mouvement vers le dehors.



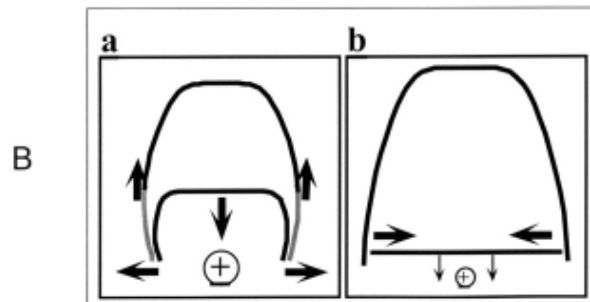
Lynda Gaillard



# Adaptation à la distension aiguë



- Longueur optimale (L0) : 100% tension max.
- Distension : position plus inspiratoire. Fibres raccourcies.
- 40-50% L0 : **force très réduite (nulle) !!!**
- TLC correspond à environ à 30% de raccourcissement (chien anesthésié).



- Réduction de la zone d'apposition.
- Modification de l'**orientation des fibres** de la zone d'apposition
- Modification de la **géométrie du dôme (Loi de Laplace)**.

Examen : Signe de **Hoover**.

# Distension chronique (BPCO)

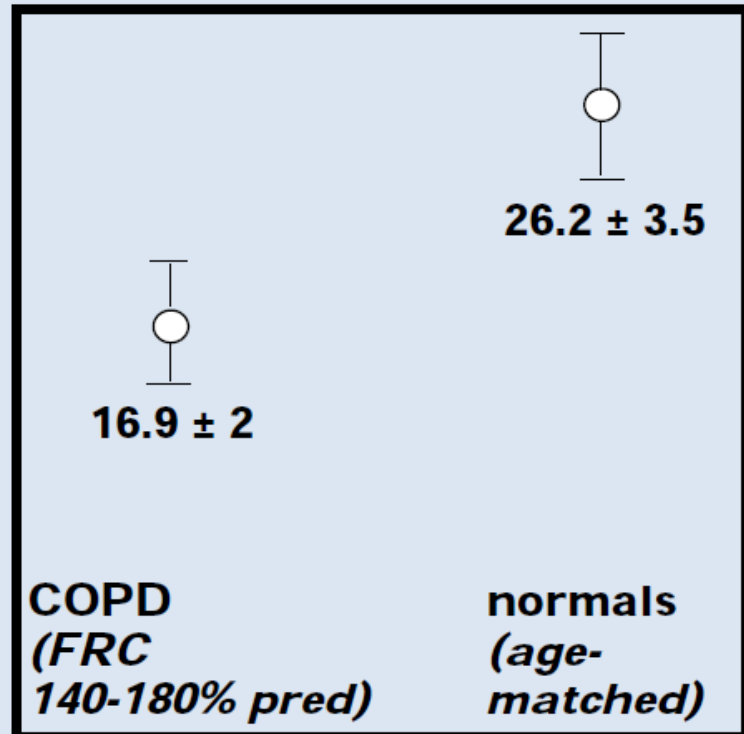
- **Adaptation des unités contractiles d'un muscle :**
  - Raccourcissement : diminution du nombre de sarcomères.
  - Allongement : augmentation nombre de sarcomères
  - Longueur des sarcomères tend à être restaurée à sa longueur initiale.
- **Diaphragme :**
  - Modèle animal : emphysème expérimental (hamster)
  - BPCO: Similowski T et al. NEJM. 1991, 325 : 917-923
    - BPCO distendus : CRF 140-180% prédite

# Adaptations à la distension

- Similowski T, Yan S, Gauthier AP, Macklem PT, Bellemare F. Contractile properties of the human diaphragm during chronic hyperinflation. *N Engl J Med* 1991; 325: 917–923.

- Twitch Pdi **basses** : allant de 10.9 - 26.6 cmH2O
- Moins diminués que la baisse attendue correspondant à la distension (aigue).
- Ppl/Pdi plus favorable

Pdi (cmH2O)  
(*phrenic stimulation*)





