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Postgraduate Course 18
Advanced respiratory and cardiovascular testing

Saturday, 26 September 2015
14:00 - 17:30

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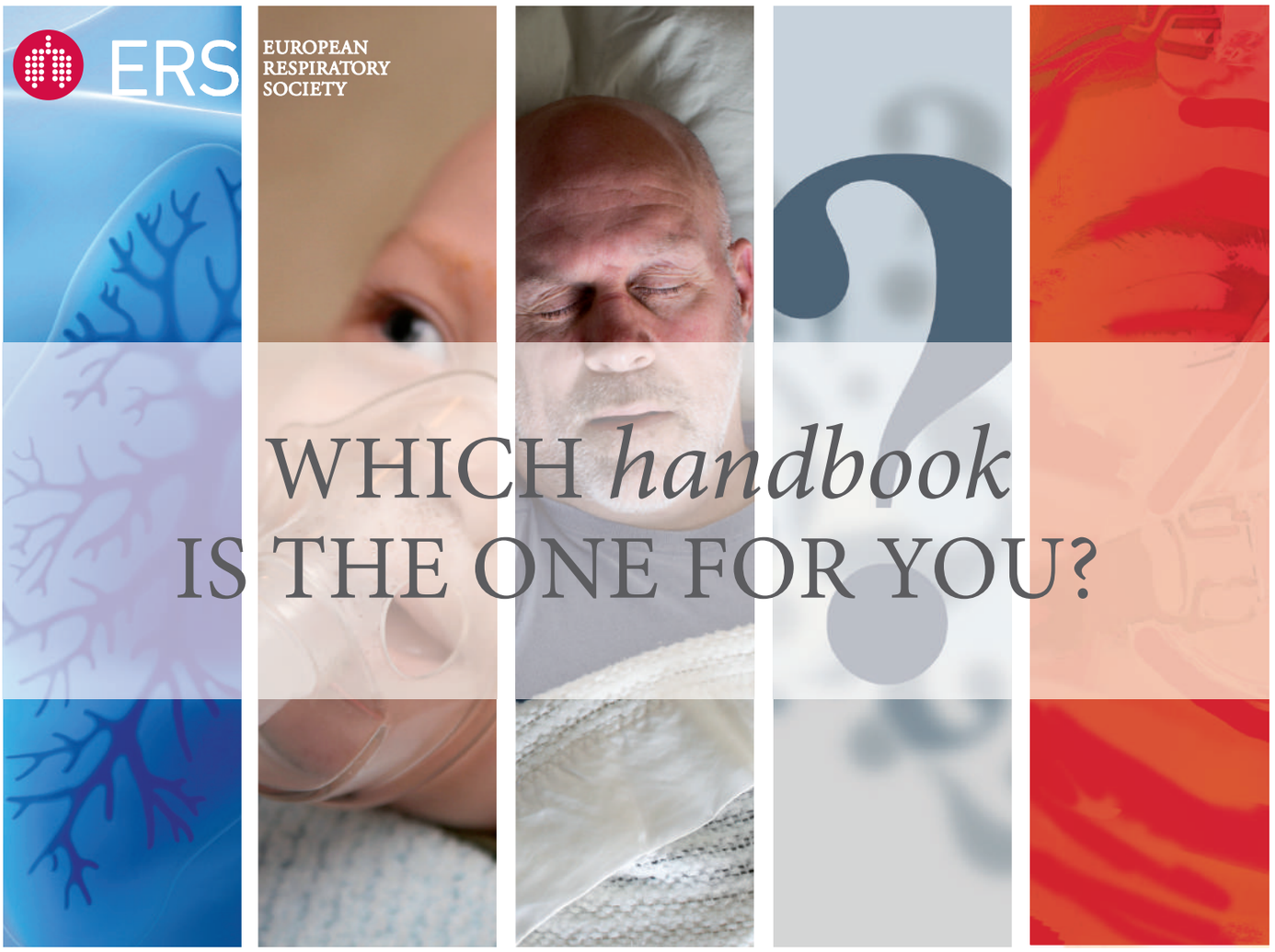
Postgraduate Course 18
Advanced respiratory and cardiovascular testing

AIMS: *At the end of the course, the participants will understand the physiological constraints of exercise tolerance and its application in clinical practice; appreciate the optimal methods for testing lung mechanics and spirometry; understand the different formats of exercise tests, their advantages and disadvantages, and their different prognostic values in adults and children; and appreciate the usefulness of exercise testing for evaluating pharmacological and non-pharmacological interventions in clinical practice.*

TARGET AUDIENCE: *Pulmonologists, respiratory therapists, respiratory physicians, clinical researchers, general practitioners, research fellows, intensivists, nurses, and trainees.*

CHAIRS: B. Fauroux (Paris, France), S Ward (Crickhowell, United Kingdom)

COURSE PROGRAMME **PAGE**



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european respiratory society every breath counts

Respiratory mechanics: changes in disease

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AIMS

- To discuss the physiological basis of lung mechanics in healthy and lung disease.
- To discuss role of physiological basis of dyspnoea.

Flow-Volume Loop in Healthy

In healthy young individuals, V'_E increases during exercise by a progressive expansion of tidal volume (V_T) to approximately 60% of the vital capacity or 75% of TLC. At this operating lung volume, the diaphragm muscle fibres are maximally shortened and further increases in V'_E may be achieved solely through increases in breathing frequency. To ensure a progressive and harmonious expansion of V_T, EELV usually decreases leading, therefore, to a concurrent increase in IC during exercise. The magnitude of EELV reduction varies with the type and intensity of exercise, with average reductions between 0.3-1.0L below relaxation volume of the respiratory system. The most important advantage of the decrease in EELV (or increase in IC) during exercise is that of allowing V_T to increase by encroaching almost equally on the expiratory and inspiratory reserve volumes (ERV and IRV, respectively) without end-inspiratory lung volume (EILV = EELV + V_T) encroaching on the stiffer upper portion of respiratory system's pressure-volume relationship, where there is increased elastic loading. Healthy young subjects are able to increase their V_T during exercise by encroaching on the ERV (thus reducing the EELV) because they have sufficient expiratory flow reserve at that lung volume to accommodate their V_T within the ERV available. In other words, the flow rates and the volume changes seen during maximal exercise are well within the maximal flow-volume loops obtained at rest, showing no significant expiratory flow-limitation (i.e. impingement of tidal flow-volume loops on the maximal flow-volume loop).

The situation is different in elderly (but healthy) subjects, in whom progressive structural changes in the connective tissue matrix of the lung parenchyma causes loss of the static lung elastic recoil pressures which drive expiratory flow. The net result of this physiological agerelated decline of expiratory flow, particularly over the effort-independent portion of the maximal expiratory flow-volume curve, is the occurrence of expiratory flow limitation. In addition, FRC and RV are usually increased with reciprocal decreases of IC and VC, respectively, while TLC is generally preserved in the elderly.

In contrast to youth, elderly individuals are less able to reduce EELV (or increase IC) during exercise because of expiratory flow-limitation. At high levels of V'_E, therefore, reduction in dynamic IC can occur as a result of reduced lung emptying and gas trapping. This can constrain V_T expansion and increase the elastic work on the inspiratory muscles.

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1. Laviolette L, Laveneziana P; ERS Research Seminar Faculty. Dyspnoea: a multidimensional and multidisciplinary approach. Eur Respir J. 2014 Jun; 43(6):1750-62.
2. O'Donnell DE and Laveneziana P. Physiology and consequences of lung hyperinflation in COPD. Eur Respir Rev 2006; 15: 100, 61-67
3. O'Donnell D.E., Ofir D., Laveneziana P. Patterns of cardiopulmonary response to exercise in lung diseases. In: Ward SA, Palange P, eds. Clinical Exercise Testing. European Respiratory Monograph, June 2007, Volume 12, Number 40, Chapter 3, pg 69-92.
4. Laviolette L, Laveneziana P; ERS Research Seminar Faculty. Dyspnoea: a multidimensional and multidisciplinary approach. Eur Respir J. 2014 Jun; 43(6):1750-62.

EVALUATION

1. Dynamic lung hyperinflation is defined as:
   a. an increase in expiratory reserve volume
   b. a temporary and variable increase in end-inspiratory lung volume (EILV) beyond its baseline value
   c. a temporary and variable increase in end-expiratory lung volume (EELV) beyond its baseline value
   d. a plateau in tidal volume (VT) response

2. The neuroventilatory dissociation (NVD) influences dyspnoea mostly in:
   a. healthy subjects
   b. patients with respiratory disorders
   c. both
   d. neither

3. Exertional dyspnoea in COPD strictly correlates with:
   a. decrease in FEV1
   b. increase in dynamic lung hyperinflation and constraints in VT expansion
   c. both
   d. neither

4. Perception of exertional dyspnoea in COPD is principally associated with:
   a. increased work/effort
   b. unsatisfied inspiration
   c. both
   d. neither

5. The intensity of dyspnoea in patients with weak respiratory muscles is:
   a. greater than in healthy
   b. lower than in healthy
   c. as much as in healthy

Advanced respiratory and cardiovascular testing In health and respiratory disease

Respiratory mechanics: changes in disease

Dr. Pierantonio Laveneziana

Amsterdam, 26 September 2015

Service d'Explorations Fonctionnelles de la Respiration, de l'Exercice et de la Dyspnée (EFRED)
Département "R3S" (Respiration, Réanimation, Réhabilitation, Sommeil)

Groupe Hospitalier Pitié-Salpêtrière Charles Foix
Assistance Publique-Hôpitaux de Paris

Sorbonne Universités, UMR_S 1158, INSERM et Université Pierre et Marie Curie (Paris 6)
Neurophysiologie Respiratoire Expérimentale et Clinique

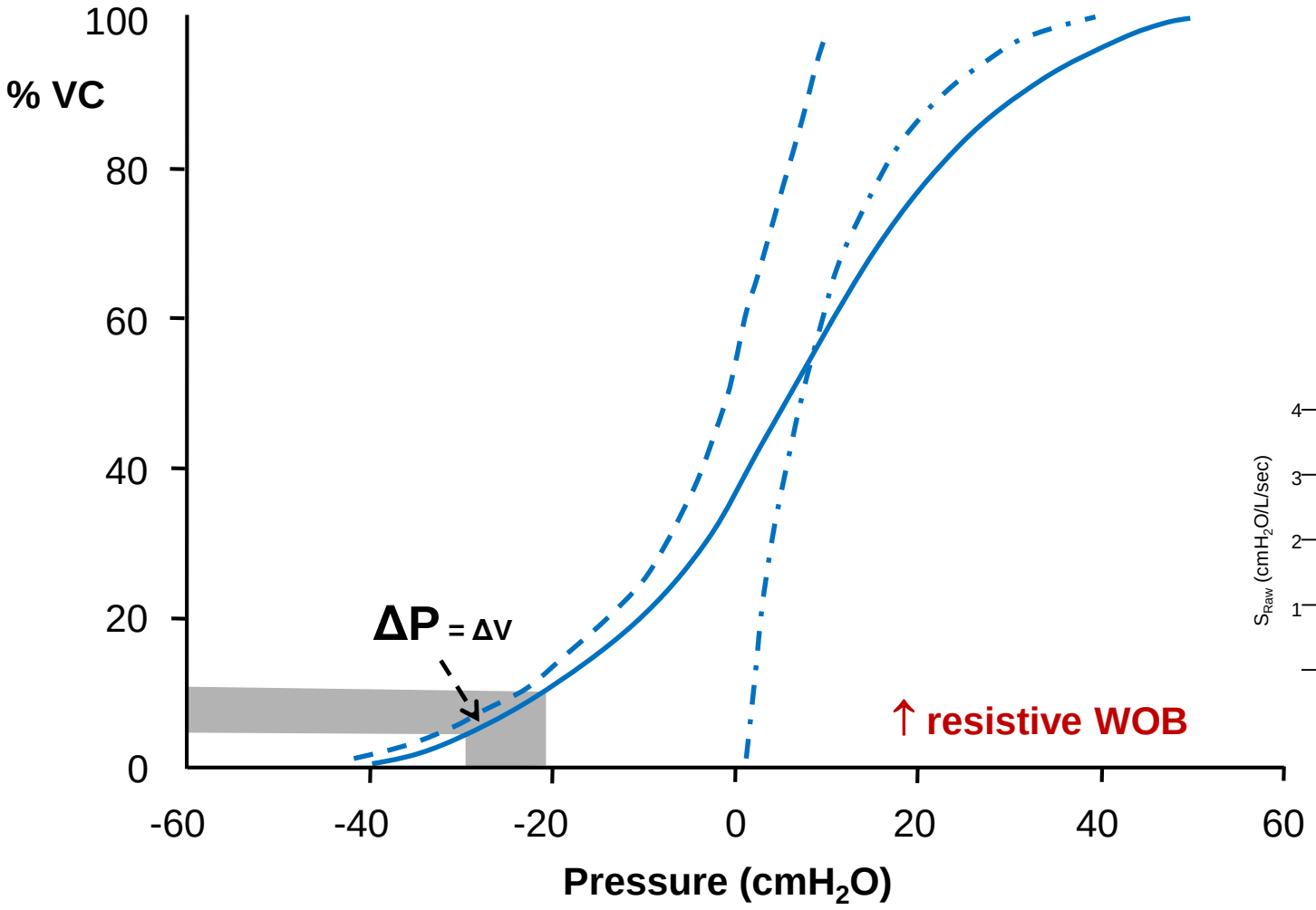
Conflicts of interest

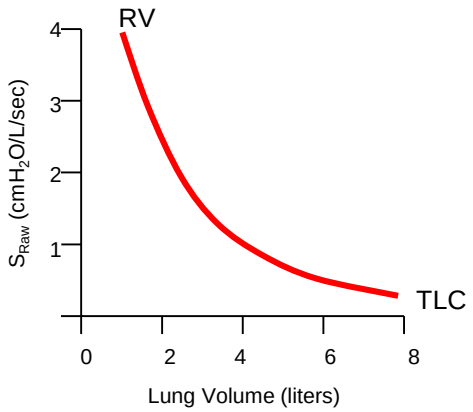
- Nothing to disclose

AGENDA

- **Ventilatory Mechanics**
  - ✓ **Pressure-Volume relationship**
  - ✓ **Flow-Volume Loops**
  - ✓ **Lung Hyperinflation**
  - ✓ **Tidal volume constraints**
- **Exertional Dyspnoea (Denis O'Donnell)**

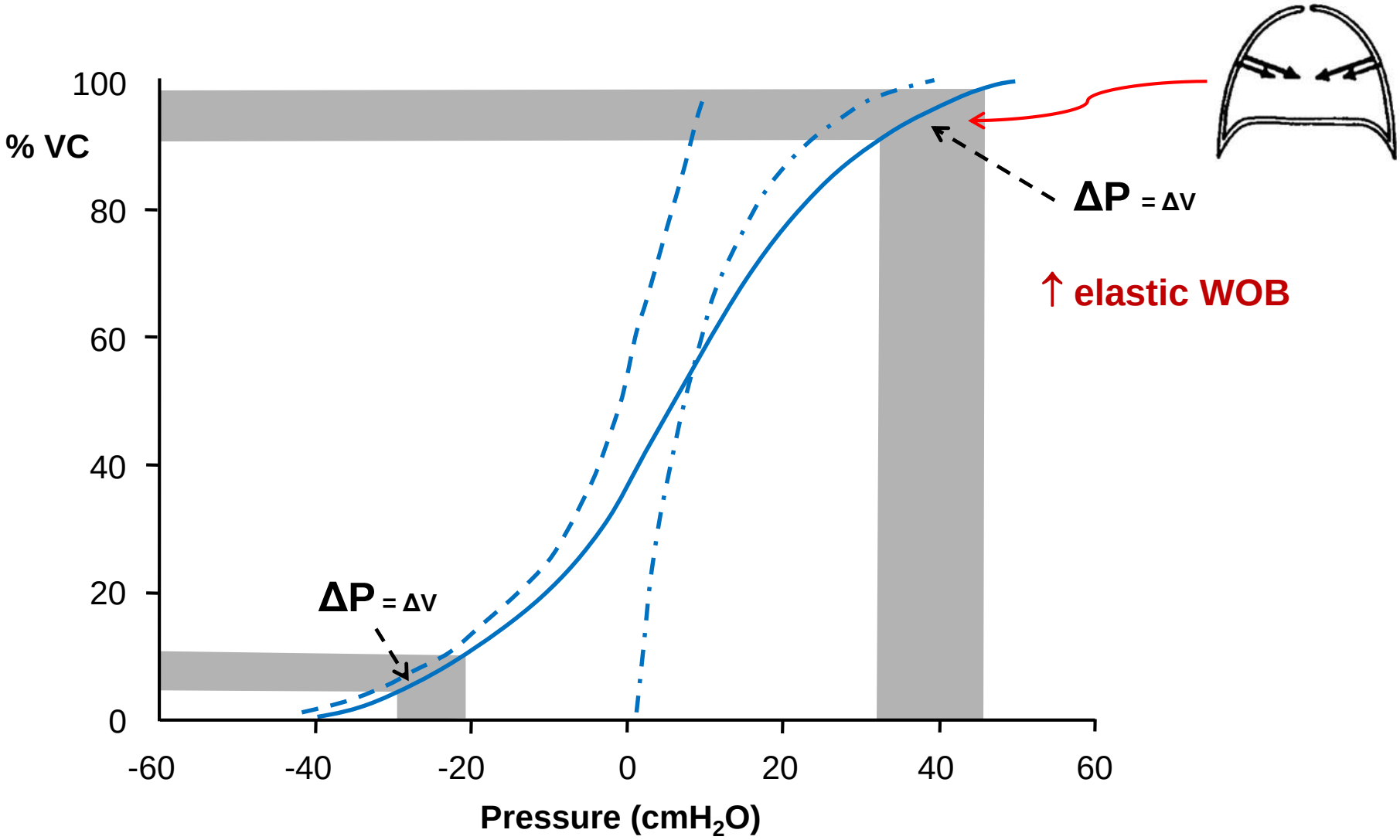
Ventilatory Mechanics: Healthy



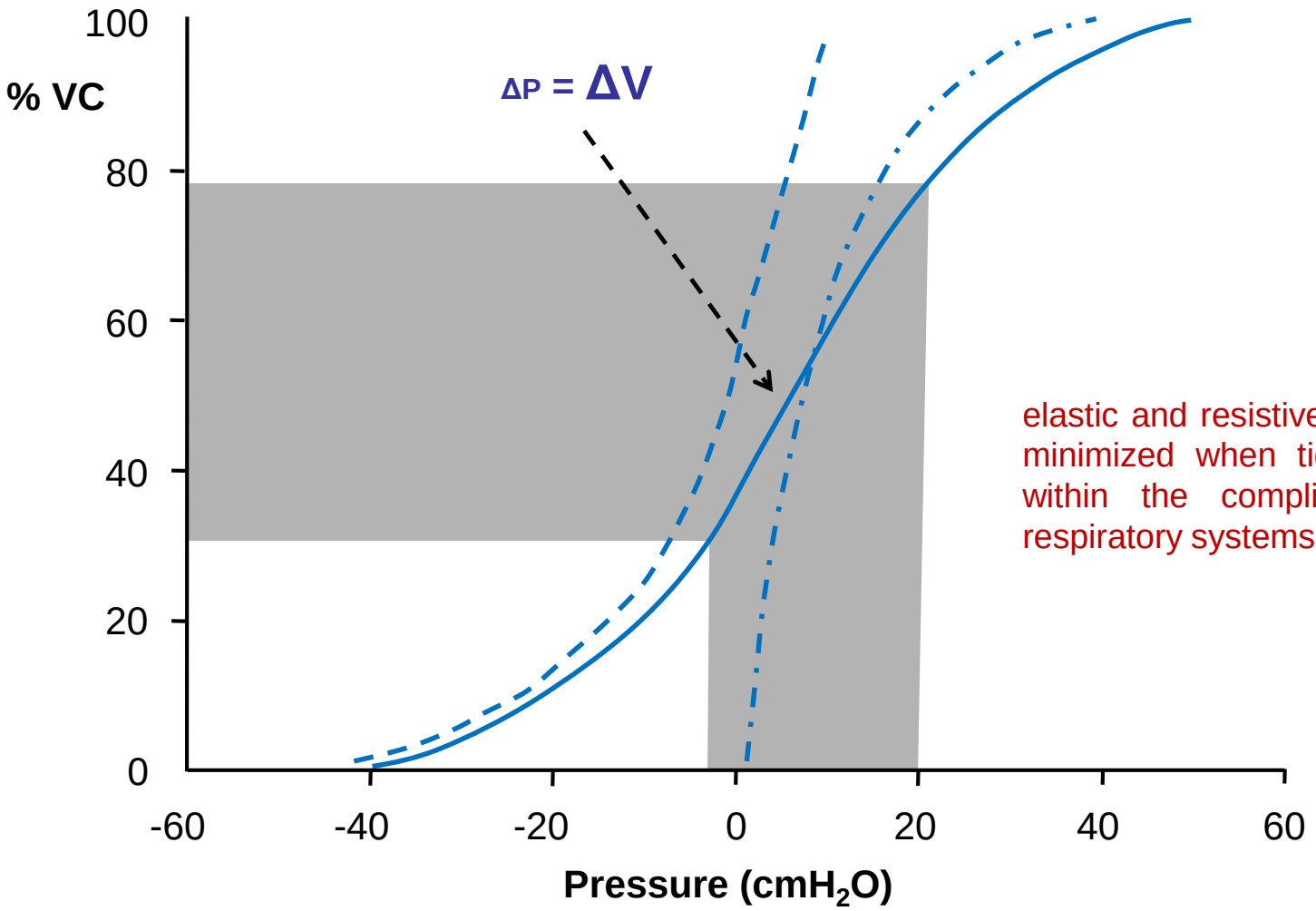


S_{Raw} ↓ as lung volume ↑ because the airways distend as the lungs inflate, and bigger airways have lower resistance (*Poiseuilles' Law*). The opposite is also true, of course!