# Diaphragme – BPCO & ventilation

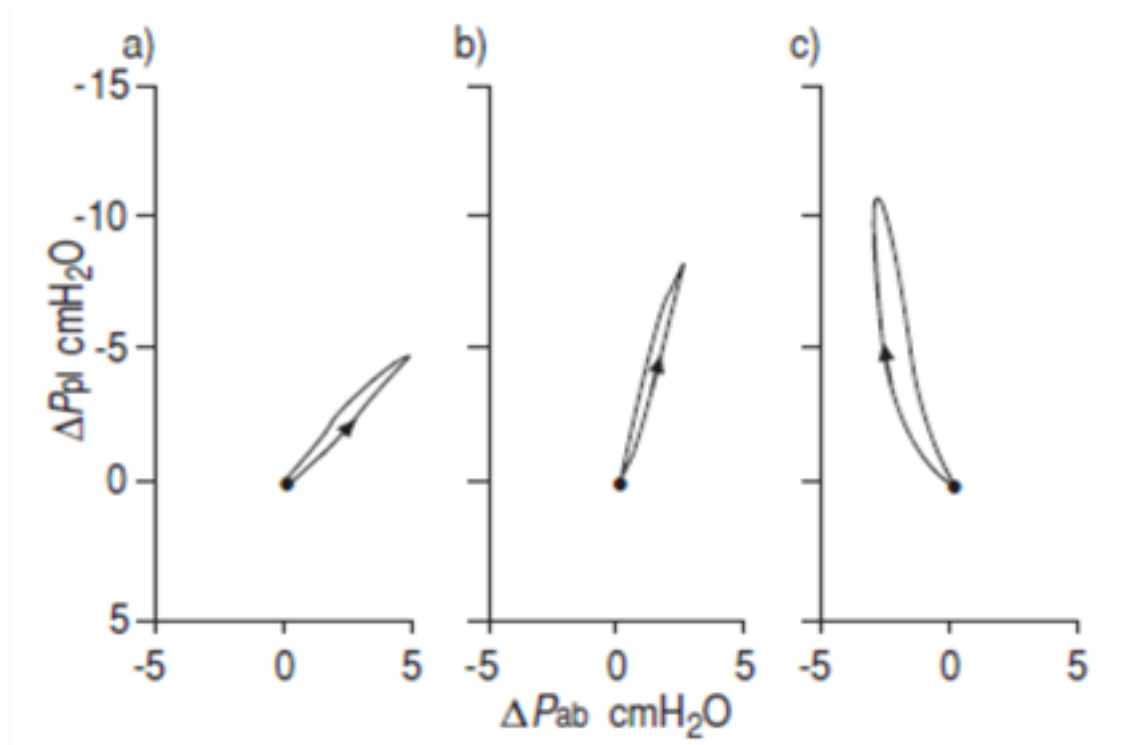


Fig. 3. – Inspiratory pressure generation during tidal breathing: a) in a normal subject; b) in a patient with moderately severe chronic obstructive pulmonary disease (COPD); and c) in a patient with severe COPD. The pleural pressure swing ( $\Delta P_{pl}$ ) is on the ordinate, and the abdominal pressure swing ( $\Delta P_{ab}$ ) is on the abscissa. The closed circle in each panel corresponds to end-expiration, and the arrow marks the inspiratory phase of the breathing cycle. In the normal subject,  $P_{ab}$  increases during inspiration by about as much as  $P_{pl}$  decreases. However, in the patient with moderately severe COPD,  $\Delta P_{pl}$  is greater but  $\Delta P_{ab}$  is smaller. The patient with severe COPD may have a decrease in  $P_{ab}$  during inspiration, which corresponds to a cranial displacement of the diaphragm and an inward displacement of the ventral abdominal

# Cellular adaptations in the diaphragm in COPD

**TABLE 1.** CHARACTERISTICS OF THE PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND THE CONTROL SUBJECTS.

CHARACTERISTIC	CONTROLS (N=10)	PATIENTS (N=6)	P VALUE
	mean $\pm$ SE		
Age (yr)	49 $\pm$ 7	59 $\pm$ 4	0.30
Height (cm)	167 $\pm$ 2	164 $\pm$ 5	0.58
Weight (kg)	67 $\pm$ 3	68 $\pm$ 4	0.78
Spirometry*			
Forced expiratory volume in 1 sec			
Liters	2.00 $\pm$ 0.29	0.95 $\pm$ 0.19	0.01
Percent of predicted	69 $\pm$ 3	33 $\pm$ 4	<0.001
Forced expiratory volume in 1 sec: forced vital capacity (%)	70 $\pm$ 4	38 $\pm$ 3	<0.001
Lung volume (% of predicted)*			
Residual volume	111 $\pm$ 14	259 $\pm$ 25	0.002
Functional residual volume	100 $\pm$ 8	194 $\pm$ 19	0.006
Total lung capacity	89 $\pm$ 8	145 $\pm$ 7	0.001

\*Lung function was measured only in the patients and the four control subjects who underwent surgery. Spirometry and plethysmographic lung volumes were assessed with conventional techniques, and the values were compared with predicted values.<sup>26,27</sup>

**TABLE 2.** COMPOSITION OF MYOSIN HEAVY CHAINS AND FIBER TYPES PRESENT IN THE COSTAL DIAPHRAGM.\*

VARIABLE	I	Ila	Ilb
	percent		
Myosin heavy chains†			
Controls (n=10)	45 $\pm$ 2	39 $\pm$ 2	17 $\pm$ 1
Patients (n=6)	64 $\pm$ 3	29 $\pm$ 3	8 $\pm$ 1
P value	<0.001	0.01	<0.001
Type of fiber‡			
Controls (n=4)	46 $\pm$ 3	39 $\pm$ 2	15 $\pm$ 1
Patients (n=4)	61 $\pm$ 4	31 $\pm$ 3	8 $\pm$ 2
P value	0.01	0.09	0.01

\*Plus-minus values are means  $\pm$  SE. An unpaired t-test was used to compute the statistical significance of the differences between groups. Because of rounding, not all categories total 100 percent.

†Values were obtained by SDS-PAGE.

‡Values were obtained by immunohistochemical analysis.

Levine et al., NEJM, 1997

# Adaptation cellulaire du diaphragme dans la BPCO (2)

Table 1. – Main anthropometric, functional and structural characteristics of the patients

Patient No.	Age yrs	BMI kg·m <sup>-2</sup>	FEV <sub>1</sub> /FVC %	FEV <sub>1</sub> %ref <sup>1</sup>	FRC %ref	RV/TLC %	P <sub>a</sub> O <sub>2</sub> mmHg	P <sub>1,max</sub> %ref	n <sub>mit</sub> mt·μm <sup>-2</sup>	L <sub>sar</sub> μm
<b>COPD patients</b>										
1	69	25	45	44	170	61	98	38	0.82	2.16
2	47	27	54	46	126	37	88	100	0.91	2.16
3	68	24	43	53	NA	NA	87	67	0.52	2.38
4	53	25	61	55	126	58	75	90	0.70	2.10
5	62	25	68	62	115	39	89	111	0.53	1.90
6	67	27	63	62	106	51	80	121	0.58	2.11
7	46	20	57	64	100	32	100	96	0.43	2.14
8	46	29	67	67	109	39	80	172	0.47	2.05
9	64	29	67	67	130	46	62	153	0.47	2.29
10	53	20	66	67	162	56	68	37	0.64	1.91
11	70	24	68	71	206	65	79	44	0.74	1.84
Mean±SD	59±10	25±4	60±9	60±9	135±34	48±11	82±12	94±45	0.62±0.16	2.09±0.16
<b>Non-COPD patients</b>										
12	46	22	71	80	109	31	87	124	0.33	2.27
13	51	27	73	80	102	37	84	156	0.43	2.37
14	66	28	76	81	NA	NA	NA	156	0.28	1.96
15	69	23	72	85	128	44	95	109	0.83	2.13
16	63	23	76	88	88	38	100	144	0.44	1.94
17	59	24	71	89	102	33	88	95	0.51	2.37
18	64	22	71	96	101	29	95	128	0.49	2.21
19	68	29	79	96	88	28	91	72	0.48	2.50
20	71	23	72	99	87	29	79	107	0.35	2.12
Mean±SD	62±8	25±2	74±3	88±7	100±14	33±6	90±7	121±28	0.46±0.16	2.21±0.19

## Subcellular adaptation of the human diaphragm in chronic obstructive pulmonary disease

M. Orozco-Levi\*, J. Gea\*, J.L. Lloreta<sup>†</sup>, M. Félez\*, J. Minguella<sup>†</sup>, S. Serrano<sup>†</sup>, J.M. Broquetas\*

# Etude ultrastructurale du diaphragme

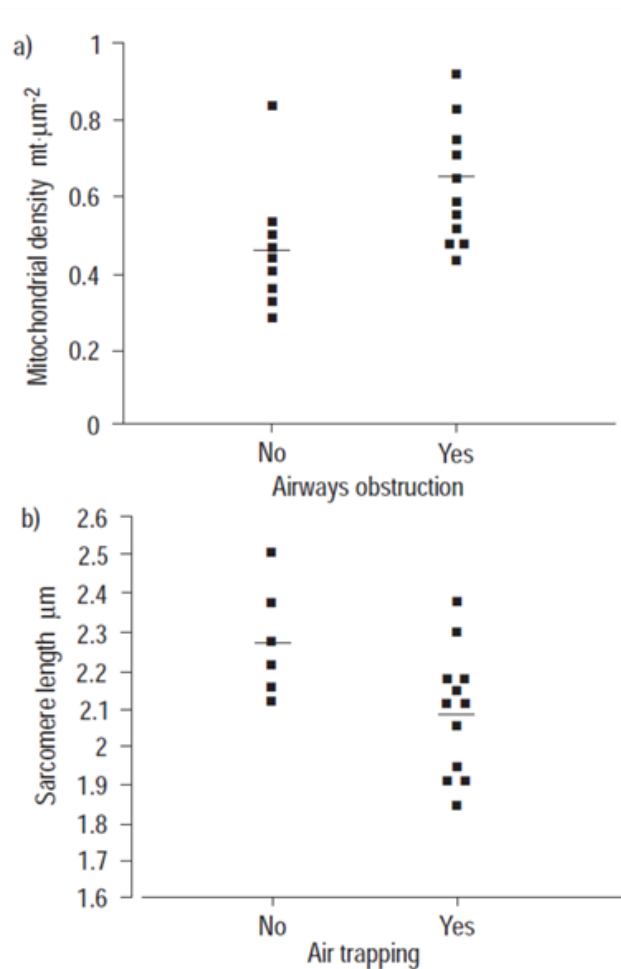


Fig. 1. – Differences in a) diaphragmatic mitochondrial density ( $n_{mit}$ ) with reference to airways obstruction, and b) in the length of sarcomeres ( $L_{sar}$ ) with reference to air trapping ( $p < 0.05$ , both). mt: mitochondrial transections.