Ventilatory Mechanics: Healthy

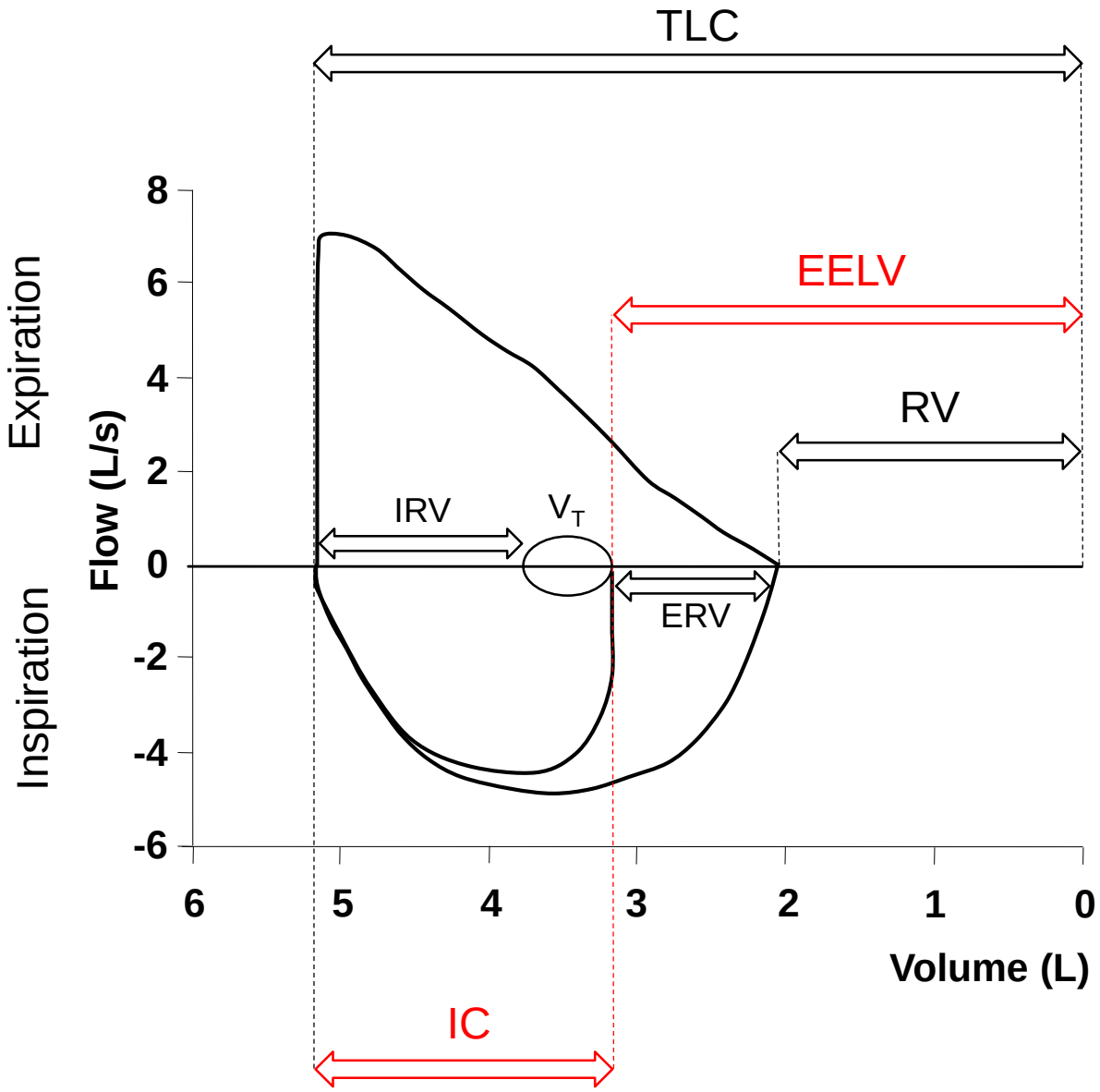


Ventilatory Mechanics: Healthy

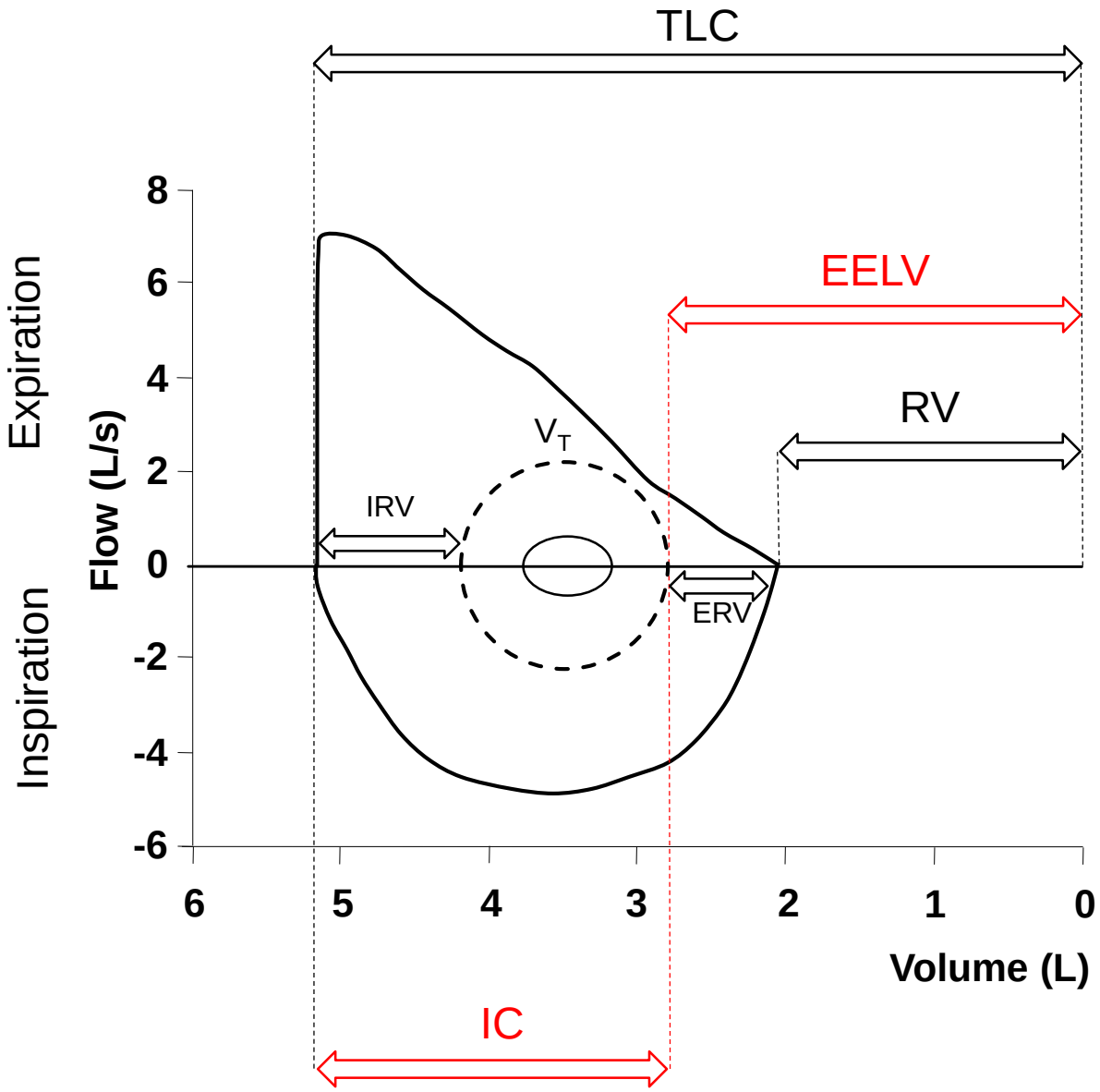


elastic and resistive work of breathing is minimized when tidal breathing occurs within the compliant portion of the respiratory systems P-V curve

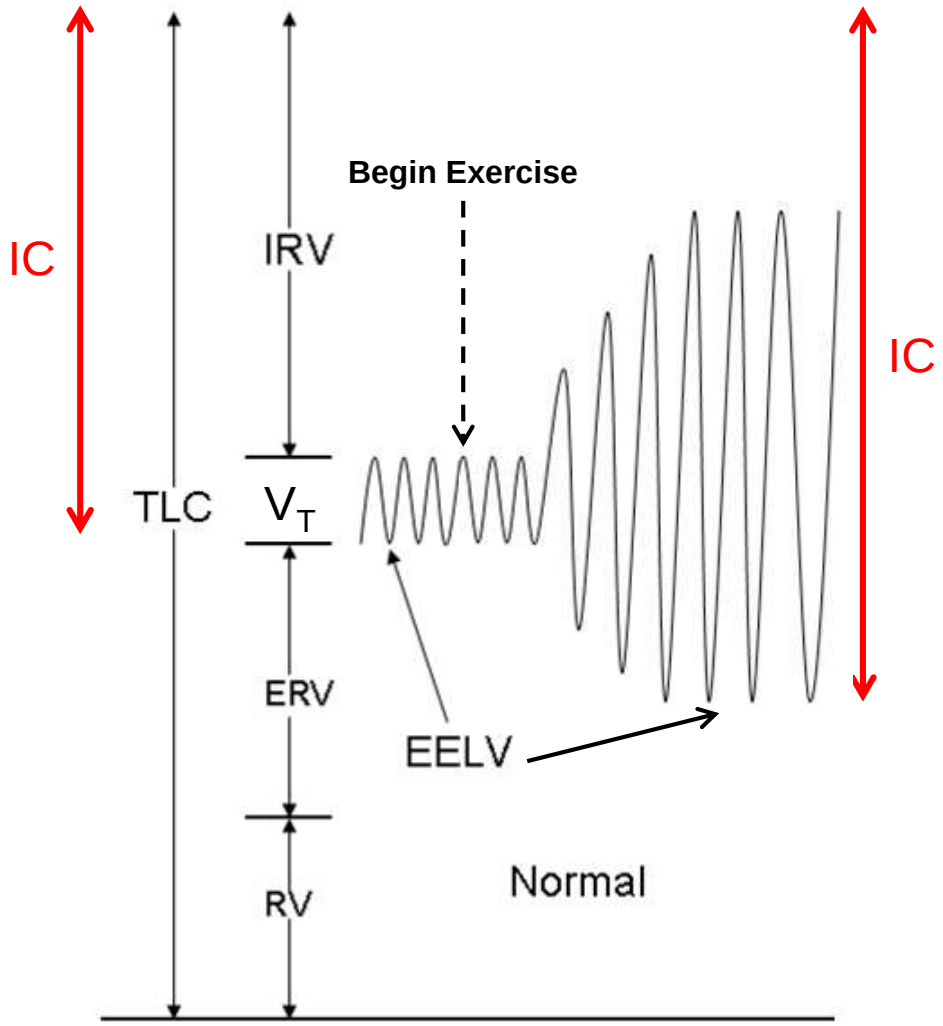
Ventilatory Mechanics: Healthy



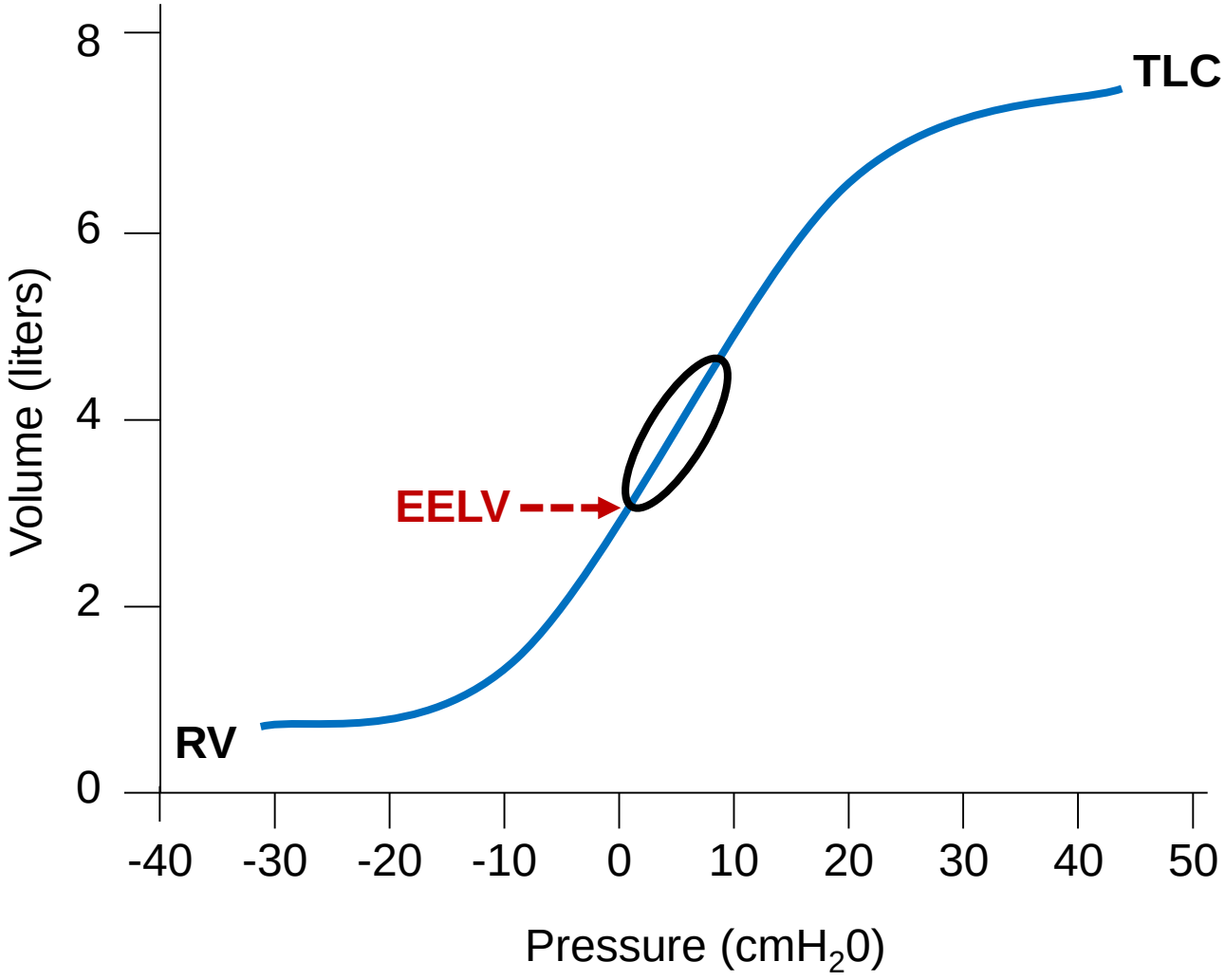
Ventilatory Mechanics: Healthy



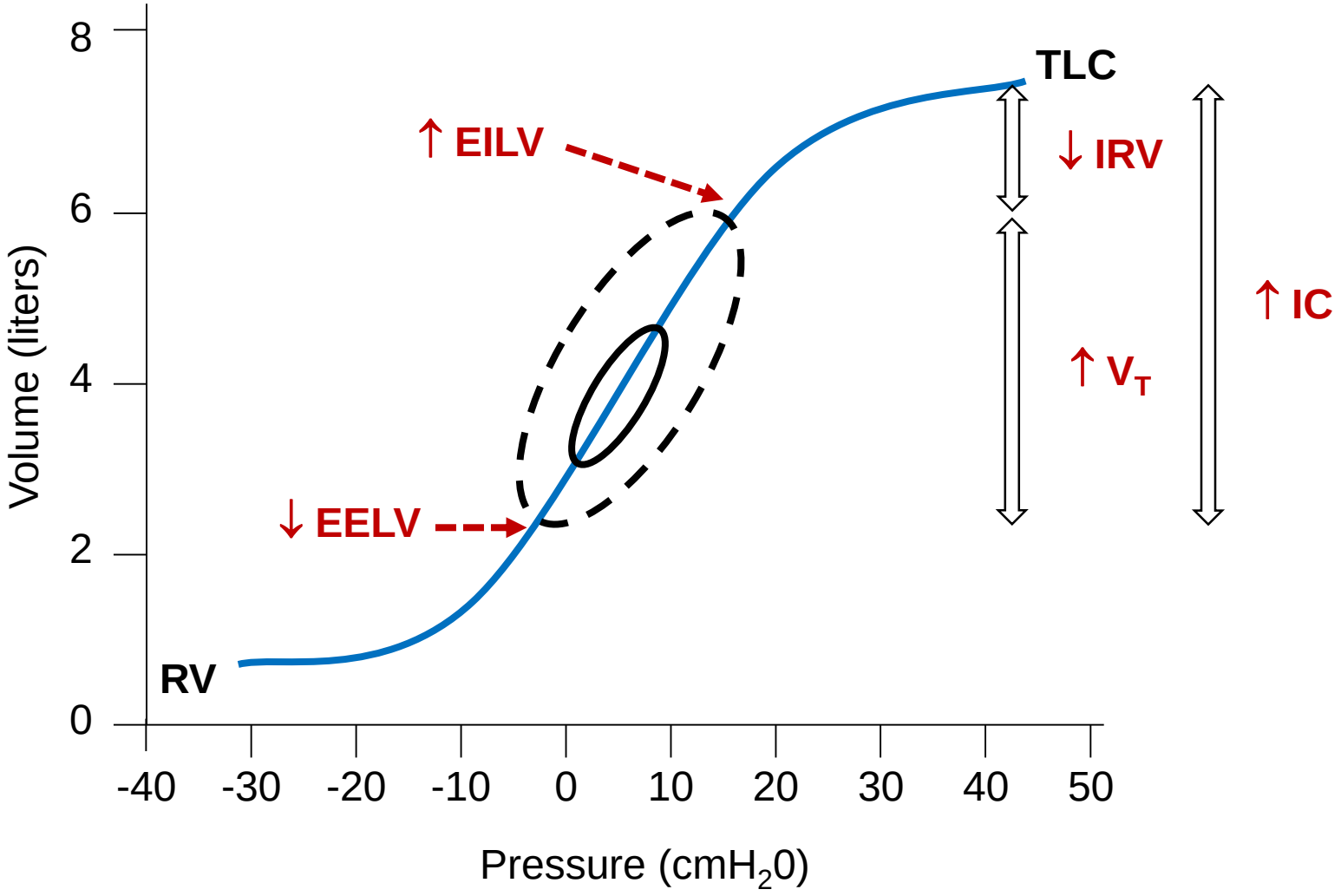
Ventilatory Mechanics: Healthy



Ventilatory Mechanics: Healthy



Ventilatory Mechanics: Healthy



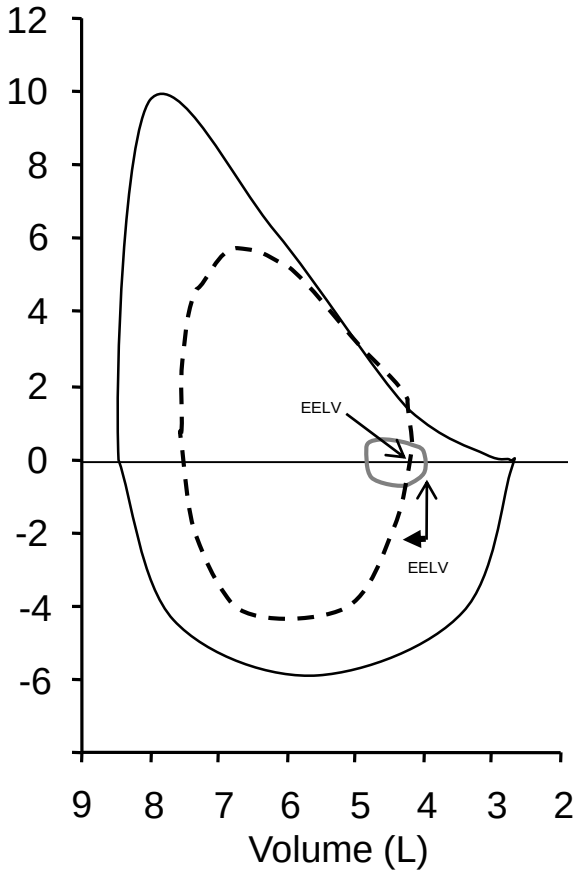
Ventilatory Mechanics: Healthy

The precise control of operating lung volumes (i.e., ↑ EILV and ↓ EELV) during exercise allows V_T to expand within the compliant (or linear) portion of the respiratory systems P-V relationship, which helps to:

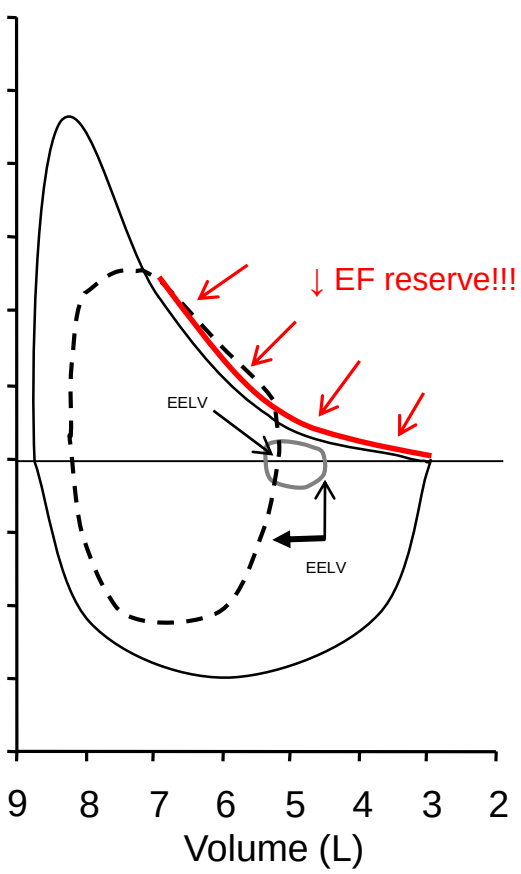
1. maintain alveolar gas exchange
2. minimize the work or O_2 cost of breathing
3. preserve the harmonious relationship between central ventilatory drive (respiratory effort) and the simultaneous mechanical response of the respiratory system (V_T expansion), i.e., neuromechanical coupling of the respiratory system
    - ✓ thereby minimizing the perception of exertional respiratory discomfort

Ventilatory Mechanics: Healthy vs COPD

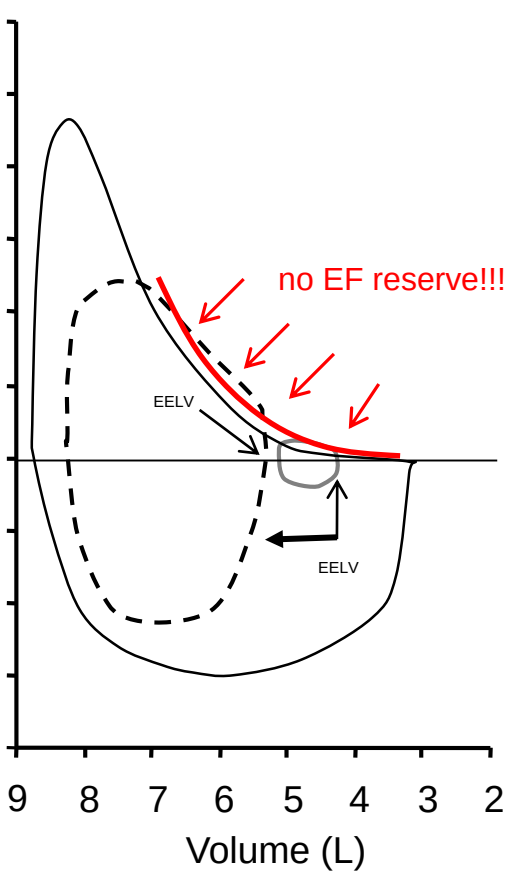
Older Male
Age = 66 yrs



Mild COPD
Age = 67 yrs



Severe COPD
Age = 65 yrs



Laveneziana P, et al. Appl. Physiol. Nutr. Metab. 2007; 32: 1225-1238

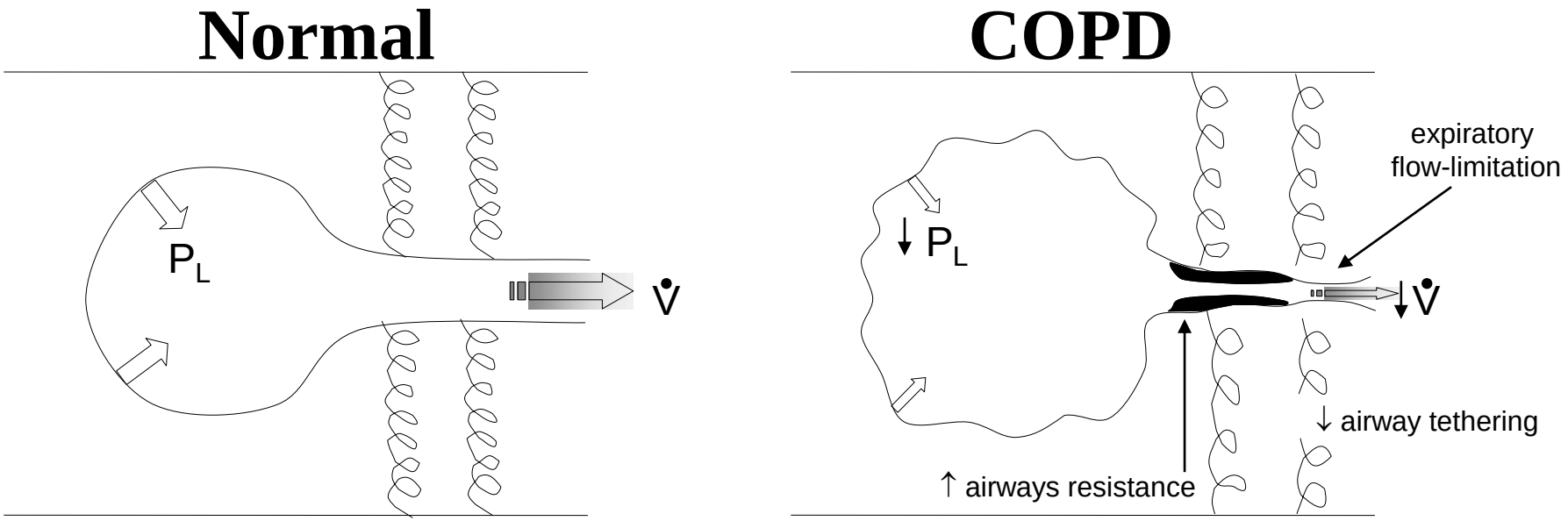
Ventilatory Mechanics: Healthy vs COPD

- **Dynamic hyperinflation: a temporary and variable increase in end expiratory lung volume (EELV) beyond its baseline value**

- **EELV: volume of gas left in the lung at the end of a quiet breath out**

Ventilatory Mechanics: COPD and dynamic hyperinflation

- Gas dilution techniques
- Exercise body plethysmography
- Respiratory inductance plethysmography
- Optoelectronic plethysmography
- Inspiratory capacity measurements

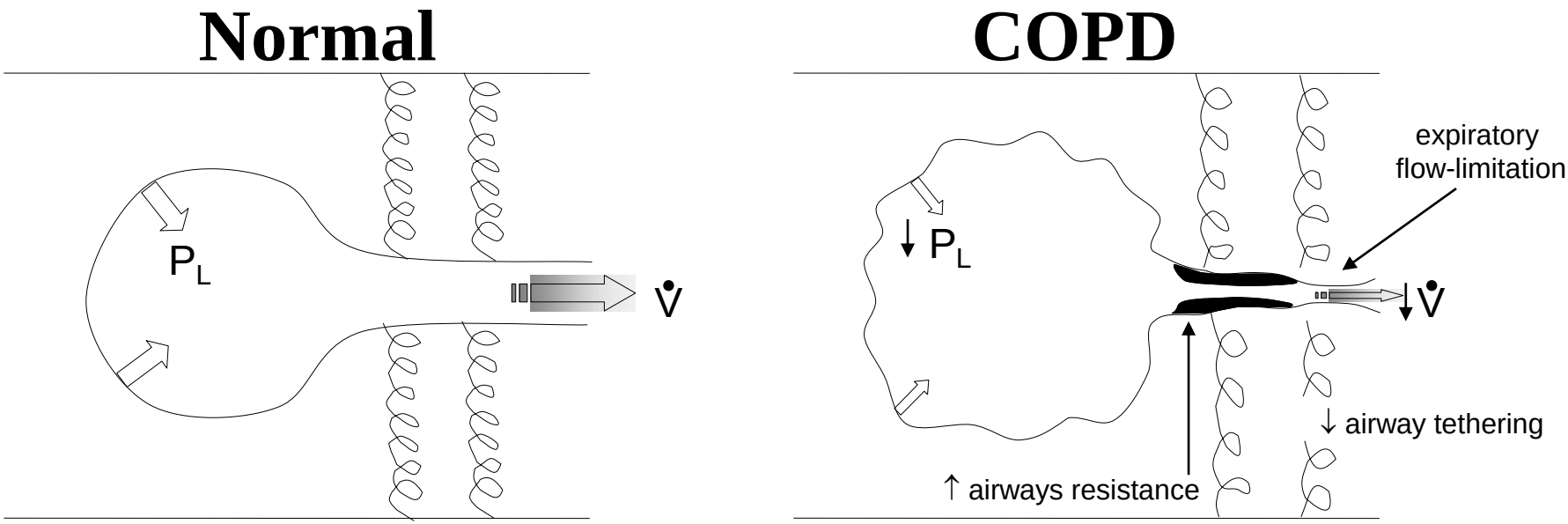


Expiratory flow-limitation

↑ mechanical time-constant for lung emptying (compliance x resistance)

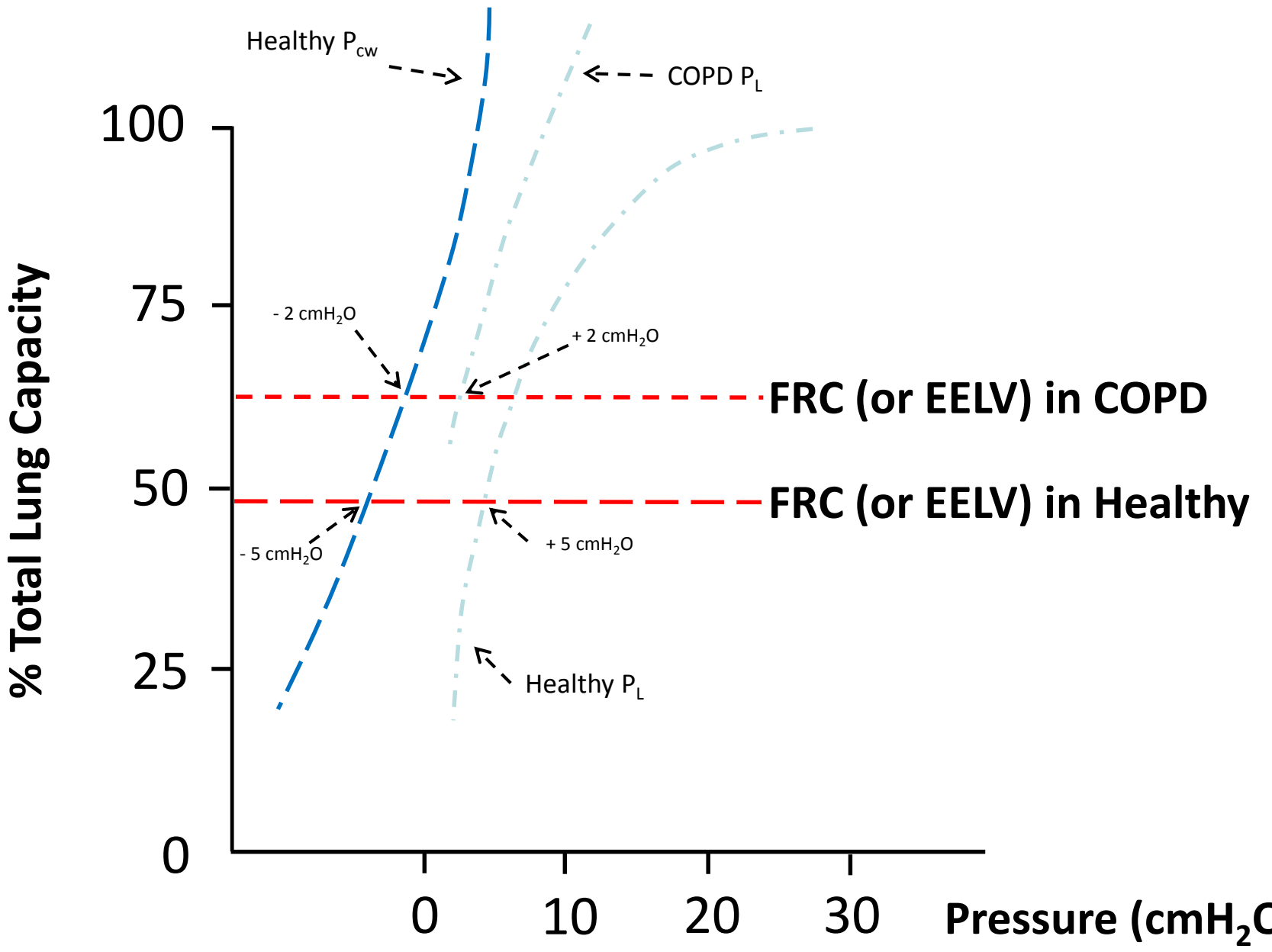
Expiratory time available is insufficient to allow EELV to return to its baseline value

Gas retention or air trapping or lung hyperinflation

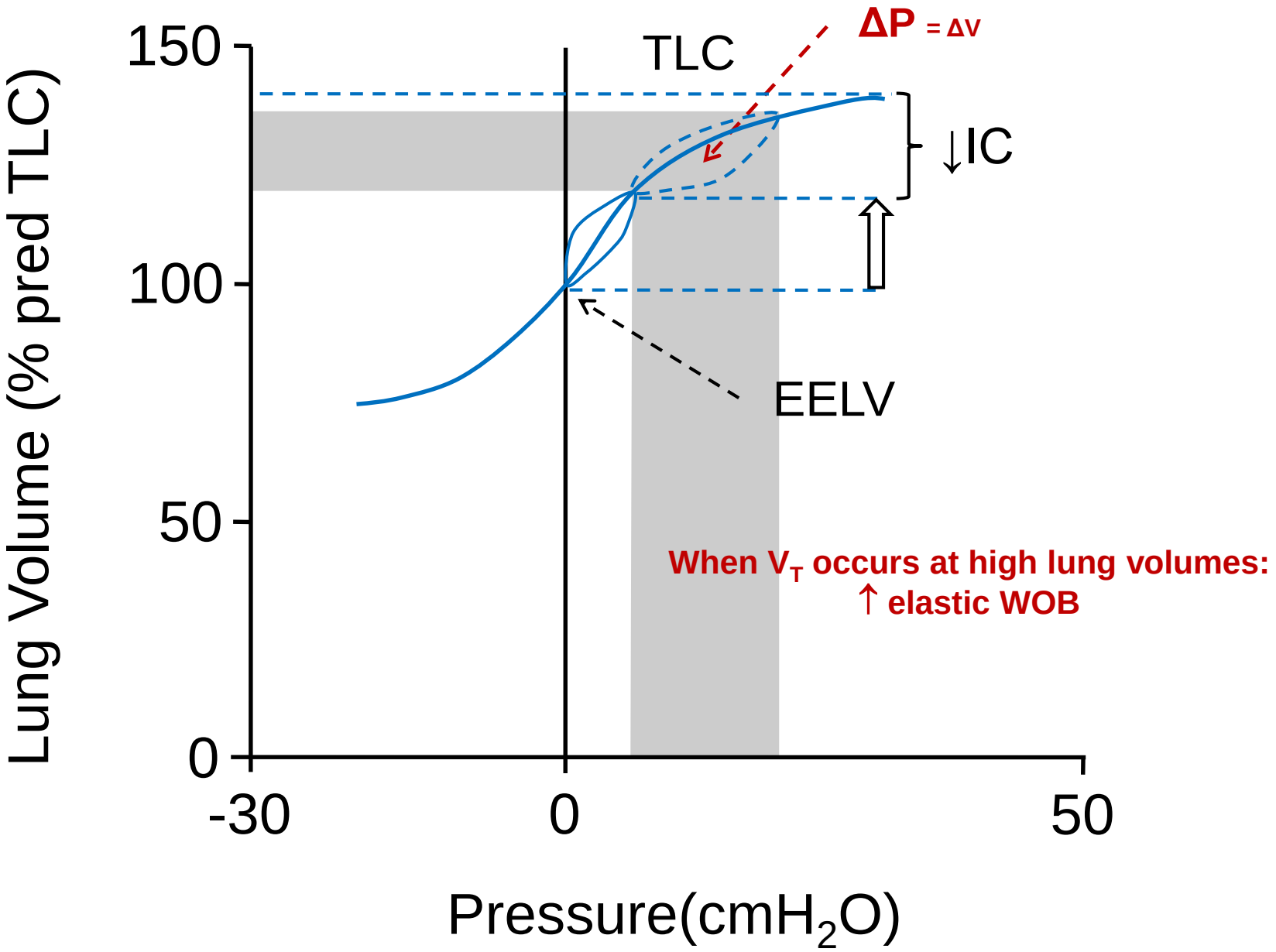


In other words, lung emptying during expiration becomes incomplete because it is interrupted by the next inspiration and EELV therefore exceeds the natural relaxation volume of the respiratory system (Palv > Patm)

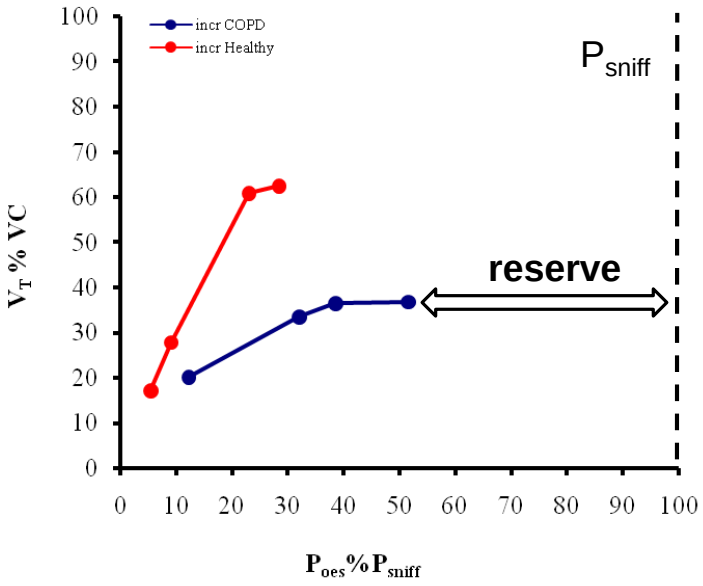
Ventilatory Mechanics: Healthy vs COPD



Ventilatory Mechanics: COPD



Ventilatory Mechanics: COPD

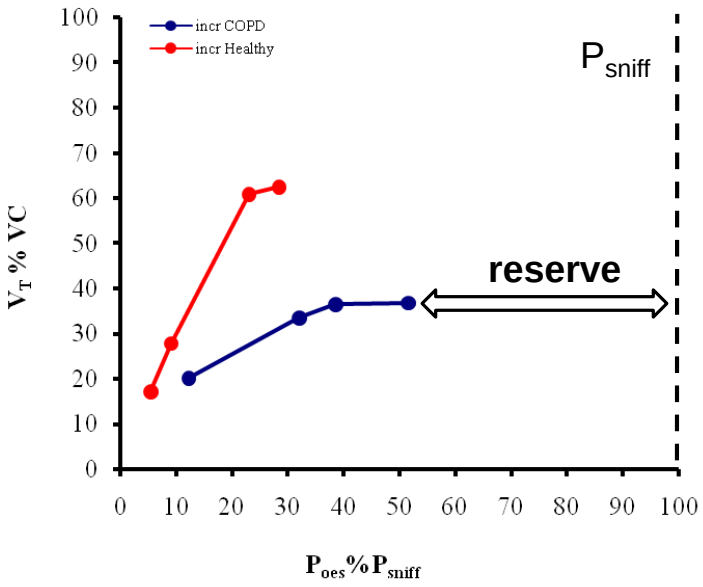


Lung hyperinflation (static and/or dynamic EELV increase) places the inspiratory muscles, especially the diaphragm, at a significant mechanical disadvantage by shortening its fibers, thereby compromising its force generating capacity [Laghi F and Tobin MJ. Am J Respir Crit Care Med 2003; 168: 10-48]

In the presence of static lung hyperinflation this functional muscle weakness is mitigated, to some extent, by long term adaptations which causes a leftward shift of the length-tension relationship, thus improving the ability of the muscles to generate force at higher lung volumes:

- shortening of diaphragmatic sarcomeres [Orozco-Levi M, et al. Eur Respir J 1999; 13: 371-378]
- decrease in sarcomere number [Supinski GS, Kelsen SG. Effect of elastase-induced emphysema on the force-generating ability of the diaphragm. J Clin Invest 1982; 70: 978-988]

Ventilatory Mechanics: COPD



In patients with chronic lung hyperinflation, adaptive alterations in muscle fiber composition (an increase in the relative proportion of slow-twitch, fatigue resistant, type I fibres) [Levine S, et al. N Engl J Med 1997; 337: 1799-1806; Mercadier JJ, et al. Am J Physiol 1998; 274(4 Pt 1): L527-534]

and oxidative capacity (an increase in mitochondrial concentration and efficiency of the electron transport chain) [Orozco-Levi M, et al. Eur Respir J 1999; 13: 371-378]

are believed to preserve the functional strength of the overburdened diaphragm [Similowski T, et al. N Engl J Med 1991; 325: 917-923]

and make it more resistant to fatigue [Orozco-Levi M, et al. Eur Respir J 1999; 13: 371-378; Levine S, et al. N Engl J Med 1997; 337: 1799-1806; Mador MJ, et al. Am J Respir Crit Care Med 2000; 161: 118-123]

Inspiratory muscles in COPD

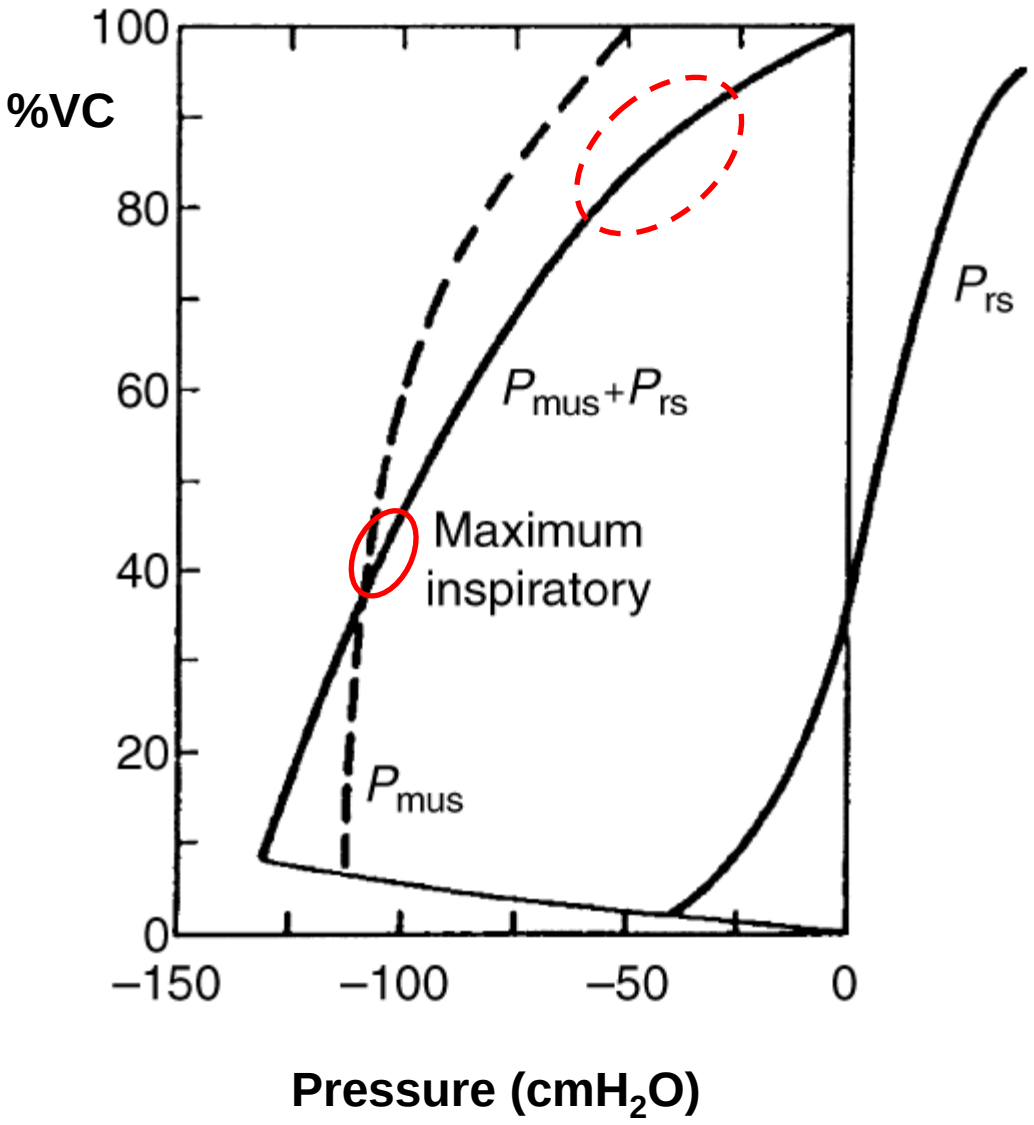
Table 1 Quadriceps and diaphragm structure and function in patients with COPD compared with controls

	Quadriceps	Diaphragm
Strength	Reduced	Unchanged
Endurance	Reduced	Increased
Overall CSA	Reduced	Unchanged
Single-fiber CSA	Reduced in type IIX	Reduced in type I
Fiber type shift	Type I to II	Type II to I
Capillary and mitochondrial density	Reduced	Increased
Metabolism – oxidative: glycolytic ratio	Reduced	Increased

Abbreviation: CSA, cross-sectional area.

Donaldson AV et al International Journal of COPD 2012

Ventilatory Mechanics: COPD



In this regard, Similowski and colleagues demonstrated that the reduction in pressure-generating capacity of the inspiratory muscles of stable COPD patients was related to lung hyperinflation and that diaphragmatic function in such patients was comparable to normal subjects when measurements were compared at the same lung volume

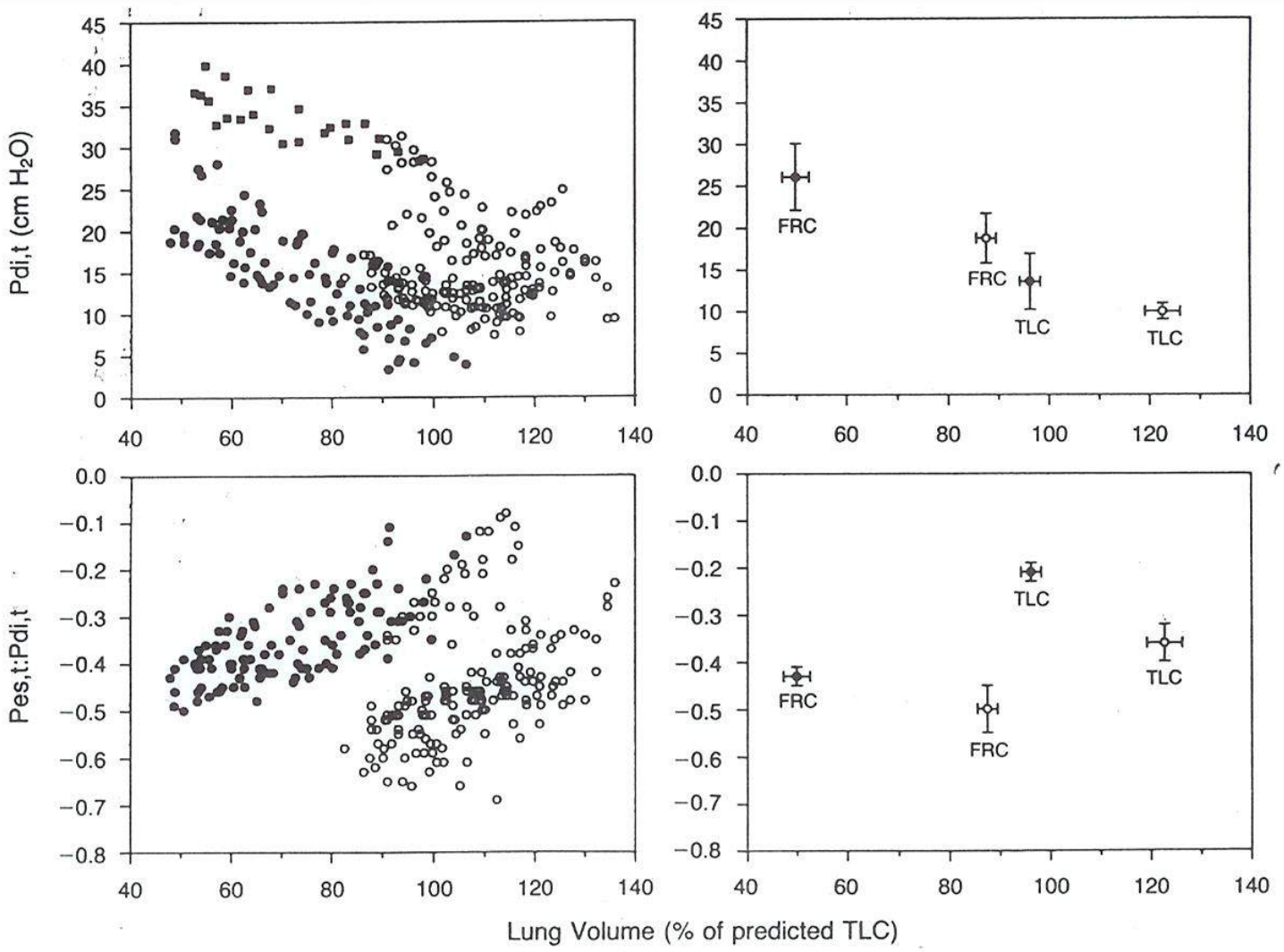
- Similowski T, et al. N Engl J Med 1991; 325: 917-923

The evidence that measurable fatigue develops in COPD is inconclusive, even at the limits of tolerance

- Mador MJ et al., Am J Respir Crit Care Med 2000; 161: 118-123
- Bye PT et al., Am Rev Respir Dis 1985; 132: 236-240
- Sinderby C et al., Am J Respir Crit Care Med 2001; 163: 1637-1641
- Polkey MI et al. Am J Respir Crit Care Med 1995; 152: 959-964