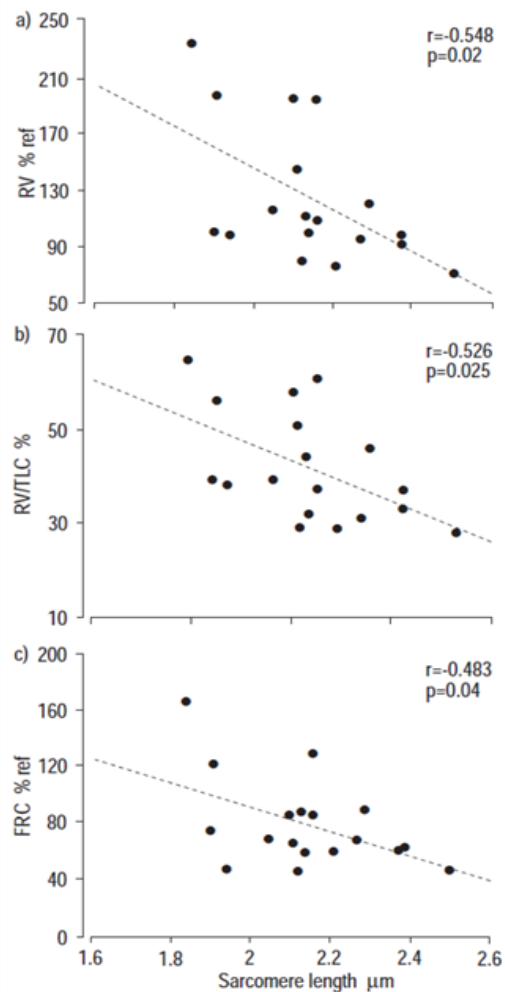
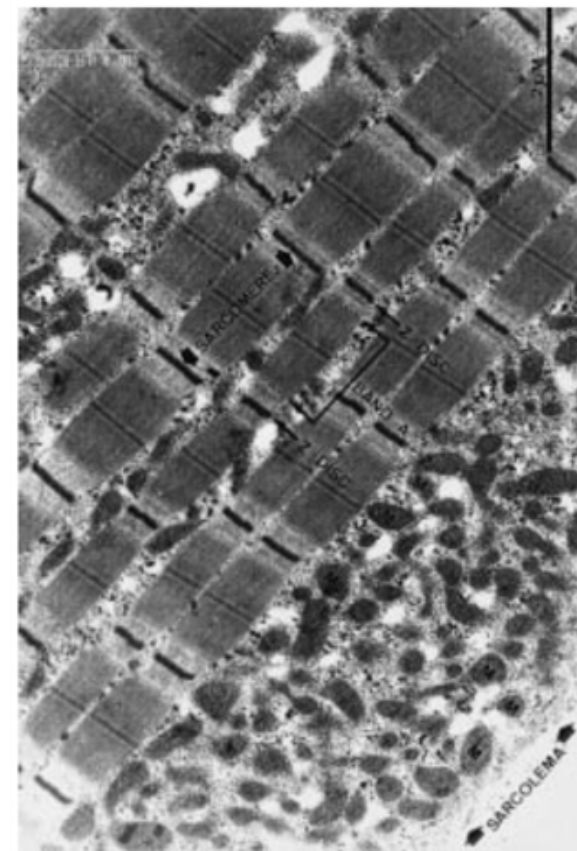


Fig. 5. – Plots of length of sarcomeres ( $L_{sar}$ ) with static lung volumes for a) residual volume (RV), b) RV/total lung capacity (TLC), and c) functional residual capacity (FRC). ref: reference. - - - - : regression.