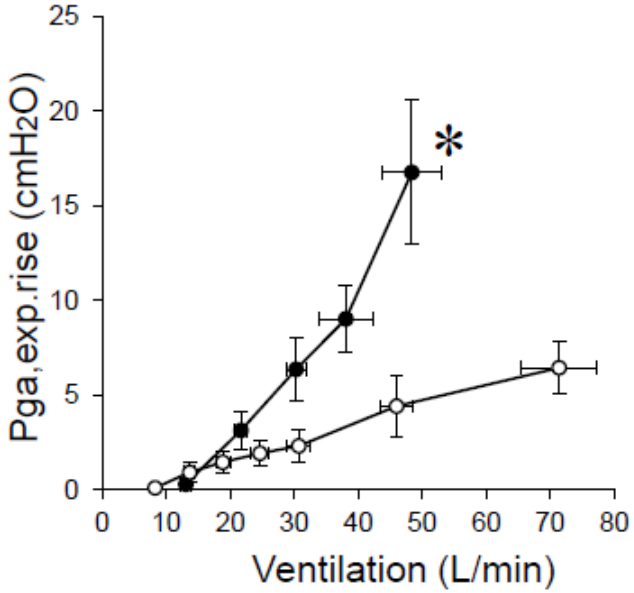
Inspiratory muscles in COPD

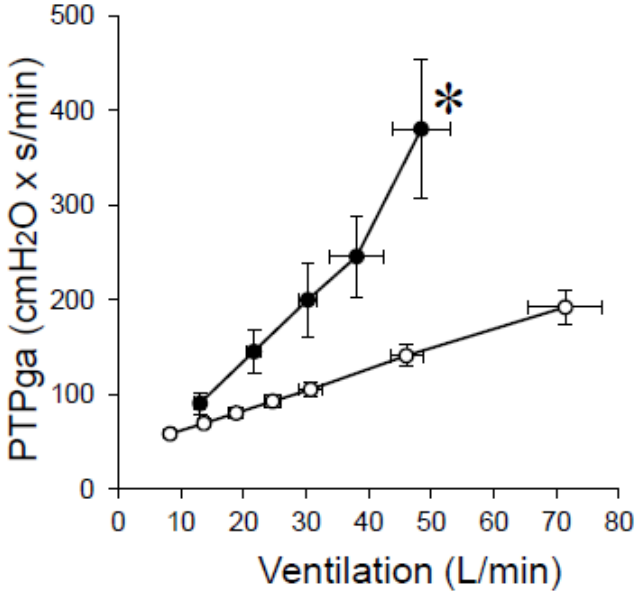
Contractile Properties of the Human Diaphragm during Chronic Hyperinflation

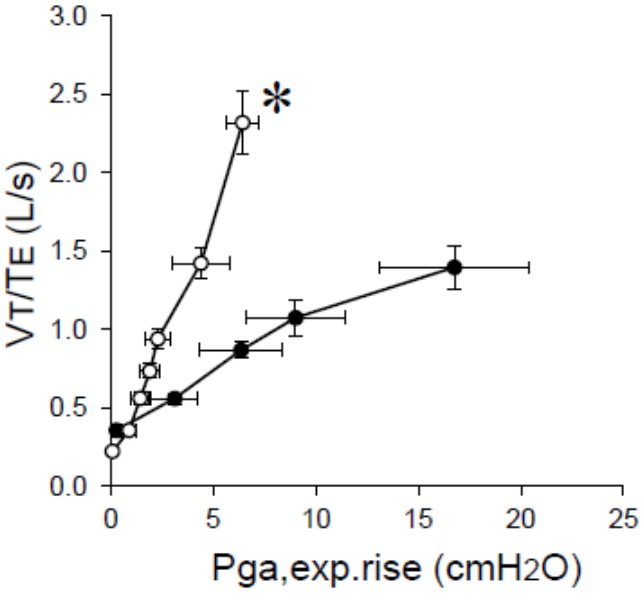


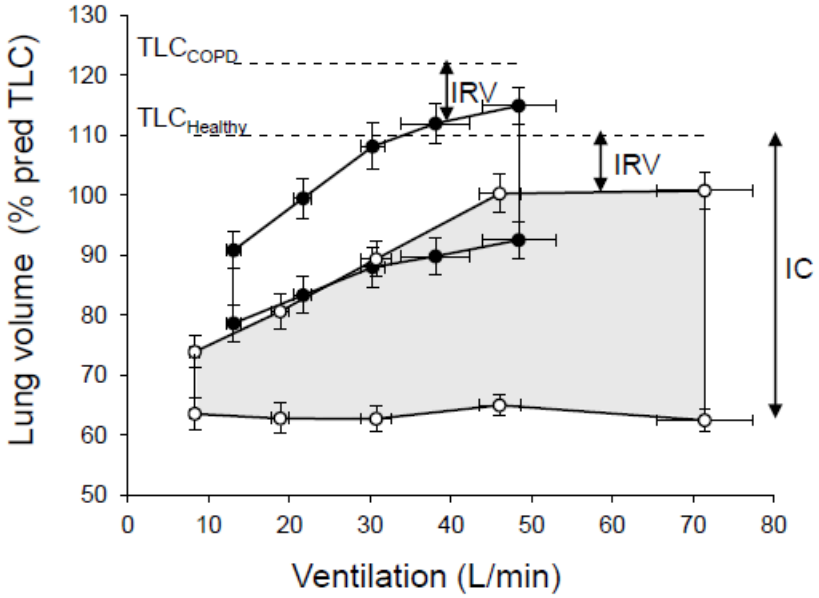
Similowski T et al, NEJM 1991; 325:917-23

Expiratory muscles in COPD



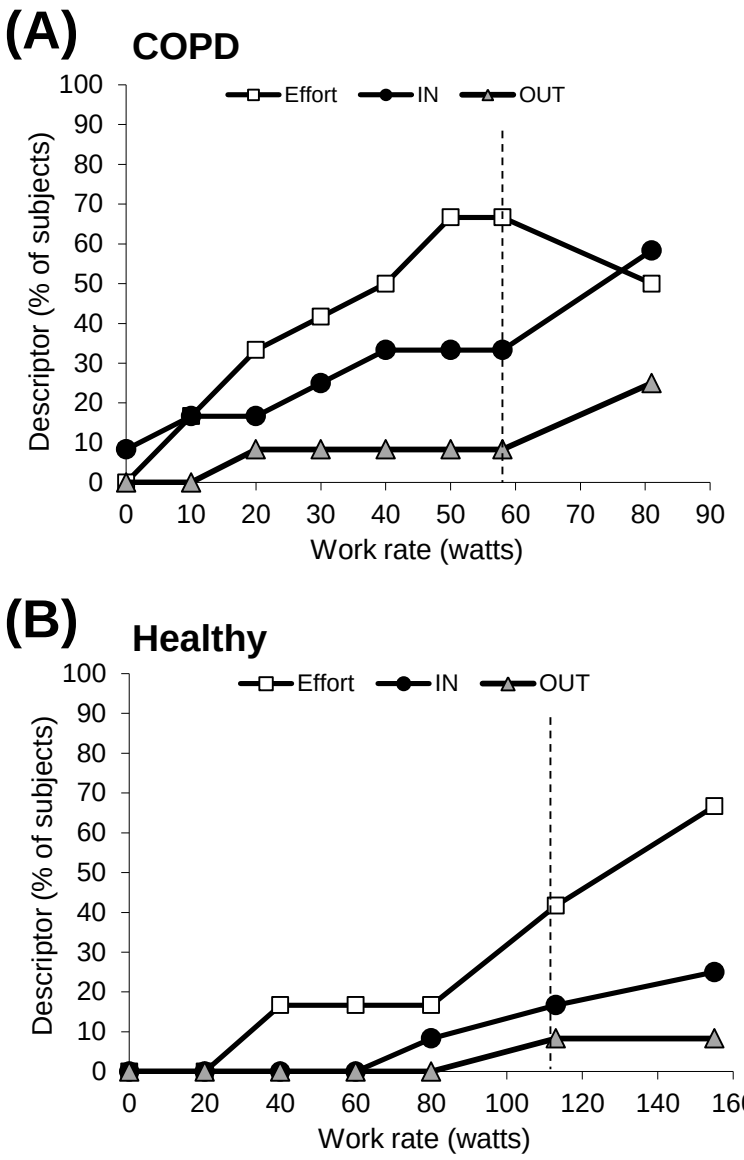


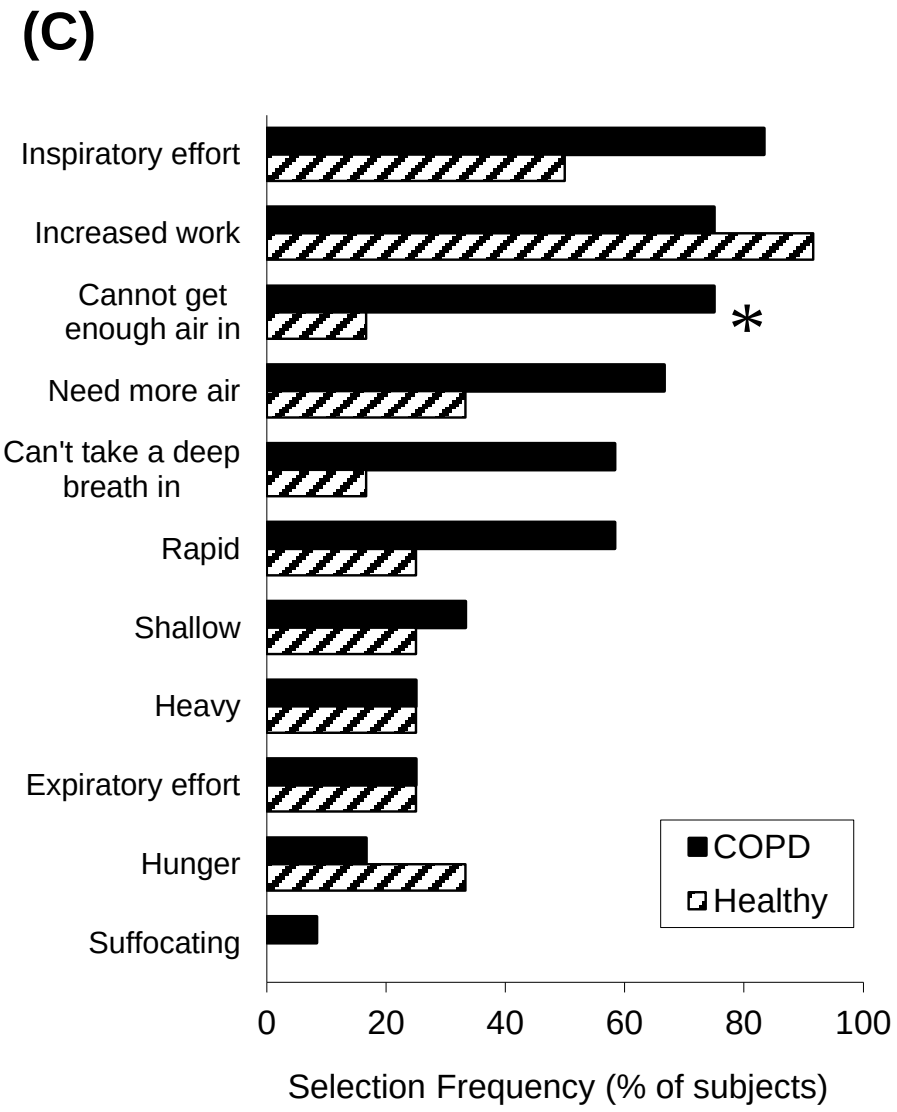




Laveneziana P et al, RESPNB 2014

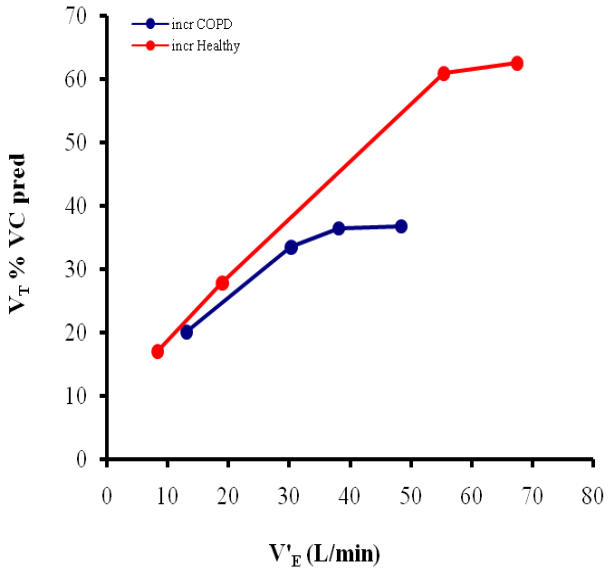
Expiratory muscles in COPD

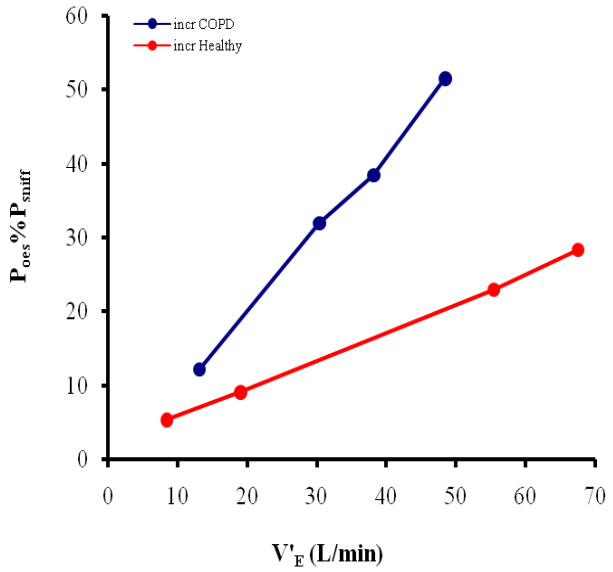


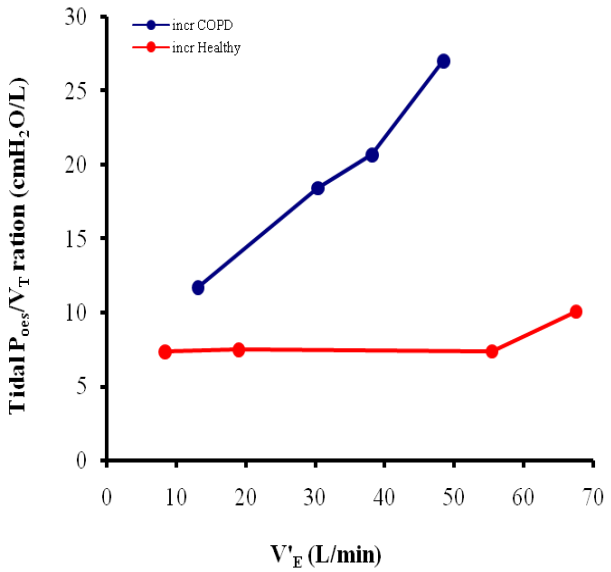


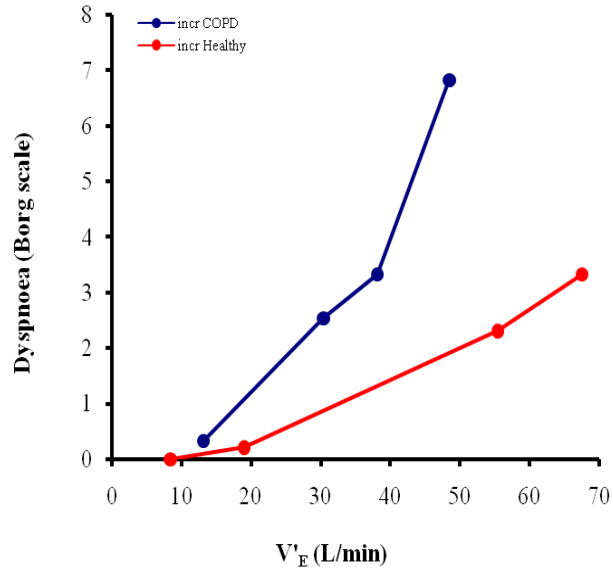
Laveneziana P et al, RESPNB 2014

Ventilatory Mechanics: COPD









COPD is characterized by DH (80-85%) with attendant mechanical restraint of V_T expansion during progressive exercise…

DH significantly ↑ the effort required to achieve a given ventilation during exercise (↑ elastic/threshold loads + functional weakness of insp muscles)

Despite ↑ respiratory effort, V_T is mechanically constrained (→ tachypnoea; ↓CL_{dyn}, ↑V_D/V_T, ↑ $PaCO_2$) with early ventilatory limitation to exercise. Consequently, the relationship between respiratory effort and thoracic displacement ↑ progressively during exercise

The widening disparity between respiratory effort and volume displacement (panel C) contributes importantly to the ↑ perception of exertional dyspnea and thus exercise intolerance

Laveneziana P et al, AJRCCM 2011
O'Donnell DE et al, JAP 2006

Negative effects of DH during exercise

- ↑ Elastic/threshold loads
- Inspiratory muscle weakness

} ↑P_{es}/P_{Imax} 'effort'

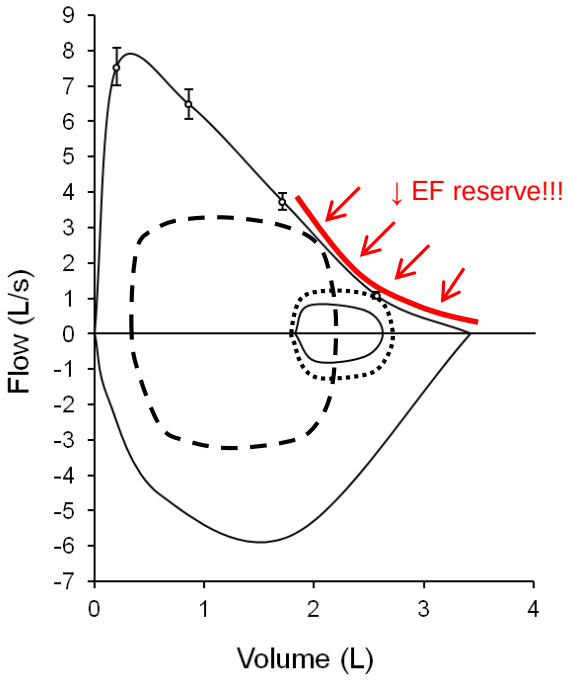
- Reduced V_T expansion

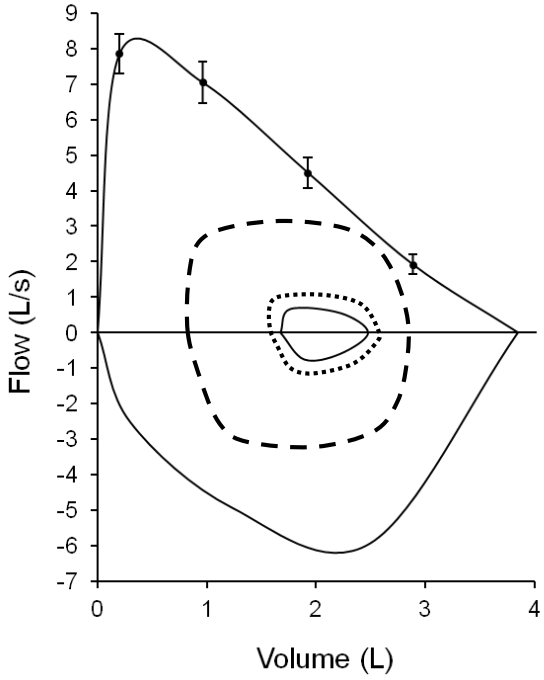
→ tachypnoea

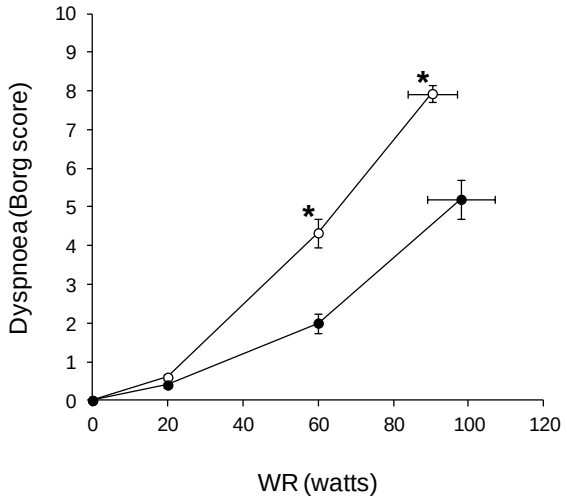
} ↓$C_L$dyn
↑V_D/V_T
↑$PaCO_2$

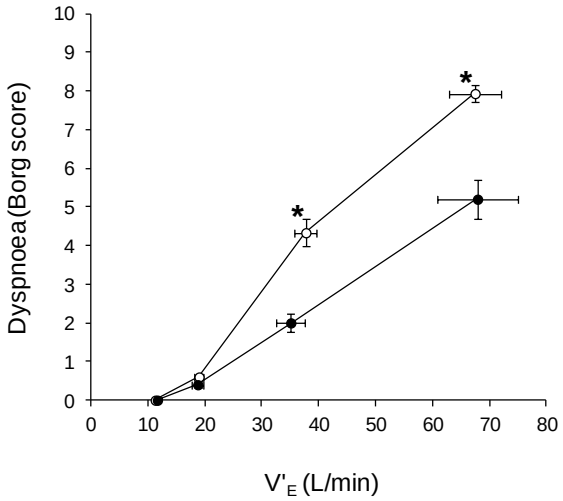
- Early ventilatory limitation to exercise
- Cardiac impairment
- ↑ Exertional dyspnoea

Ventilatory Mechanics and Exertional Dyspnoea: PAH







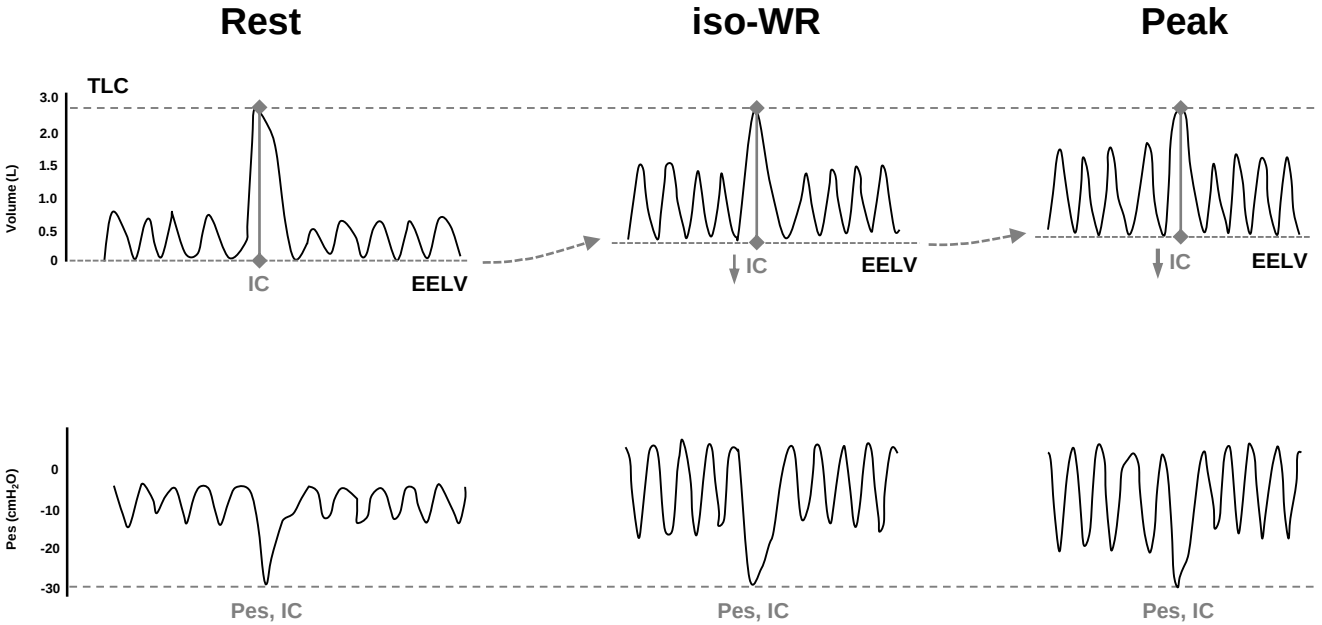


Roughly 50 to 60% of the variance of Delta Borg ratings of dyspnoea were accounted for by changes in dynamic respiratory mechanics

Roughly 30% of the variance of Delta Borg ratings of dyspnoea were accounted for by changes in V'E