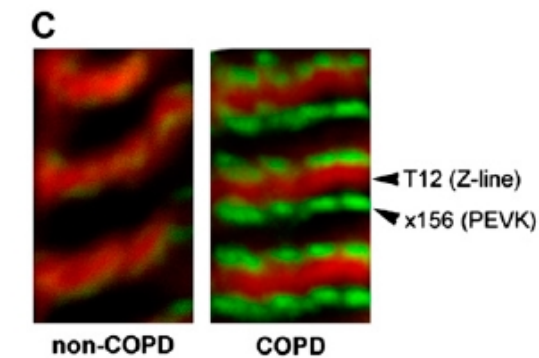
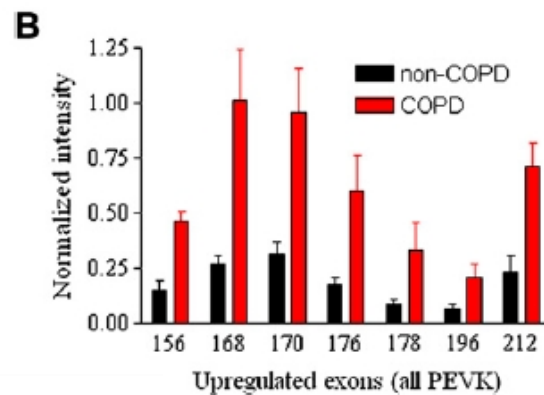
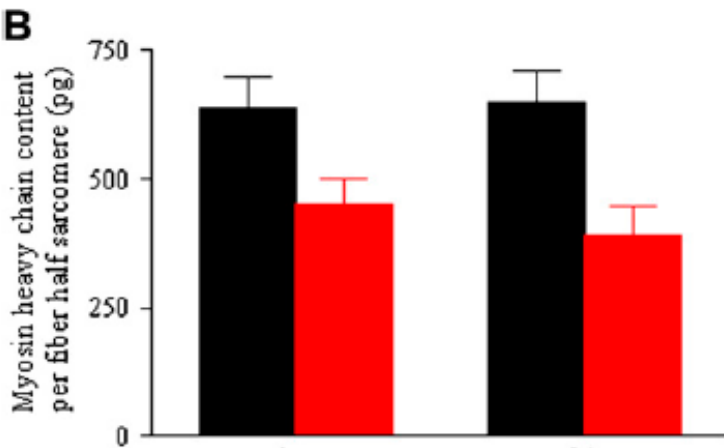
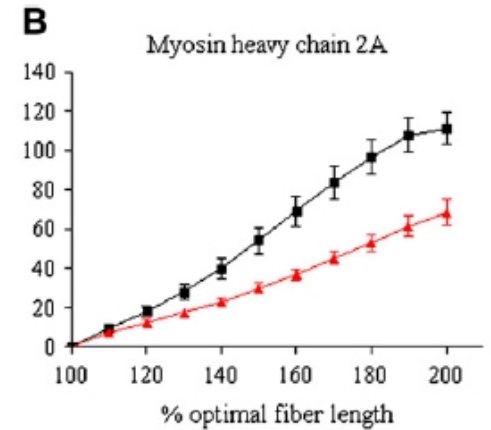
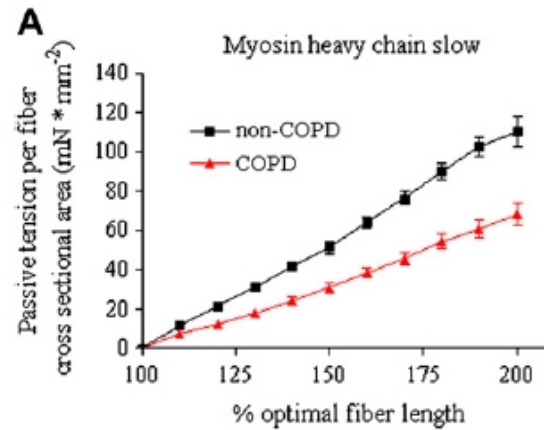
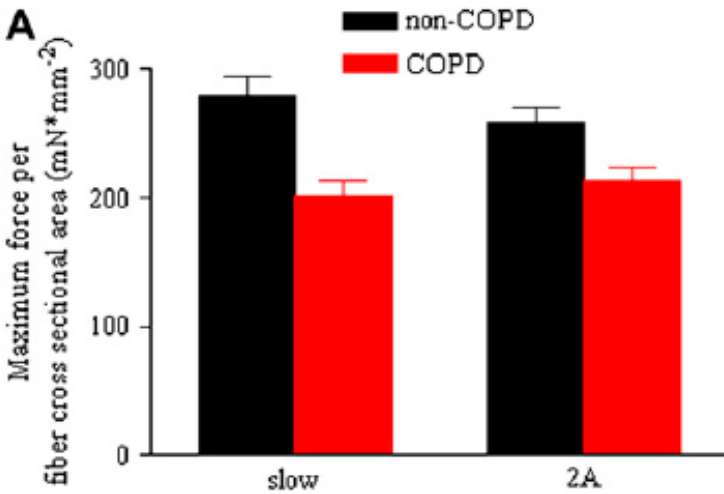


Subcellular adaptation of the human diaphragm in chronic obstructive pulmonary disease

M. Orozco-Levi\*, J. Gea\*, J.L. Lloreta\*, M. Féliz\*, J. Minguella\*, S. Serrano\*, J.M. Broquetas\*

Eur Respir J 1999; 13: 371–378  
Printed in UK – all rights reserved

# Etude sur fibre unique



## Titin and Diaphragm Dysfunction in Chronic Obstructive Pulmonary Disease

Coen A. C. Ottenheijm, Leo M. A. Heunks, Theo Hafmans, Peter F. M. van der Ven, Caroline Benoist, Honghui Zhou, Siegfried Labelit, Henk L. Granzier, and P. N. Richard Dekhuijzen