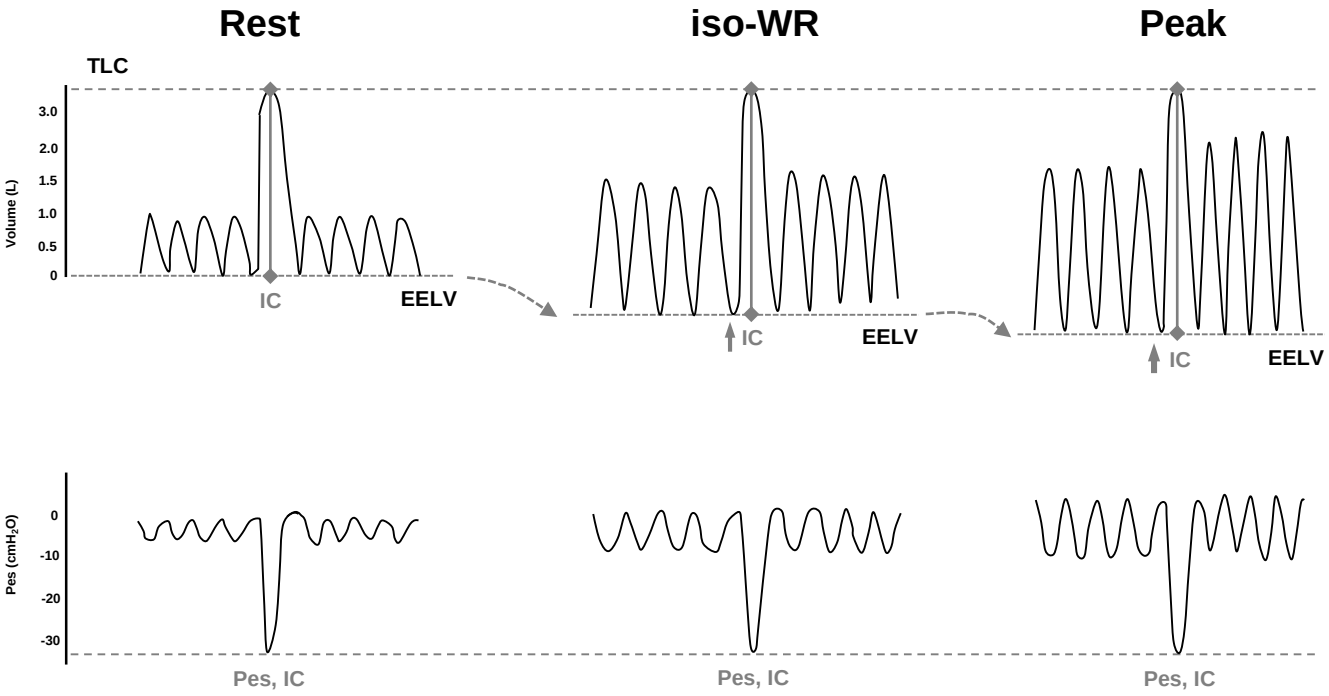
Laveneziana P et al, ERJ 2013

PAH-H



No resp muscle weakness/fatigue

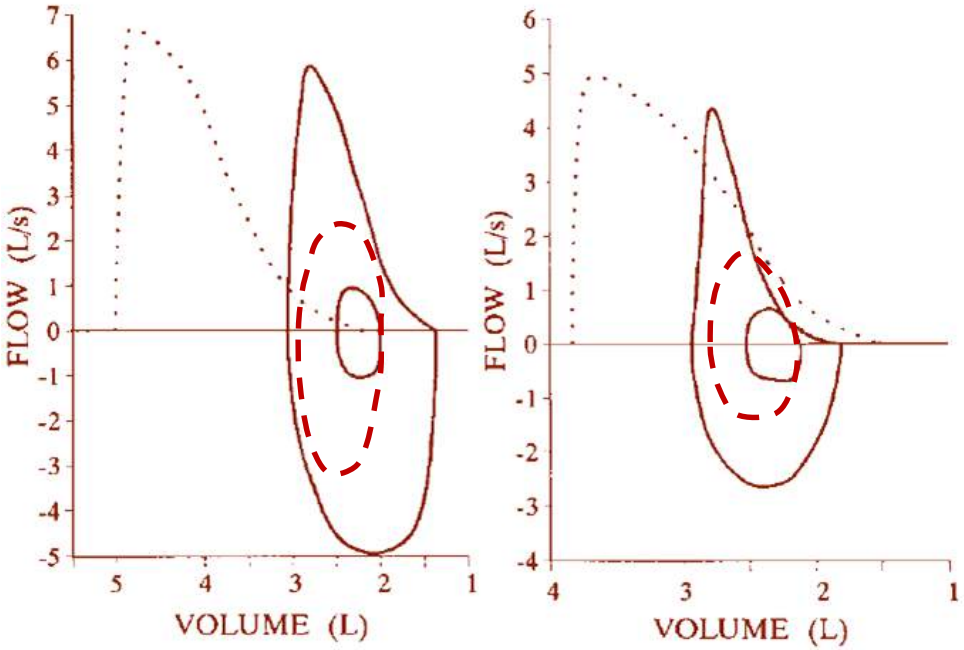
PAH-NH

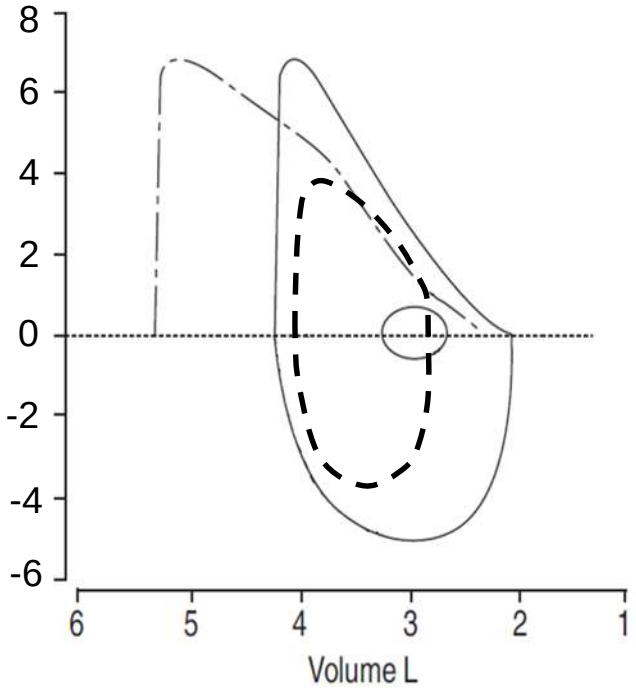


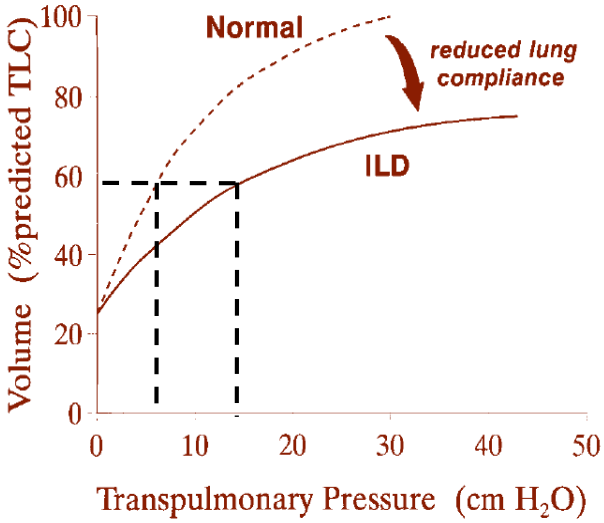
No resp muscle weakness/fatigue

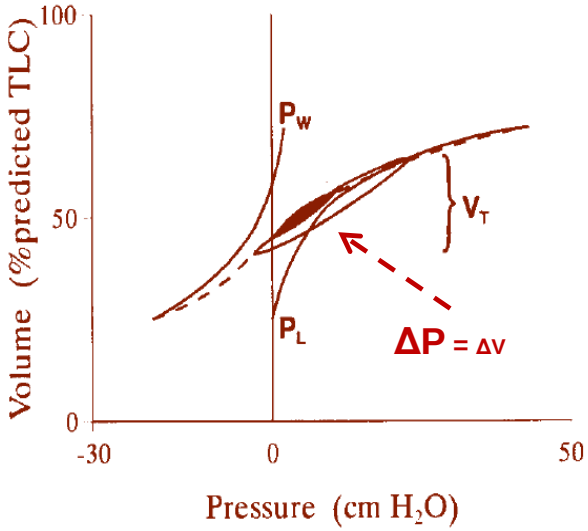
Laveneziana P, ERJ 2015

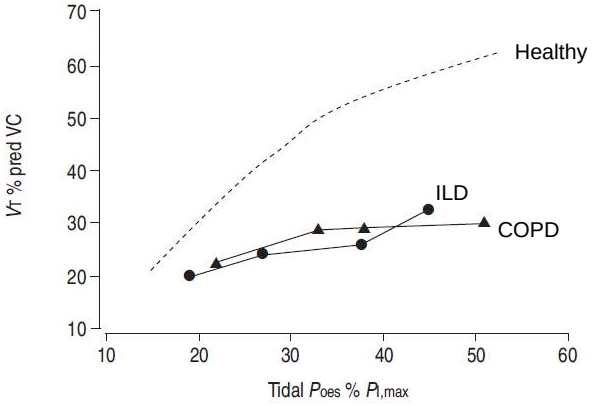
Ventilatory Mechanics and Exertional Dyspnoea: ILD











O'Donnell DE, Ofir D, Laveneziana P. Eur Respir Mon 2007; 40: 69-92

Thanks !

Measurement of Dyspnoea in Health and Disease

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AIMS

- To understand current concepts on the physiological origins of exertional dyspnoea in common chronic obstructive and restrictive lung diseases:
- To present a physiological rationale for dyspnoea amelioration based on current neuro-physiological constructs.
- To briefly review methods to measure multidimensional dyspnoea across its sensory intensity, affective and impact domains, giving appropriate examples.

SUMMARY

Activity-related dyspnoea is the most common symptom of patients with chronic lung diseases and underpins perceived poor health status. Our understanding of the nature and source of dyspnoea continues to grow but successful amelioration of this distressing symptom can remain elusive, especially in those with advanced lung diseases.

According to the 2012 ATS definition, dyspnoea is: "A subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity". A central recommendation of the ATS group was that dyspnoea should be measured across three major domains: sensory-perceptual experience (intensity, quality), affective distress and symptom impact or burden on daily living.

Physiology of dyspnoea

Norman Jones, the great Canadian physiologist, summarized his thoughts on the origins of dyspnoea as follows: "Breathlessness can be seen to result from the imbalance between the demand for breathing and the ability to achieve the demand". Indeed, in most clinical situations where patients report severe dyspnoea, ventilatory demand-capacity imbalance is present. Thus, in patients with chronic lung conditions, ventilatory demand reaches or exceeds maximal ventilatory capacity (MVC) during physical exertion. In other words, for a given work rate the ratio of ventilation (VE) to MVC is abnormally high compared with healthy controls. Similarly, the ratio of respiratory muscle effort (measured by esophageal manometry) to maximal possible respiratory effort is increased at a given work rate or VE in patients with lung disease versus healthy controls.

Dyspnoea and increased respiratory neural drive (RND)

Increased RND (compared with normal) is a common final pathway in dyspnoea causation in patients with chronic lung diseases during activity. The motor output of respiratory centers in the medulla and cortex cannot currently be measured directly. However, ventilatory output (tidal volume *breathing frequency) provides an indirect measure of RND in patients with milder lung disease. Ventilatory output measured in this way underestimates RND in advanced lung disease because of the attendant mechanical constraints. Tidal measurements of esophageal pressure and diaphragmatic electromyography (both expressed relative to maximum) also provide indirect measures of motor command output, and are uniformly amplified in patients with lung disease compared to healthy individuals. The magnitude of RND during exercise is mainly determined by the CO_2 output (VCO_2) reflecting the metabolic requirement of the task. An additional determinant in patients with lung diseases is the extent of wasted ventilation [dead space (VD)] and the regulated arterial CO_2 set-point. In most chronic lung diseases [COPD, interstitial lung disease (ILD), pulmonary arterial hypertension], the VD component of the tidal breath is abnormally high reflecting relatively reduced pulmonary blood perfusion of alveolar units with preserved or increased ventilation. This inefficiency of CO_2 elimination by the diseased lungs results in increased chemostimulation of medullary centers and consequent increased RND. It is thought (based on animal studies) that sensory information about increased RND arising from the medulla (and motor cortex) is directly conveyed to the somato-sensory cortex where it is perceived as increased sense of respiratory muscle effort.

Abnormal respiratory mechanics and dyspnoea

In healthy individuals during spontaneous breathing, tidal volume (VT) is positioned in the linear portion of the respiratory system's pressure-volume (PV) relaxation curve. Even at high exercise intensities the expanding VT remains within this linear portion of the PV curve where the force-velocity and length-tension properties of the respiratory muscles are optimized. By contrast, in COPD the PV curve is compressed from below because of lung hyperinflation but maintains its sigmoid shape. Because of the resultant reduced inspiratory capacity (IC) – indicating proximity of VT to total lung capacity (TLC) – the muscles of the respiratory system become overloaded and functionally weakened. In this scenario of "high-end mechanics", critical mechanical limits on VT expansion are in place despite near maximal RND. Similarly, in patients with lung fibrosis the sigmoidal PV curve is compressed, this time from above (reduced TLC), and VT expansion is again restricted because of the reduced IC. The growing disparity between increasing RND and VT after it has reached a plateau has been termed neuromechanical dissociation (NMD). We have postulated that NMD contributes to perceived "unsatisfied inspiration" – a distressing qualitative dimension of dyspnoea common in both obstructive and restrictive lung diseases, which is rarely (if ever!) reported in healthy individuals.

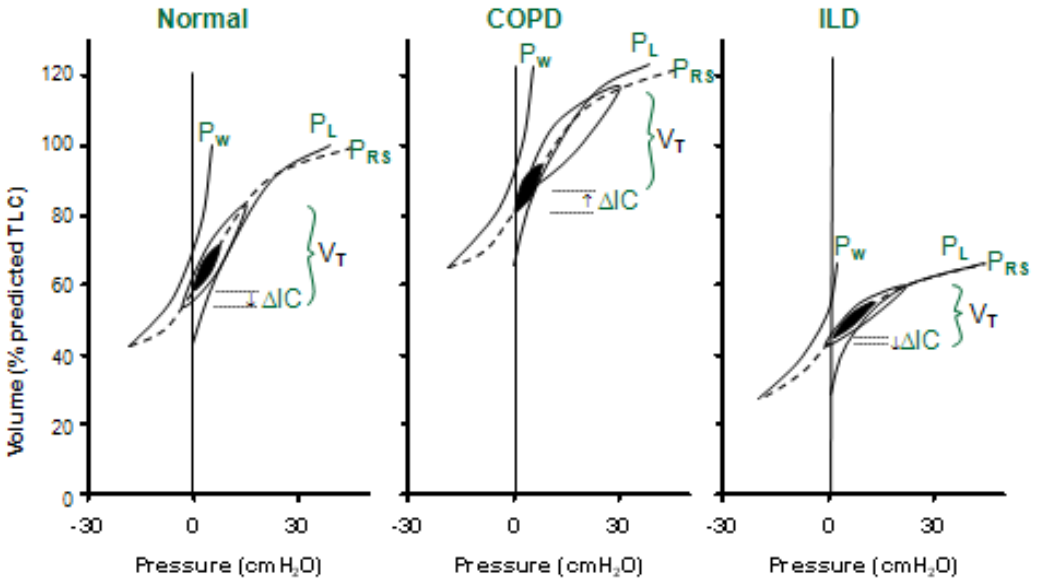

Figure 1. Pressure-volume (PV) relationships in age-matched groups of COPD patients, ILD patients and healthy controls. Tidal PV curves at rest (solid loops) and during exercise (open loops) are shown relative to the respective respiratory system PV relaxation curves (P_{RS}) (dashed lines).

The neurophysiological construct described above provides a practical basis for an approach to the alleviation of dyspnoea in individual patients with chronic lung diseases. Thus, treatment is primarily directed towards reducing RND (e.g., reducing VCO_2 or metabolic acidosis), improving mechanics (e.g., increasing IC) or modifying the affective aspect of dyspnoea (e.g., counseling, sedation).

Measuring multidimensional dyspnoea

Sensory intensity

Intensity of dyspnoea can be measured by validated instruments, such as visual analogue scales (VAS) and the Borg category scales with ratio properties, during a standardized physical task (i.e., six-minute walk distance tests, shuttle walk tests, incremental or constant work rate treadmill or cycle exercise tests). This approach allows us to evaluate the sensory intensity responses to a quantifiable stimulus (e.g., increasing work rate, oxygen uptake, or ventilation). These perceptual responses should preferably be compared with reference values from a healthy population studied under similar experimental conditions.

For the purpose of evaluating the efficacy of an intervention (e.g., supplemental oxygen, exercise training, bronchodilators, etc.) in reducing dyspnoea intensity, constant work rate (~60-80% maximum) endurance studies are preferable to incremental tests. The demonstration that following the intervention dyspnoea intensity is reduced (by 1 Borg unit) at a submaximal standardized time or ventilation, thereby allowing greater exercise tolerance, indicates that the intervention is effective. Thus, after the intervention the patient is capable of undertaking a demanding physical task with less respiratory discomfort and for a longer duration than before. This approach to dyspnoea intensity measurement during standardized physical tasks allows an assessment of the mechanisms of dyspnoea in the individual which can be targeted for treatment.

Quality of dyspnoea

Qualitative dimensions of dyspnoea are more difficult to measure during activity. One approach is to present patients with a selection of pertinent descriptor choices after exercise completion and to rank the descriptors that most faithfully represent their particular experience of dyspnoea. For example, healthy individuals invariably select descriptors that allude to increased work or effort of breathing, whereas patients with obstructive or restrictive lung conditions additionally select descriptors of "inspiratory difficulty" and "unsatisfied inspiration."

Affective components of dyspnoea

It is believed that intensity and affective components of dyspnoea have distinct neurobiologic origins: intensity reflects increased RND and central corollary discharge, and the affective responses represent increased activation of limbic and para-limbic centers of the brain. Exercise training may have differential effects on these two components. For example, affective responses (fear, anxiety, frustration, distress) to exercise can be improved following pulmonary rehabilitation in the absence of reduction in standardized Borg intensity ratings during exercise. In practice, the affective aspect of dyspnoea is difficult to measure and current approaches remain experimental.

Measuring the impact of dyspnoea

A number of "magnitude of task" questionnaires have been validated for the purpose of assessing the impact of this symptom on the ability to perform daily activities. These widely used questionnaires include the Medical Research Council (MRC) dyspnoea scale, an oxygen cost diagram (OCD), Baseline Dyspnoea Index (BDI), the dyspnoea component of the Chronic Respiratory Questionnaire (CRQ) and the activity component of the St. George's Respiratory Questionnaire (SGRQ). All scales are reproducible and have construct validity and are adequately responsive to various therapeutic interventions. They provide valuable information about the functional status of the individual patient as it relates to dyspnoea. The Transition Dyspnoea Index (TDI) has been used extensively in clinical trials: the minimal clinically important difference is 1 unit. The MRC scale, while useful in stratifying severity of dyspnoea and activity restriction, is less sensitive even in response to effective interventions such as exercise training.

Glossary

DH, dynamic lung hyperinflation
EELV, end-expiratory lung volume
EILV, end-inspiratory lung volume
EMGdi, diaphgramatic electropmyography
ERV, expiratory reserve volume
F, breathing frequency
IC, inspiratory capacity
ILD, interstitial lung disease
IRV, inspiratory reserve volume
$P_{0.1}$, negative airway pressure during the first 100 msec of an occluded inspiration (neuromuscular drive)
$PaCO_2$, partial pressure of arterial carbon dioxide
PaO_2, partial pressure of arterial oxygen
Pes, esophageal pressure
PImax, maximum inspiratory pressure
RA, room air
RV, residual volume

SaO_2, arterial oxygen saturation
TLC, total lung capacity
VAS, visual analogue scale
VC, vital capacity
VCO_2, carbon dioxide output
V_E, minute ventilation
V_T, tidal volume

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EVALUATION

1. The following statements are true except:
   Compared with healthy individuals, activity-related dyspnoea in patients with lung diseases is:
   a. Qualitatively different
   b. Similar during walking and cycling when the increase in work rate is matched
   c. Associated with lower inspiratory neural drive to the diaphragm
   d. Often the dominant exercise-limiting symptom

2. The following statements on dyspnoea measurement are true except:
   a. The Borg scale is superior to visual analogue scales (VAS) for the purpose of measuring dyspnoea intensity during a standardized stimulus
   b. The Medical Research Council (MRC) dyspnoea scale is sensitive for the evaluation of bronchodilator efficacy
   c. The minimal clinically important difference for the Transition Dyspnoea Index (TDI) is 1 unit
   d. Constant work rate endurance tests are superior to incremental tests for the evaluation of improved exercise tolerance during dyspnoea-relieving interventions

3. The following statements on dyspnoea are true except:
   a. The 2012 ATS statement recommends that dyspnoea be assessed across sensory intensity, quality, affective and impact domains
   b. Affective responses to respiratory discomfort are associated with decreased activation of the bulbo-pontine structures of the brain on functional Magnetic Resonance Imaging
   c. Qualitative descriptors of dyspnoea alluding to the sense of increased "work or effort" are common to health and disease
   d. Increased perceived expiratory difficulty is an uncommon qualitative descriptor choice of patients with chronic airway obstruction during exercise

PG18:
Measurement of Dyspnea in Health and Disease

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Conflicts of Interest

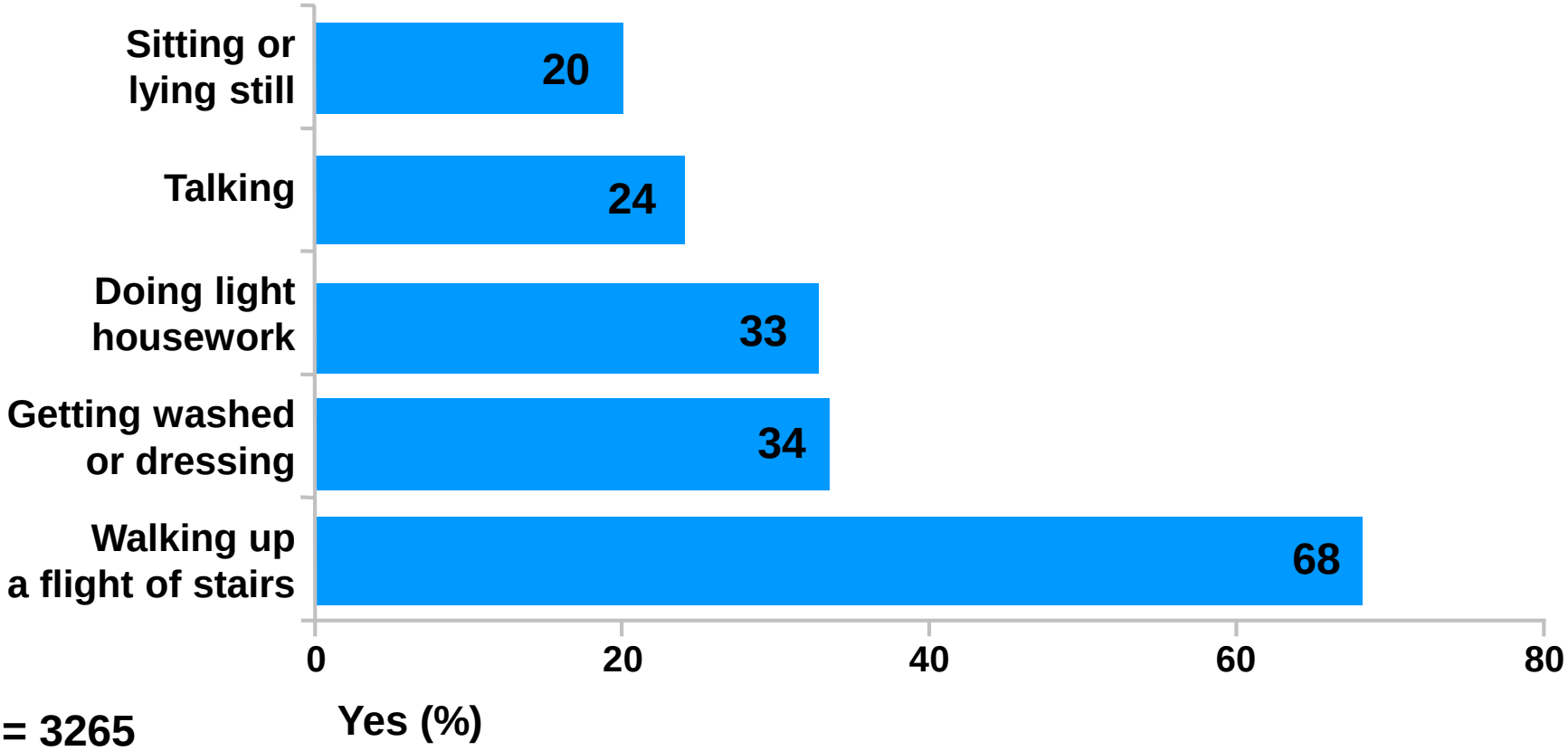
- I have served on speakers bureaus, consultation panels and advisory boards for AZ, BI, GSK and Novartis.
- I have received research funding support from AZ, BI, GSK, Novartis.