Am J Respir Crit Care Med Vol 173. pp 527-534, 2006

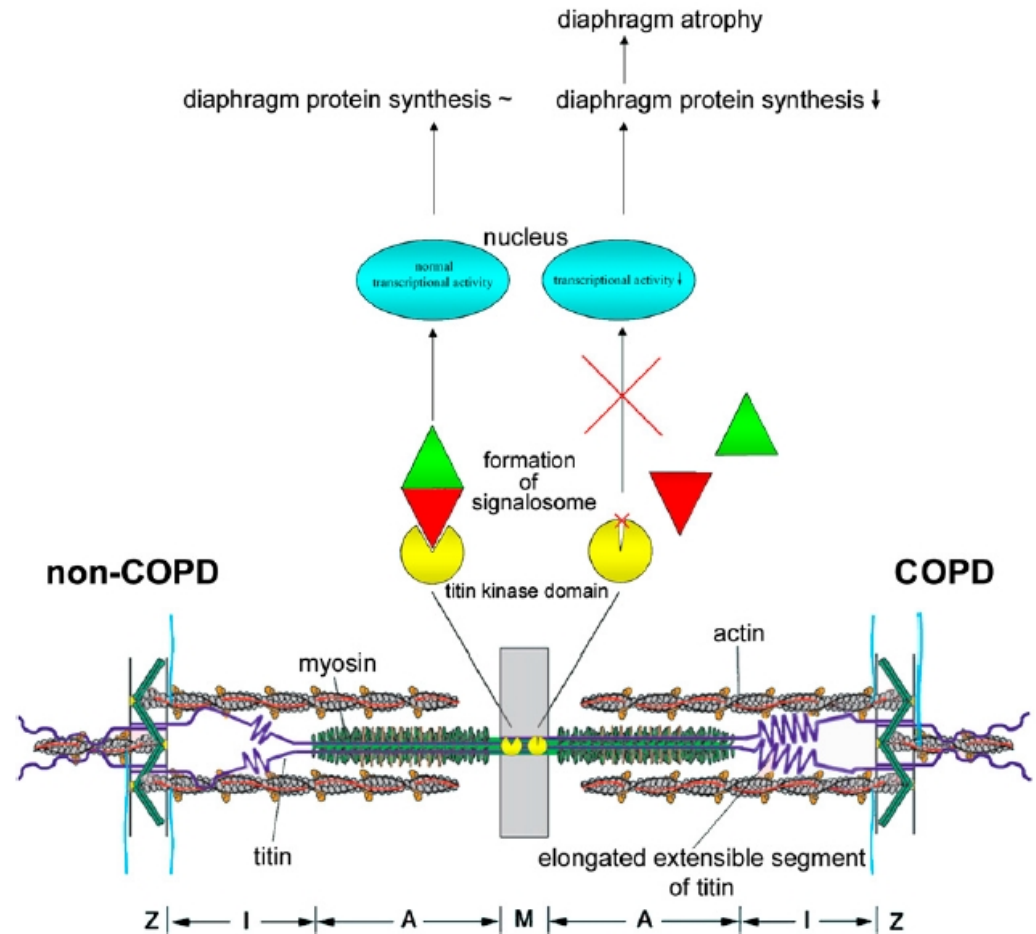
# Comportement mécanique des fibres vs expression de la Titine

- Baisse de la tension passive sur fibres étirées des BPCO.
- Les transcripts de la 'titine' :
  - Augmentation de l'expression des exons codant pour les éléments élastiques de la titine.
  - Augmentation des variants 'épicées' de la protéine.
- L'épissage alternatif du gène de la titine est impliqué dans les alterations de la tension passive du diaphragme et contribuent à la dysfonction du diaphragme.
- Ces anomalies sont précoces au cours de la maladie (GOLD I/II).



# Diaphragme & BPCO

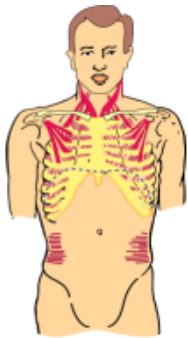
**Figure 3.** Titin and diaphragm atrophy in chronic obstructive pulmonary disease (COPD). The sarcomere is mainly composed of the thin (mostly actin) filaments, the thick (mostly myosin) filaments, and the giant filamentous molecule titin. Single titin molecules span the half sarcomere from the Z-line to the M-line. In the I-band region of the sarcomere, titin has an extensible segment that develops passive tension upon stretch. Previous work demonstrated that alternative splicing of the titin gene resulted in an elongated extensible segment reducing titin-based mechanical tension in COPD diaphragm. During contraction or passive tension, the titin kinase domain in the M-line is stressed. This mechanical tension opens the active site of the titin kinase domain and triggers the assembly of a signalosome that communicates with the nucleus and thereby regulates muscle gene expression. We hypothesize that the elongated extensible titin segment in COPD diaphragm reduces the mechanical stress on the titin kinase domain and results in impaired communication with the nucleus through preventing signalosome formation. The loss of this signaling pathway leads to diminished transcriptional activity and protein synthesis, resulting in diaphragm atrophy. The right half sarcomere represents a “COPD diaphragm sarcomere” including the elongated extensible titin segment; the left half sarcomere represents a non-COPD diaphragm, or normal sarcomere.



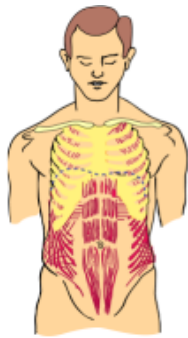
# Répartition de la Faiblesse musculaire dans la BPCO

- Baisse de la **force des muscles respiratoires**
  - Force des muscles inspireurs (59 +/- 18% controls) significativement inférieure à :
  - La force des muscles expirateurs (69 +/- 25% contrôles),
- Force des **muscles périphériques des MI** : moyenne : 75% control,  $P < 0.01$  vs sujets normaux
- Moins affectés que les **muscles des membres supérieurs** (80% et au delà).
- **Gosselink R, Troosters T, Decramer M. Distribution of muscle weakness in patients with stable chronic obstructive pulmonary disease. J Cardiopulm Rehabil 2000; 20: 353–360.**

# $P_i$ & $P_E$ max : rôle de la distension

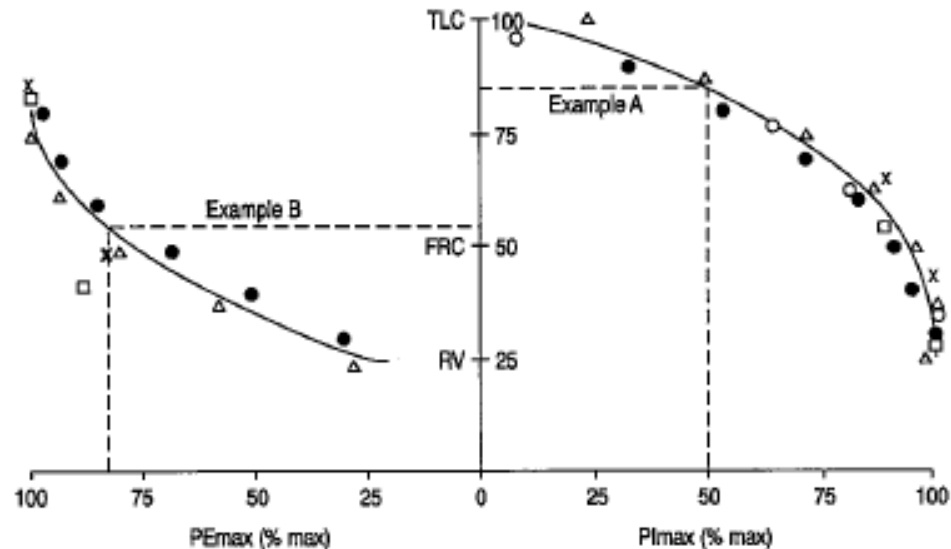


Inspiration



Expiration

- Muscles **intercostaux parasternaux** & muscles cervicaux **moins sensibles à la distension** (relation tension longueur plus favorable).
- Muscles **expirateurs** augmentent un peu leur force, mais impact inconnu.



*Figure 3.* Relationship between maximal static respiratory pressure ( $P_{i\max}$ ,  $P_{E\max}$ ) and lung volume. Pressures are expressed as a percentage of maximum and the lung volume is expressed as a percentage of TLC. Symbols are data from different studies (39). *Example A* represents a patient with emphysema whose RV is 85% TLC, at which lung volume his predicted  $P_{i\max}$  is only 50% of that at normal RV. Conversely, *Example B* represents a patient with lung fibrosis with TLC of 55% predicted, at which volume her  $P_{E\max}$  is 82% maximum. Reprinted by permission from Reference 39.

# Endurance des muscles respiratoires chez le sujet BPCO

**Endurance résistive  
incrémentale**

des muscles inspiratoires &  
expiratoires



**Hyperpnée isocapnique  
(endurance incrémentale  
par paliers de  $f_R$ )**



Spirotiger®

# Faiblesse et Endurance des muscles respiratoires chez le sujet BPCO

## •Dysfonction des muscles respiratoires :

- Faiblesse :  $P_i$ max et  $P_E$ max ↓↓ Decramer et al. 1996, Gosselink et al.2002.
- **Endurance** inspiratoire/expiratoire ↓↓
  - Ramirez-Sarmiento et al. : AmJ Repir Crit Care 2002 & Thorax 2002 [IMT]
  - Newell et al. Thorax 1989 : 18 contractions max, chute de force vs contrôles.

## •Fatigabilité des muscles respiratoires : à l'exercice (hyperventilation)

Kiroussis et al. 1996    Hopkinson et al. 2006

Mader et al. 2000

# Fatigue du diaphragme chez le BPCO

Eur Respir J 2011; 37: 236-237  
DOI: 10.1183/09031936.00095510  
Copyright©ERS 2011



PRO AND CON EDITORIALS

The case against inspiratory muscle training in COPD

M.I. Polkey\*, J. Moxham<sup>†</sup> and M. Green\*

- **Non**

- Hyperventilation : VMV (Polkey M et al.)
- Exhaustive exercise on treadmill.

- **Oui**

- Bachasson et al.
- HCWLET à 75% Pmax
- VEMS moyen : 1 – 1,5 L
- Durée : jusqu'à 20 minutes.