Outline

- Definition of dyspnea
- Mechanisms of dyspnea
- Measuring multi-dimensional dyspnea
- Summary

Confronting COPD Survey

Do you feel breathless when…

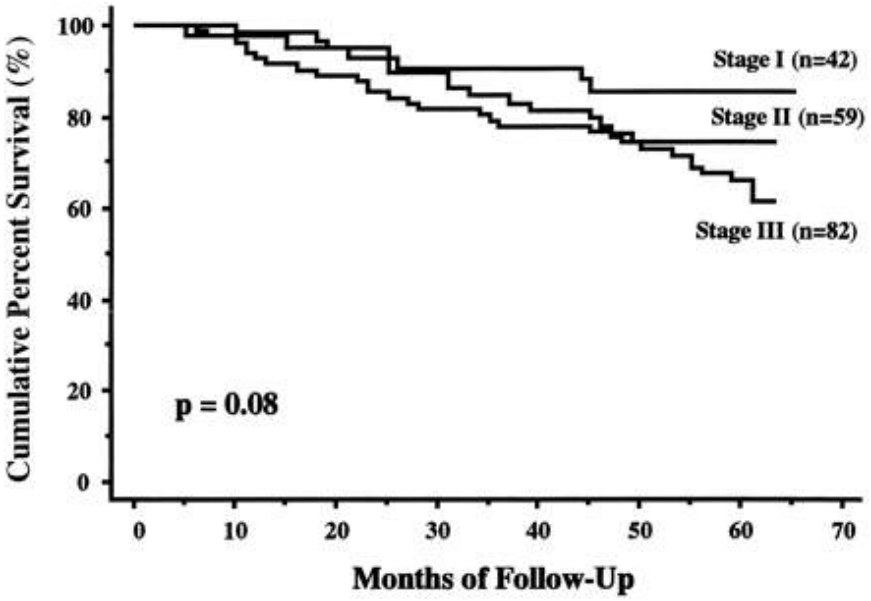


n = 3265

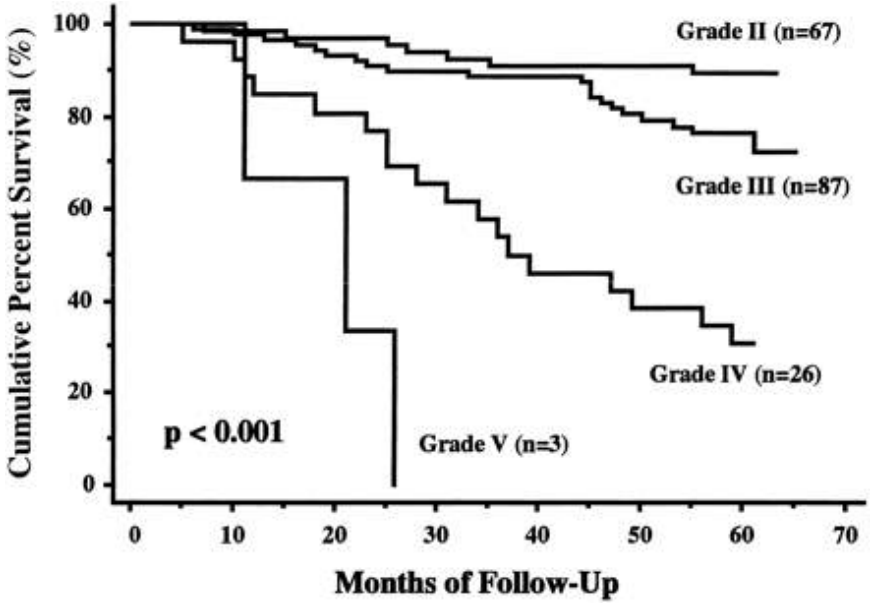
Rennard S, et al. *Eur Respir J* 2002; 20: 799–805.

Mortality in COPD

FEV_1 - ATS Staging (Nishimura, 2002)



Symptoms – MRC (Nishimura, 2002)



American Thoracic Society Documents

An Official American Thoracic Society Statement: Update on the Mechanisms, Assessment, and Management of Dyspnea

Mark B. Parshall, Richard M. Schwartzstein, Lewis Adams, Robert B. Banzett, Harold L. Manning, Jean Bourbeau, Peter M. Calverley, Audrey G. Gift, Andrew Harver, Suzanne C. Lareau, Donald A. Mahler, Paula M. Meek, and Denis E. O'Donnell; on behalf of the ATS Committee on Dyspnea

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, October, 2011

Am J Respir Crit Care Med 2012; 185(4): 435-452.

Definition of Dyspnea (ATS 2012)

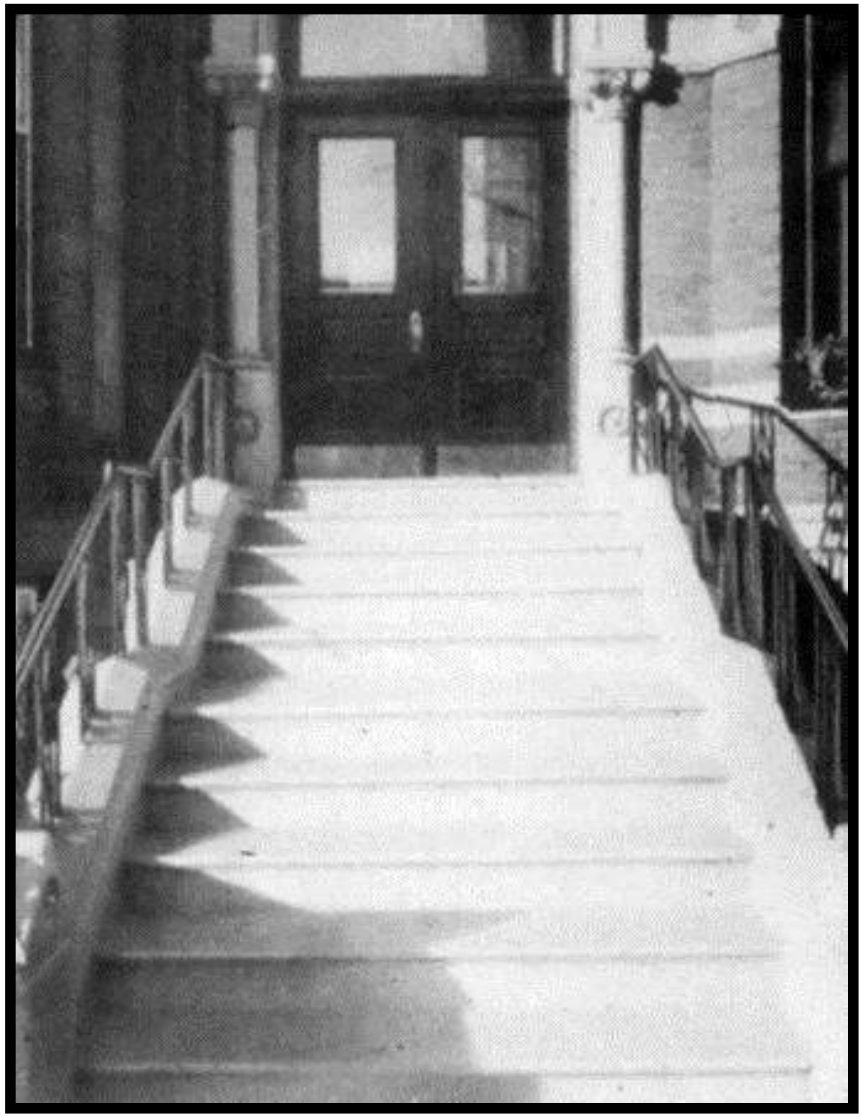
"A subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity."

Corollary:
The experience of dyspnea derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioral responses.

Parshall MB, et al; ATS Committee. *Am J Respir Crit Care Med* 2012; 185:435-52.

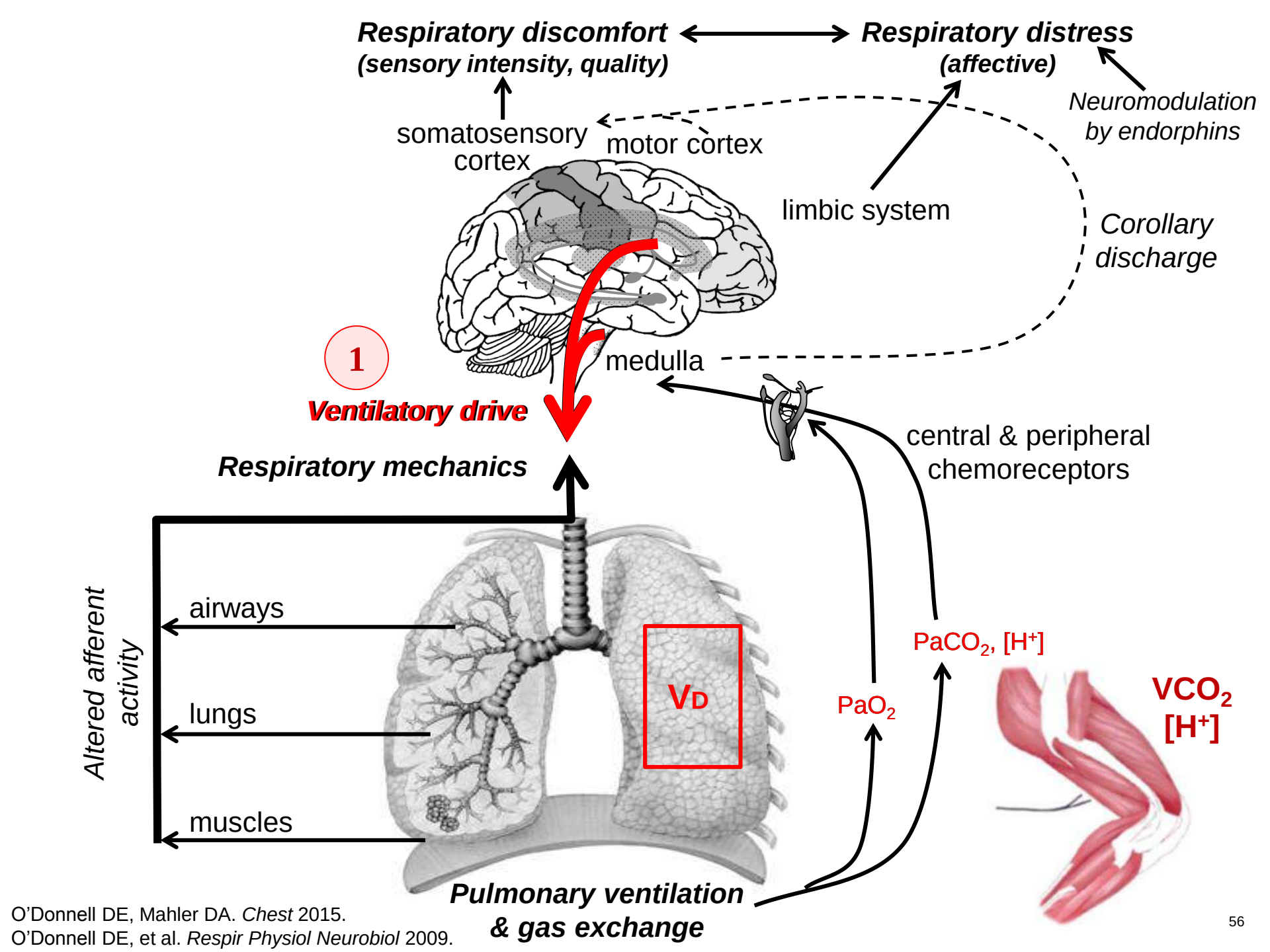
Domains of Dyspnea Measurement (ATS 2012)

Domain	Definition	Measurement
Sensory-perceptual experience	Measures of what breathing feels like	• Single-item intensity ratings (e.g., Borg scale, VAS) • Descriptors of specific sensations/clusters of related sensations
Affective distress	Measures of how distressing breathing feels	• Single-item ratings of severity of distress or unpleasantness • Multi-item scales of emotional responses such as anxiety
Symptom impact or burden	Measures of how dyspnea affects functional ability or health status	• Ratings of disability or activity limitation (e.g., MRC dyspnea scale) • Ratings of functional ability • Scales of quality of life, health status



To the patient, this is a breathtaking view.

Dyspnea Intensity: Sensory-Perceptual Domain



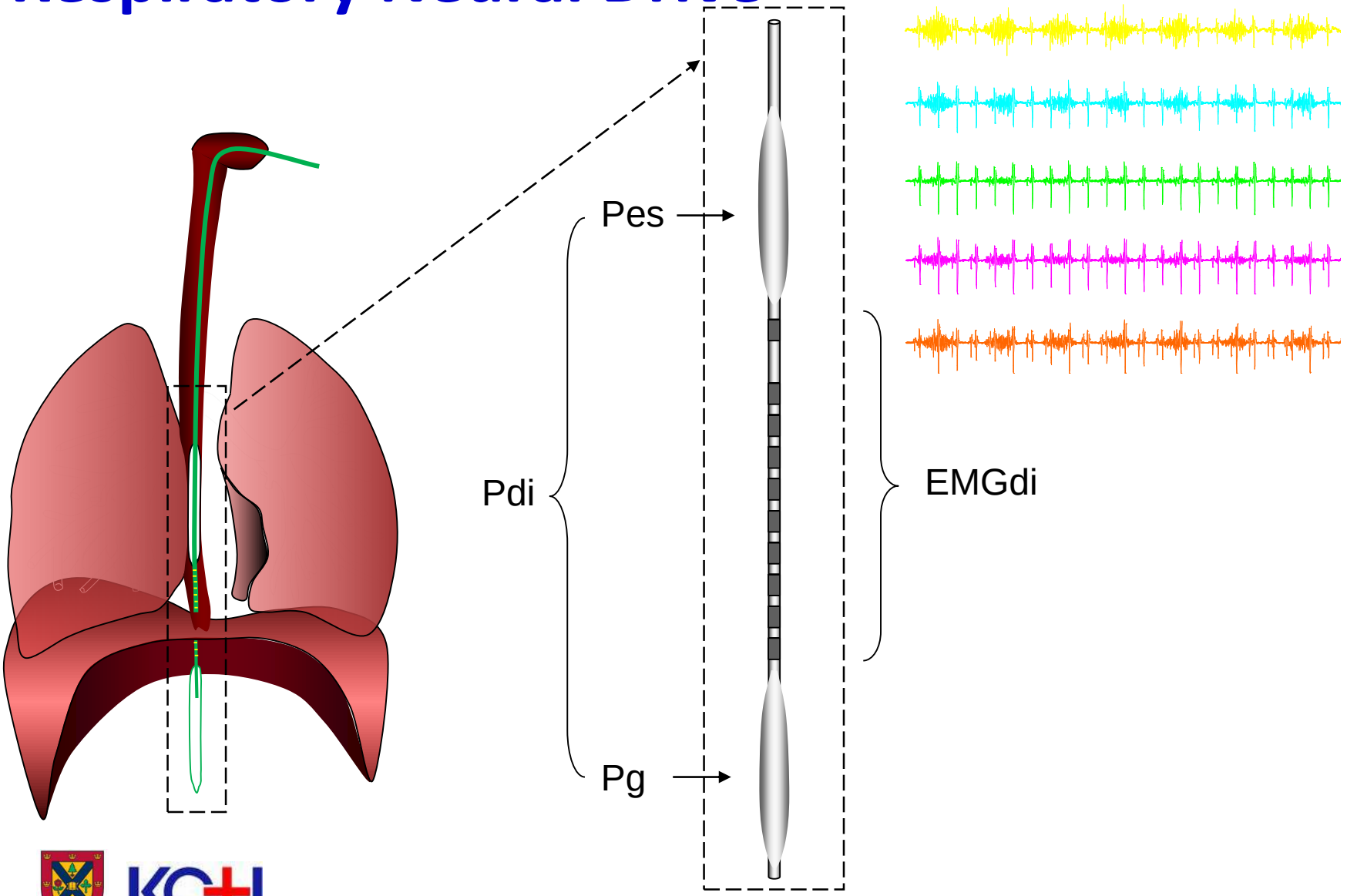
O'Donnell DE, Mahler DA. *Chest* 2015.
O'Donnell DE, et al. *Respir Physiol Neurobiol* 2009.

Indirect Indices of Respiratory Drive Increase as Disease Advances

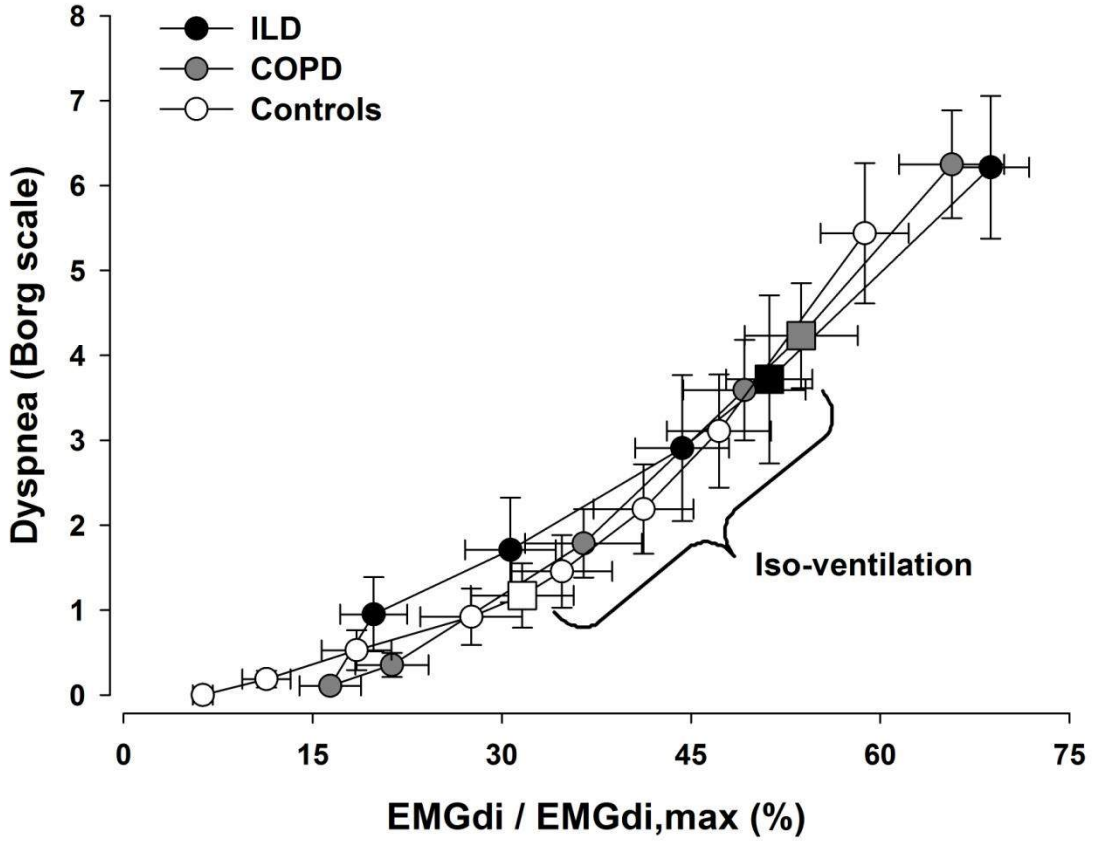
- V_E/MVC
- Respiratory effort (tidal esophageal pressure relative to maximum)
- Inspiratory neural drive to the diaphragm (EMGdi relative to maximum)

Gandevia & Hugh-Jones, Thorax 1957; LeBlanc, ARRD 1986; Jolley, ERJ 2015.

Respiratory Neural Drive



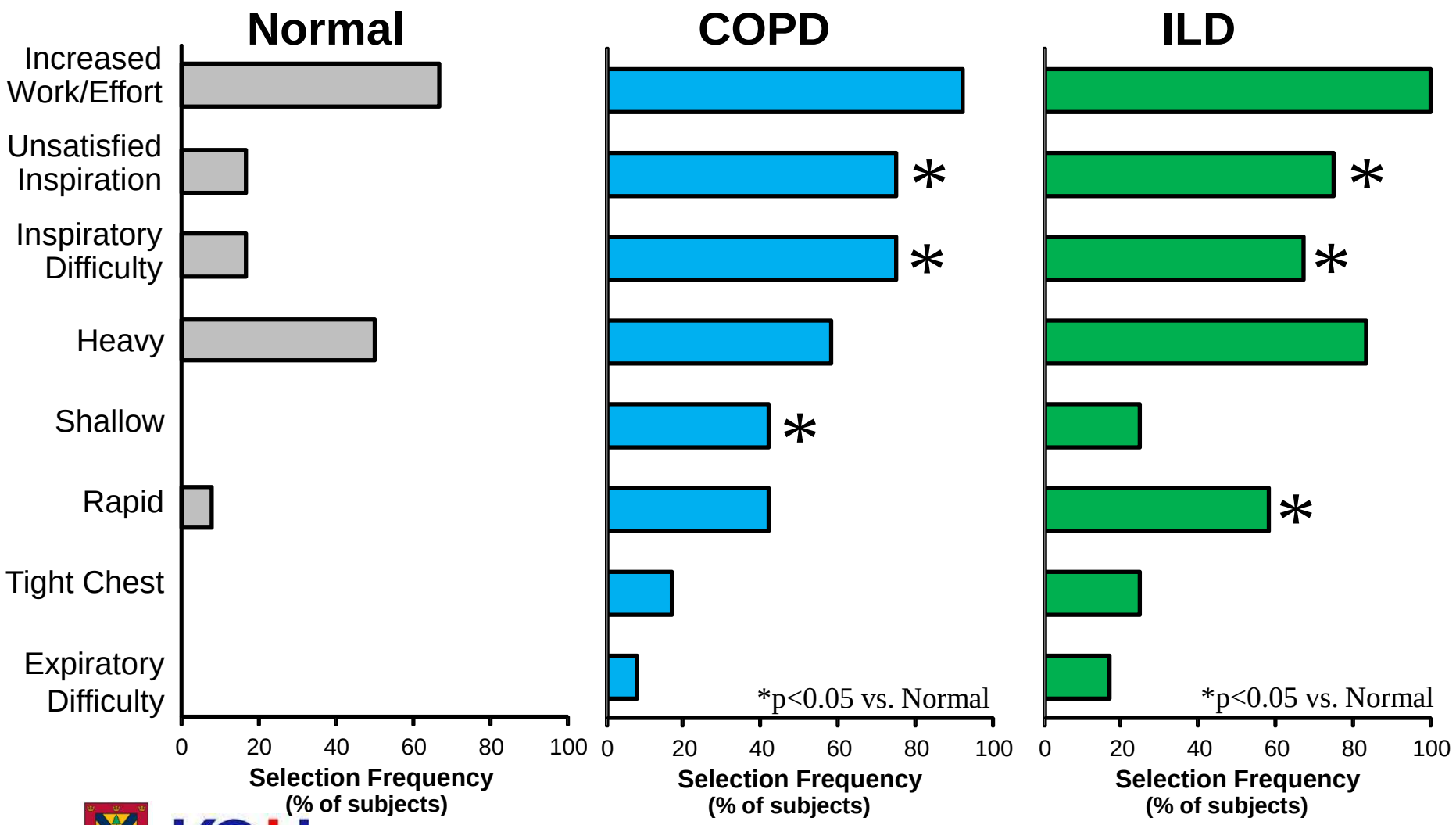
Dyspnea and Respiratory Neural Drive in COPD and ILD



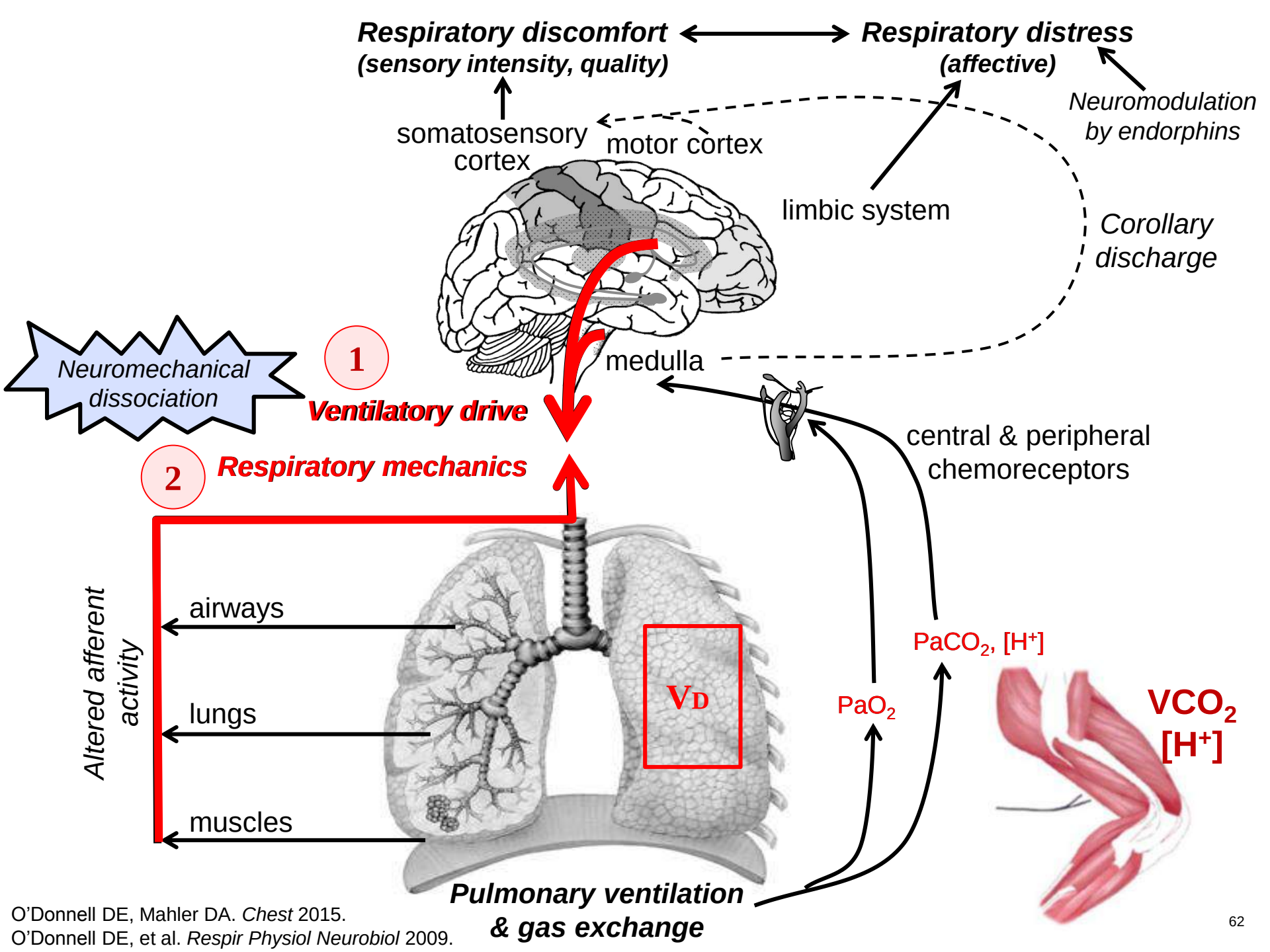
Faisal A, et al. *Manuscript in review*

Dyspnea Quality: Sensory-Perceptual Domain

Qualitative Descriptors of Exertional Dyspnea



O'Donnell DE, et al. *J Appl Physiol* 1998.



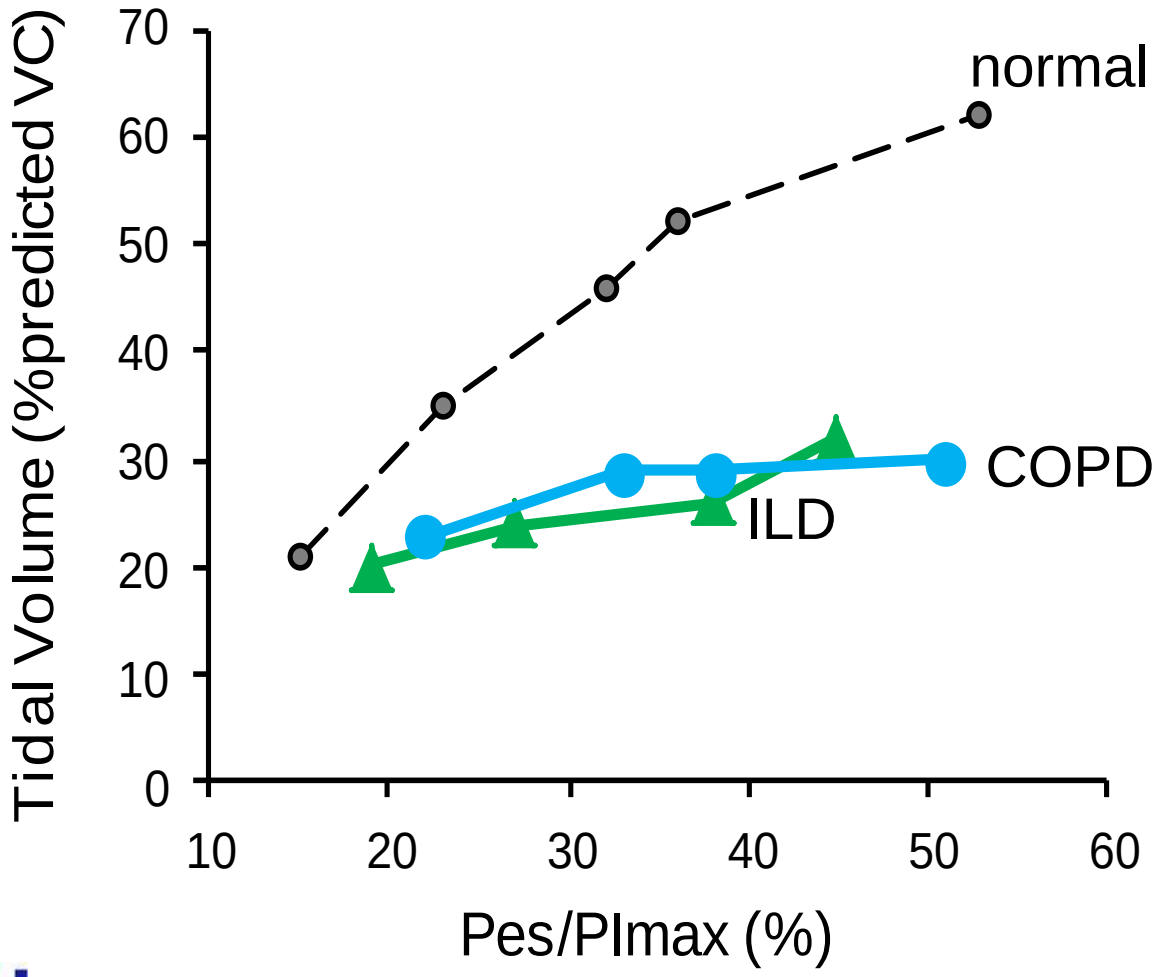
O'Donnell DE, Mahler DA. *Chest* 2015.
O'Donnell DE, et al. *Respir Physiol Neurobiol* 2009.

Neuromechanical Dissociation

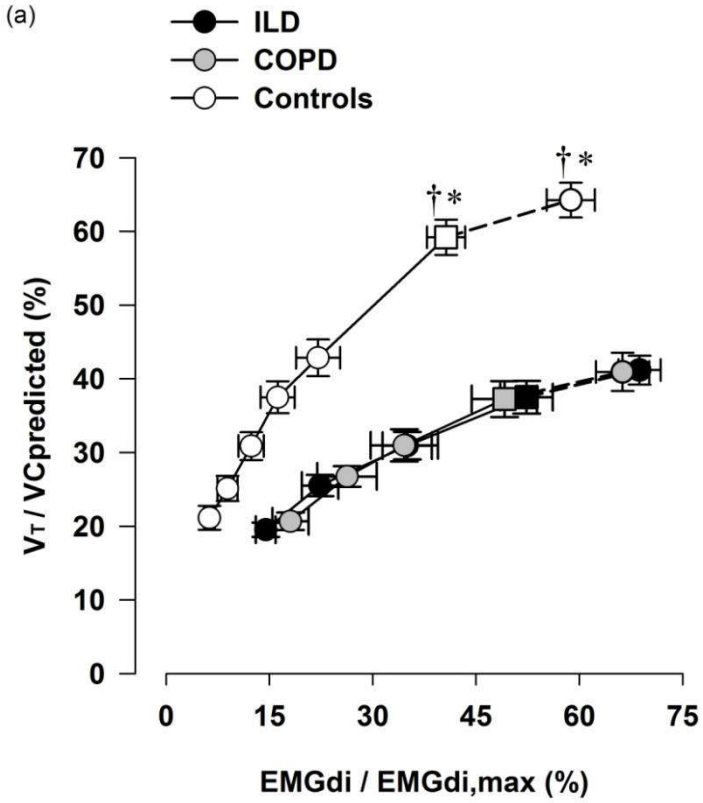
- Mechanistic studies have shown that when the spontaneous increase in V_T is constrained (either volitionally or by external imposition) in the face of increased chemostimulation, respiratory discomfort (i.e., *unsatisfied inspiration* or *air hunger*) results.

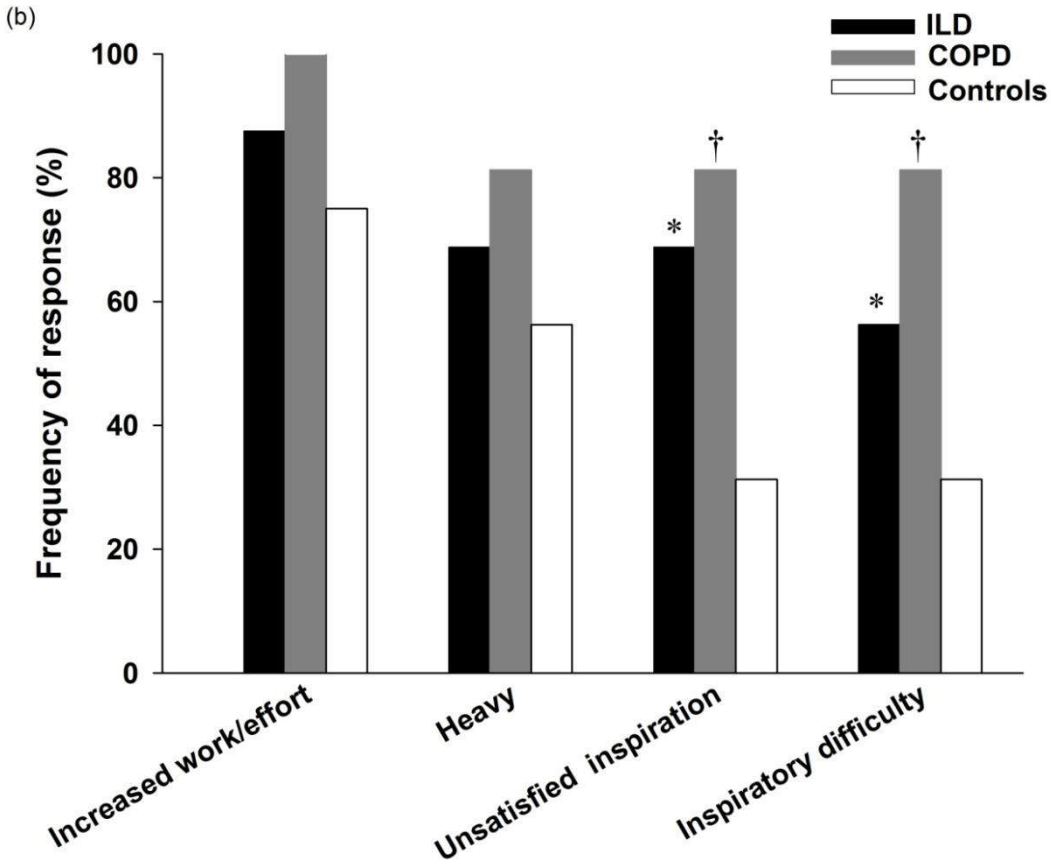
Wright GW, Branscomb BV. *Trans Am Clin Climatol Assoc* 1954; 66: 116-25.
Campbell EJM, Howell JB. *Br Med Bull* 1963; 19: 36-40.
Schwartzstein RM, et al. *Am Rev Respir Dis* 1989; 139: 1231-7.
Mannning HL, et al. *Respir Physiol* 1992; 90: 19-30.
Harty HR, et al. *J Appl Physiol* 1999; 86: 1142-50.
O'Donnell DE, et al. *J Appl Physiol* 2000; 88: 1859-69.
Evans KC, et al. *J Neurophysiol* 2002; 88: 1500-11.
Banzett RB, et al. *Am J Respir Crit Care Med* 2008; 17: 1384-90.

Neuromechanical Coupling / Dissociation



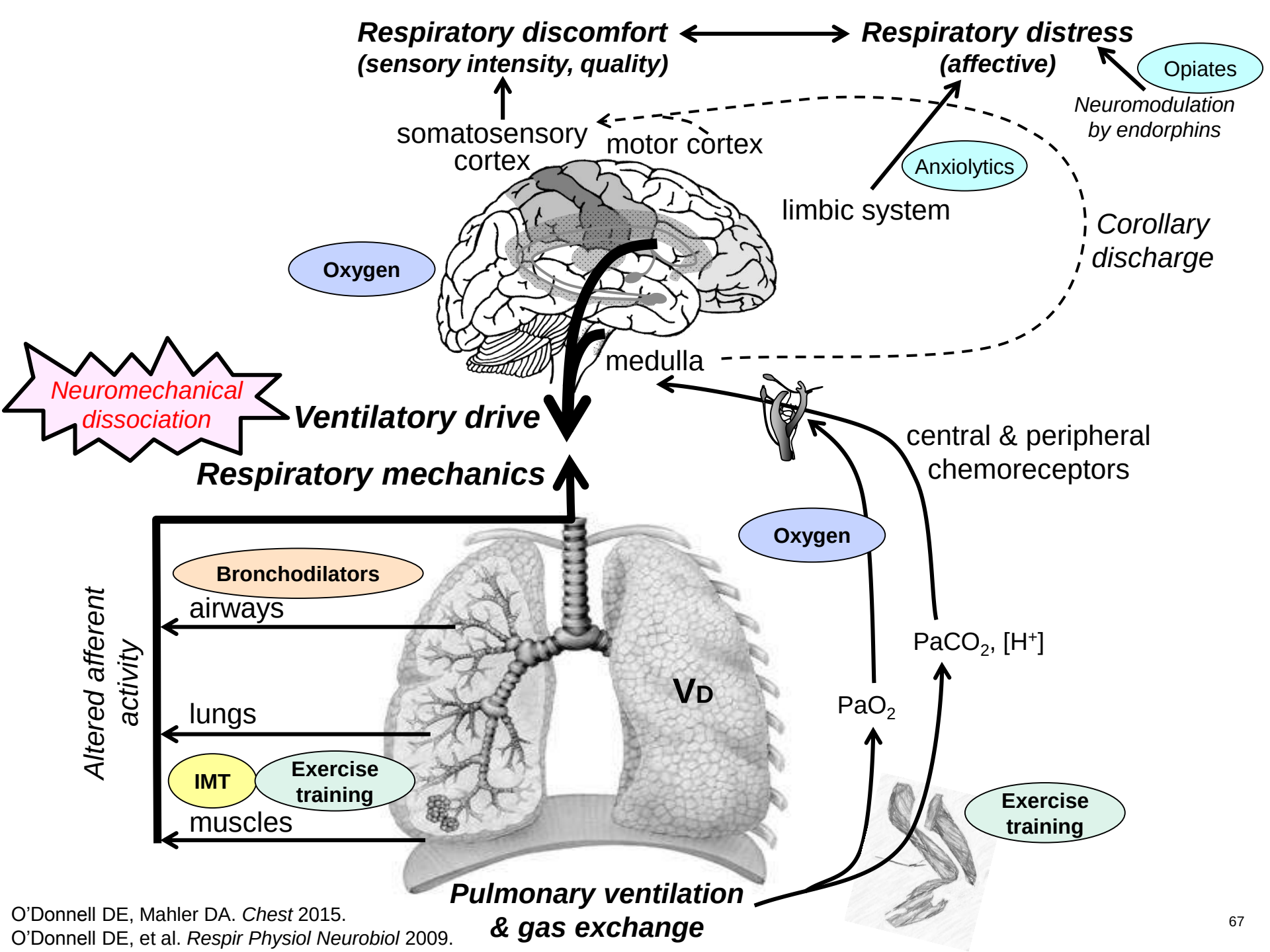
Neuromechanical Dissociation in COPD and ILD





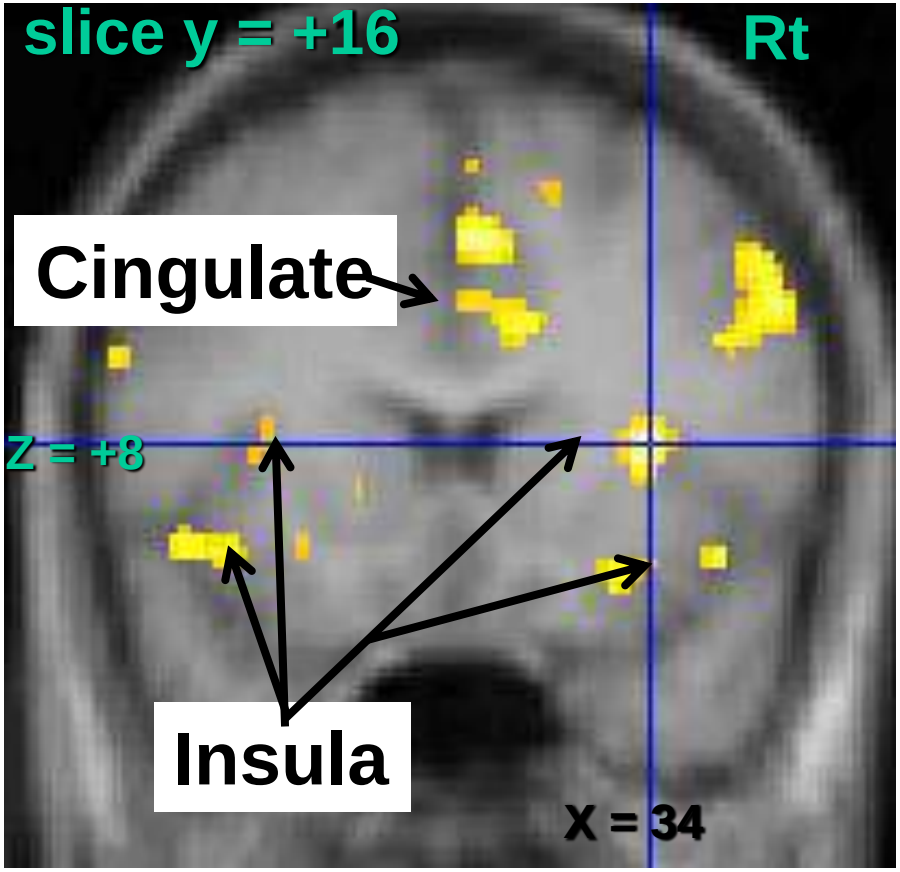
Faisal A, et al. *Manuscript in review*

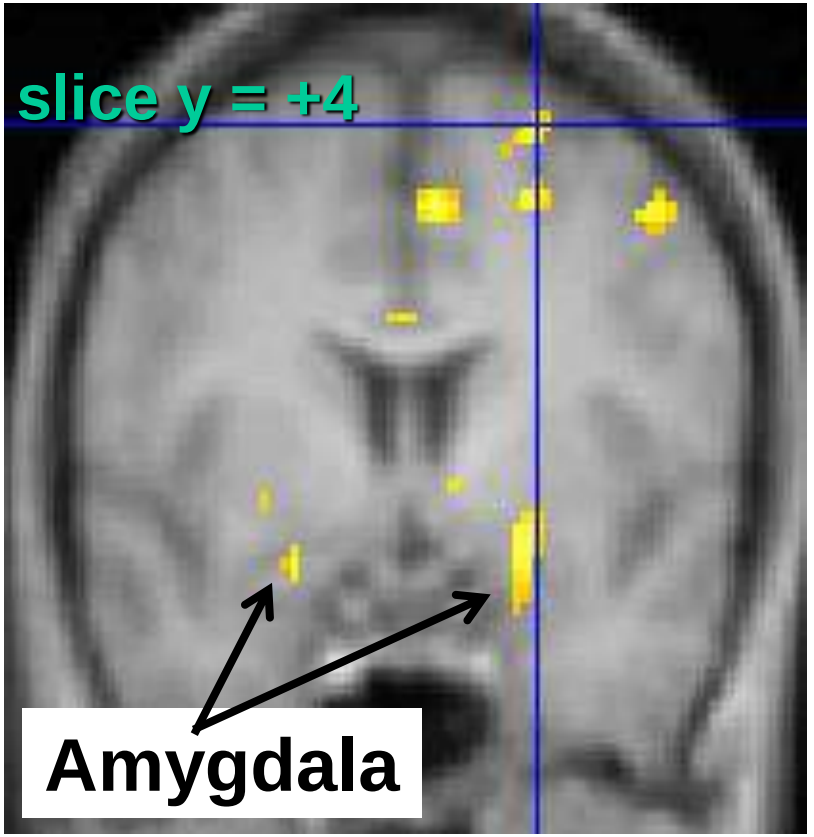
Affective Distress
"The Fear Factor"



O'Donnell DE, Mahler DA. *Chest* 2015.
O'Donnell DE, et al. *Respir Physiol Neurobiol* 2009.