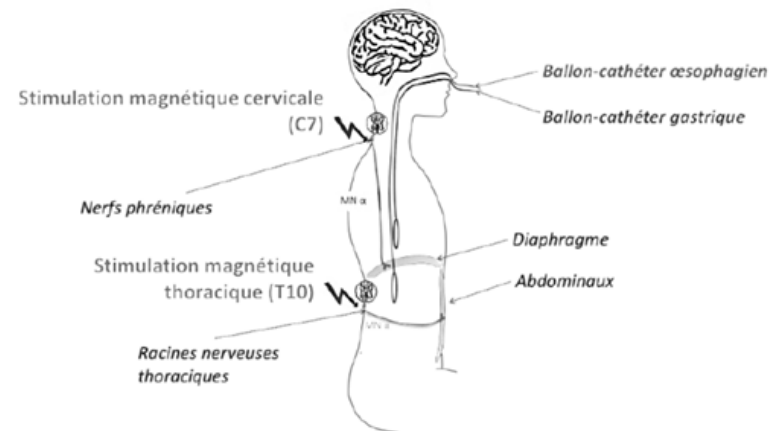


Figure 20. Schéma du dispositif expérimental.



# Fatigue des muscles respiratoires

## + Dyspnée

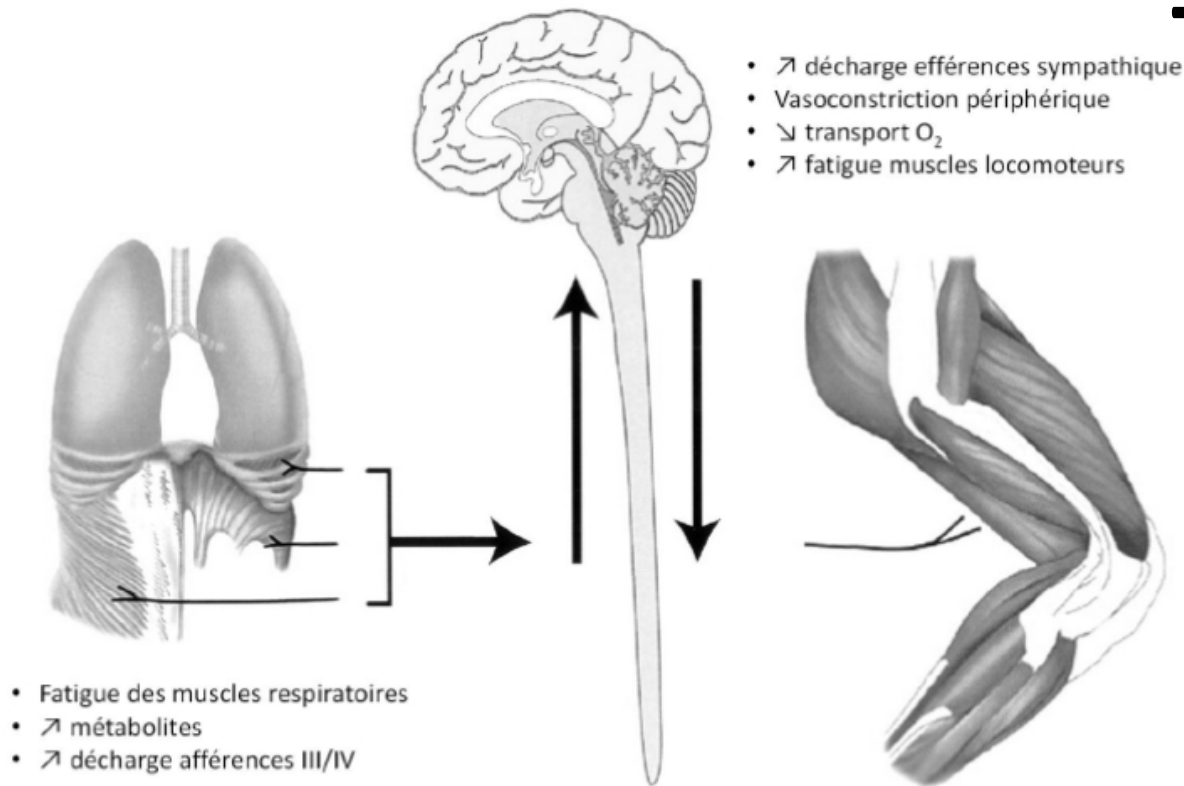


Figure 5. Le métaboréflexe respiratoire (d'après Dempsey et al. (2006))

- Baisse de la force pour une même stimulation
- Augmentation de la commande centrale
- *'Copie éfferente'* de la commande motrice sur le cortex sensoriel

# Conclusions

- Ennemi n° 1 : la **distension**, même si...
- **Compensations**, *mais* partielles
  - Au niveau des sarcomères & structure de la fibre .
- **Faiblesse** du diaphragme très probable, mécanismes complexes (distension, titine, protéasome).
- **Adaptation** au travail : typologie, densité mitochondriale. Endurance ?
- **Fatigue** possible, important à considérer (métaboR, dyspnée, effet entraînement): mais '*impédance*' du système respiratoire à prendre en compte.

Merci de votre attention