fMRI Shows Limbic Activation during Dyspnea





T statistic

4 8

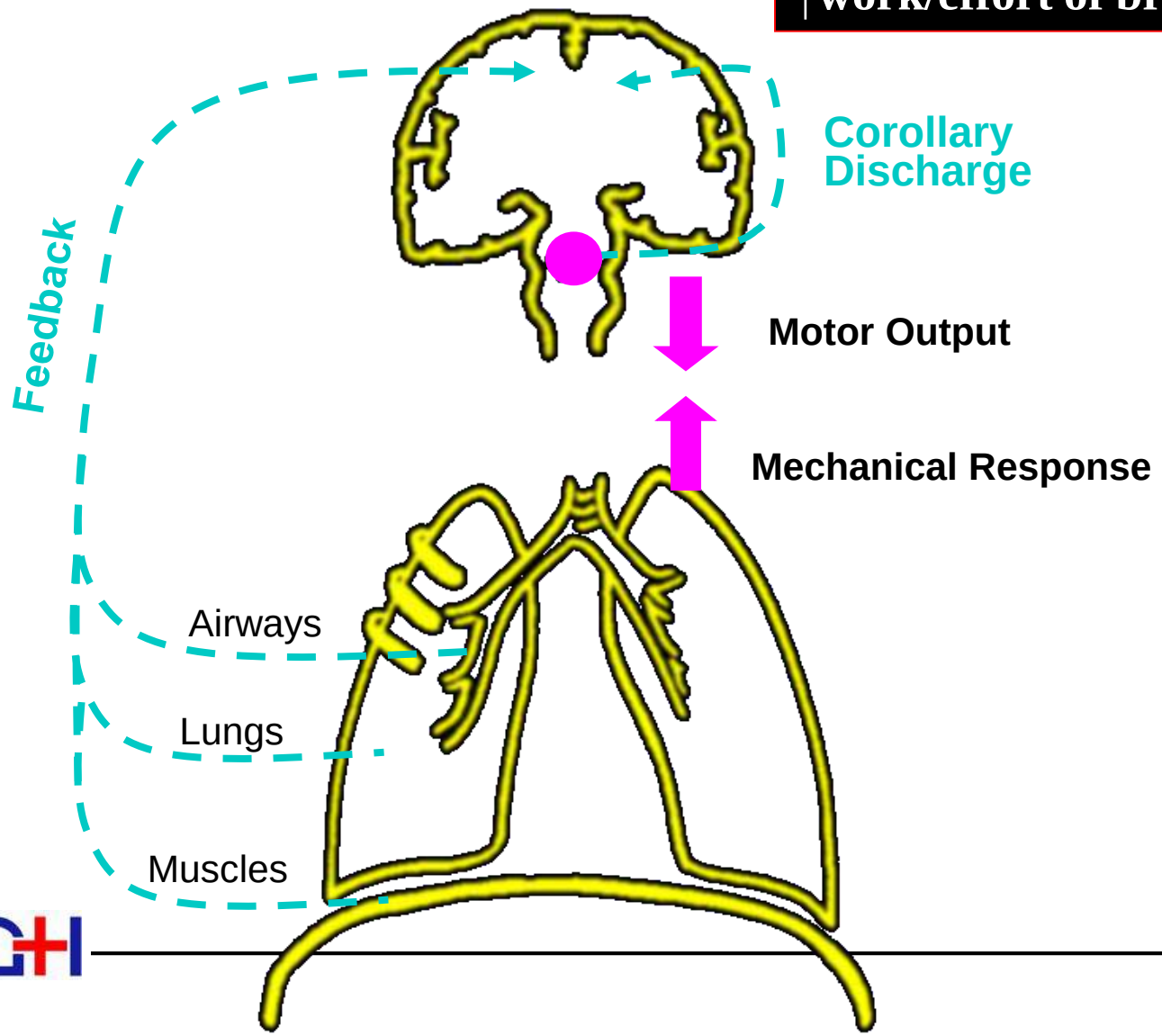
n = 6, p < 0.001 (T > 5.0)

corrected for multiple comparisons

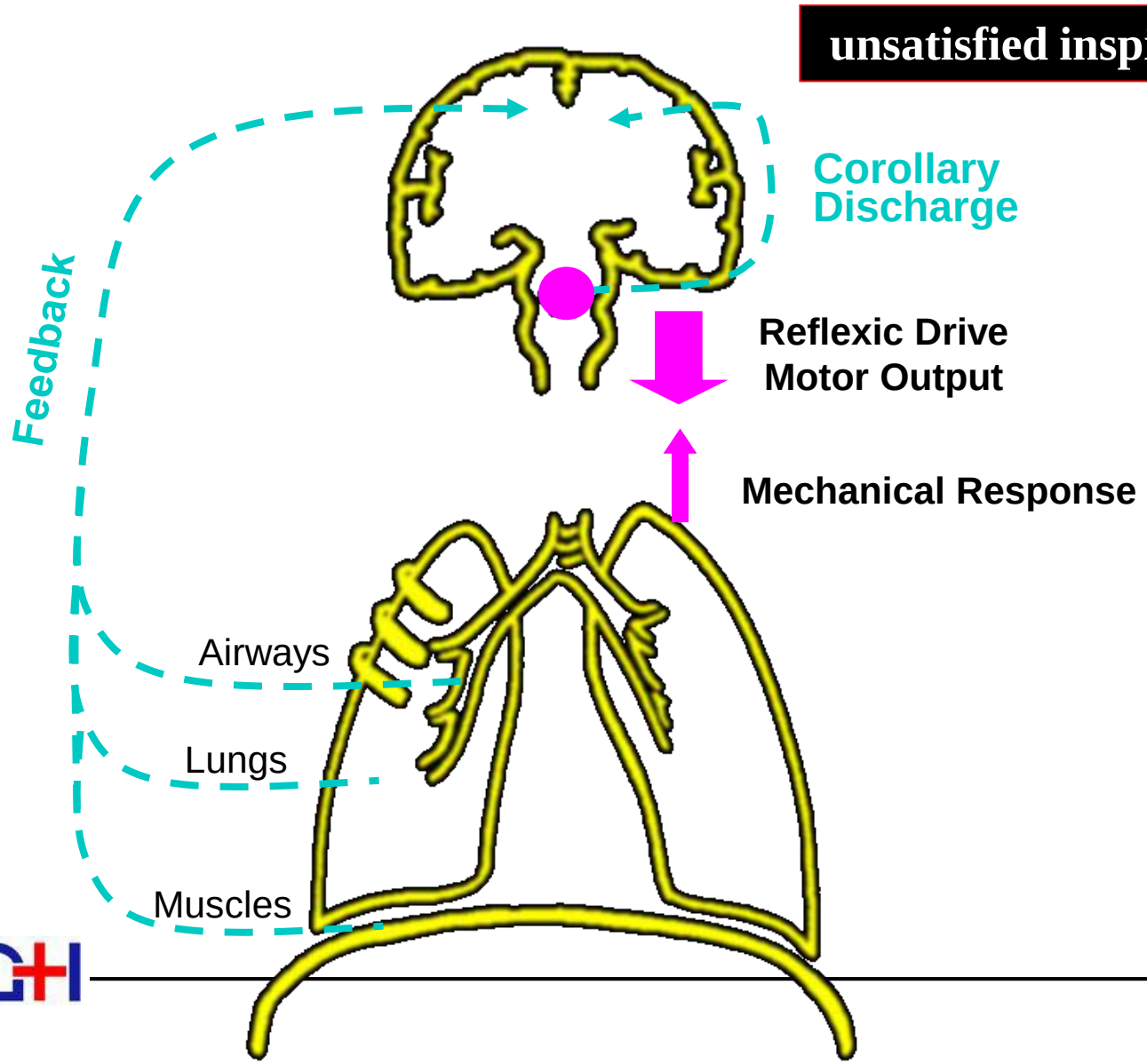
Evans KC, et al. *J Neurophysiol* 2002; 88: 1500-11.

Neuromechanical Coupling

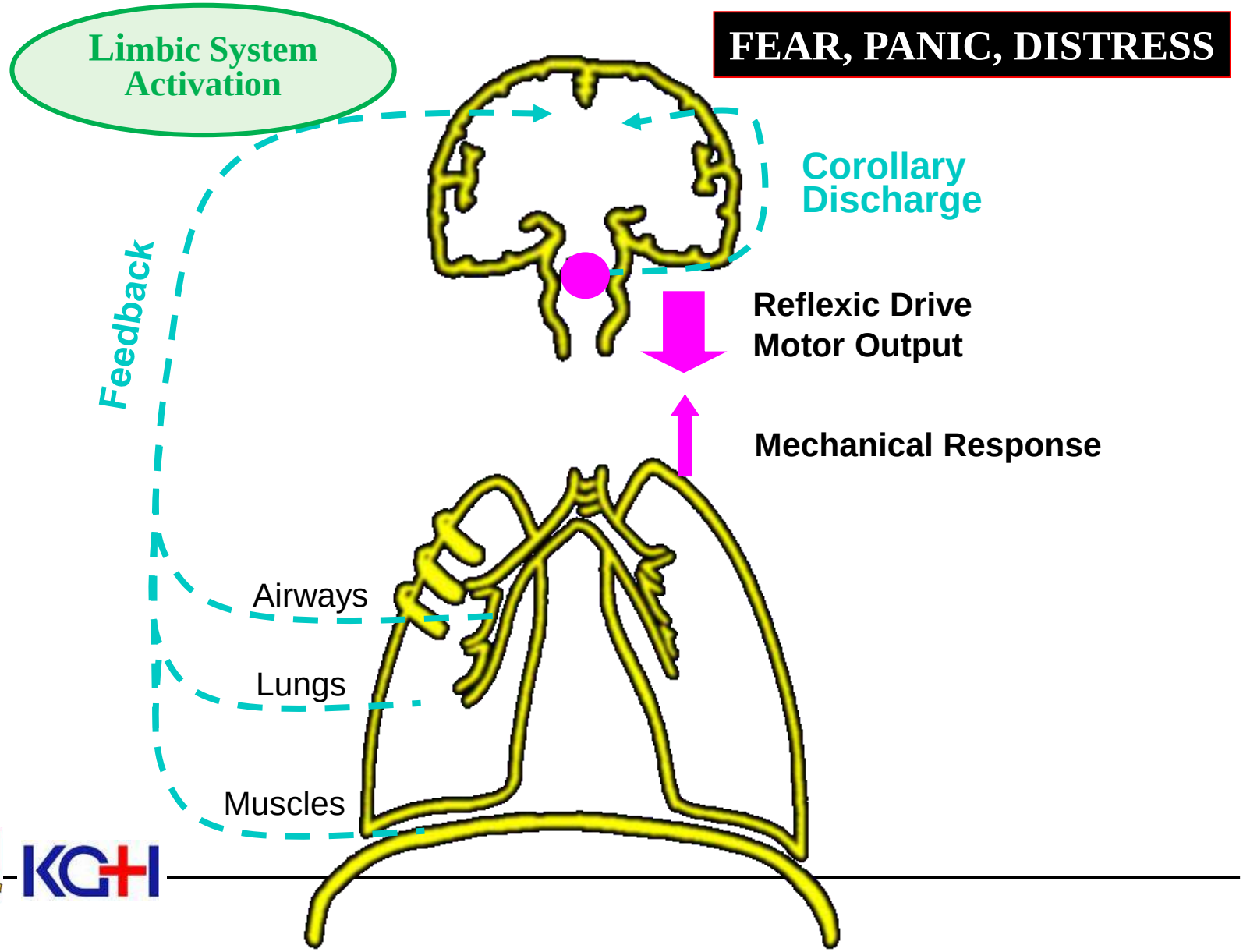
↑work/effort of breathing



Neuromechanical Dissociation



Neuromechanical Dissociation



Domains of Dyspnea Measurement (ATS 2012)

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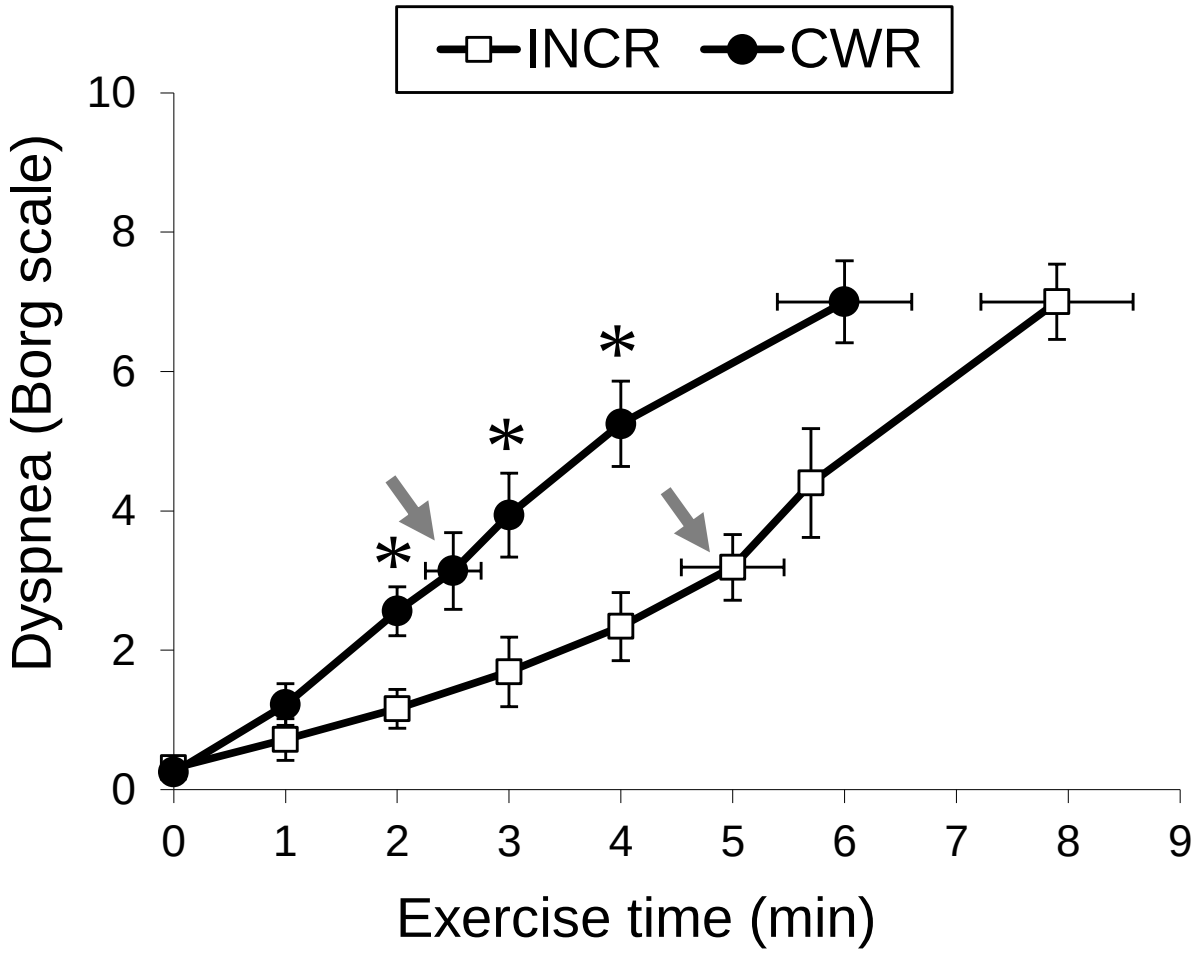
Symptom impact or burden	Measures of how dyspnea affects functional ability or health status	• MRC dyspnea scale • BDI / TDI • CRQ • SGRQ

Measuring Dyspnea During Exercise

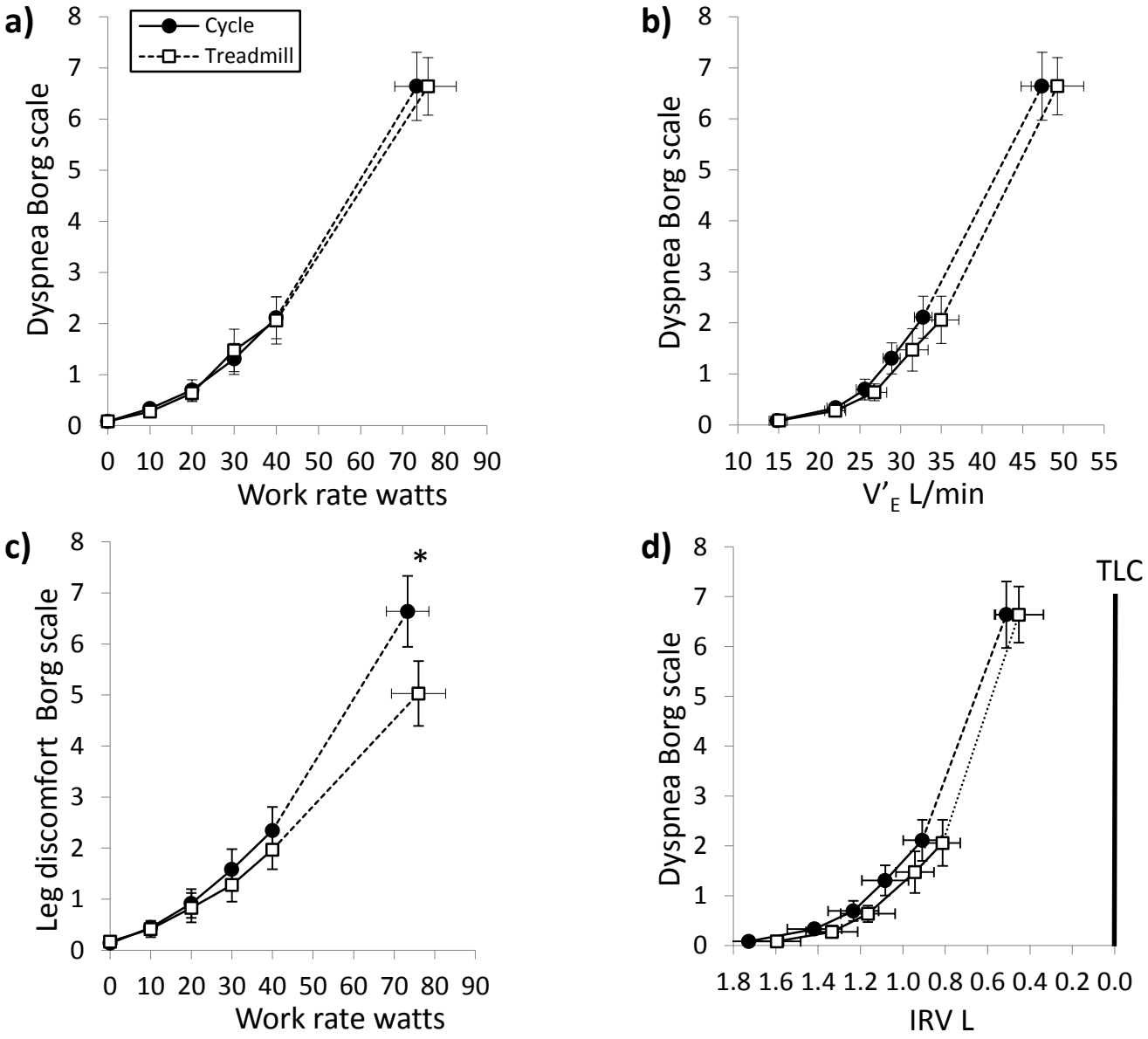
	Field Test	Lab Test
Incremental	Incremental shuttle walk	Cycle ergometry Treadmill
Submaximal	Endurance shuttle walk 6-minute walk test 12-minute walk test	Cycle ergometry Treadmill

Incremental *vs* Constant-Work Rate Exercise Testing in COPD



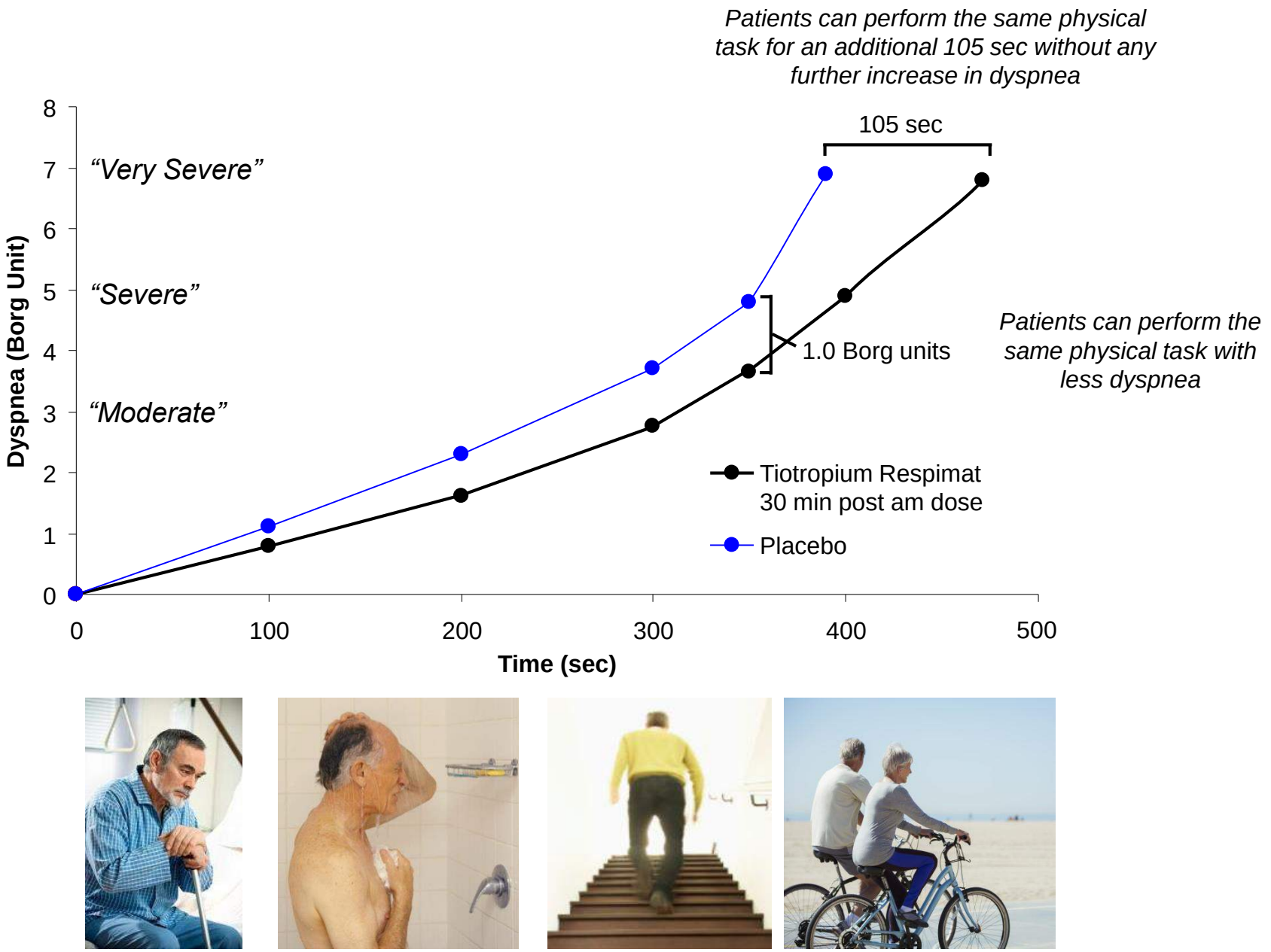
Laveneziana P, et al. *Am J Respir Crit Care Med* 2011;184:1367-73.

Cycle *vs.* Treadmill Testing in Obese Patients with COPD

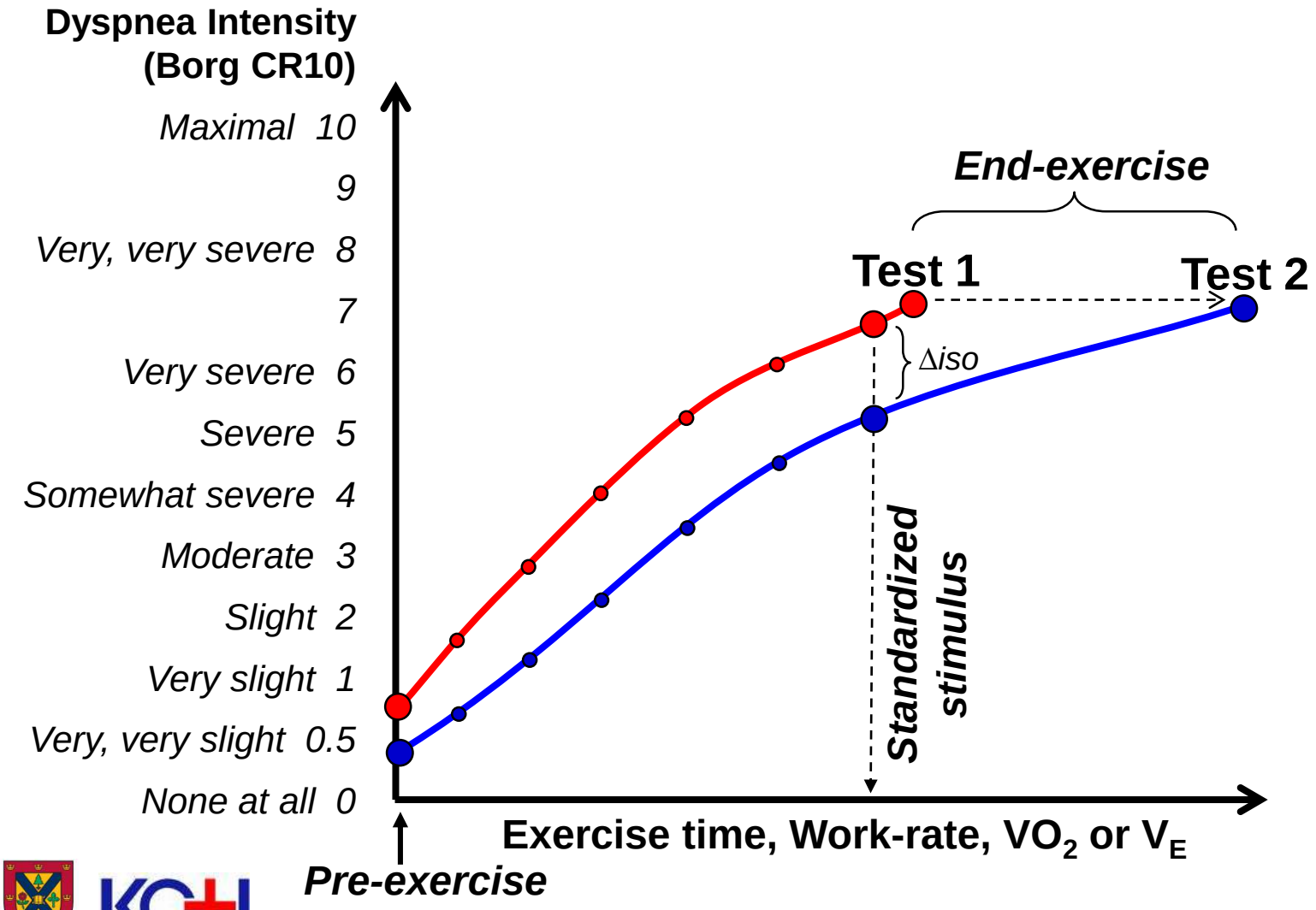


Ciavaglia C, et al. *Eur Respir J* 2014; 43: 1621-30.

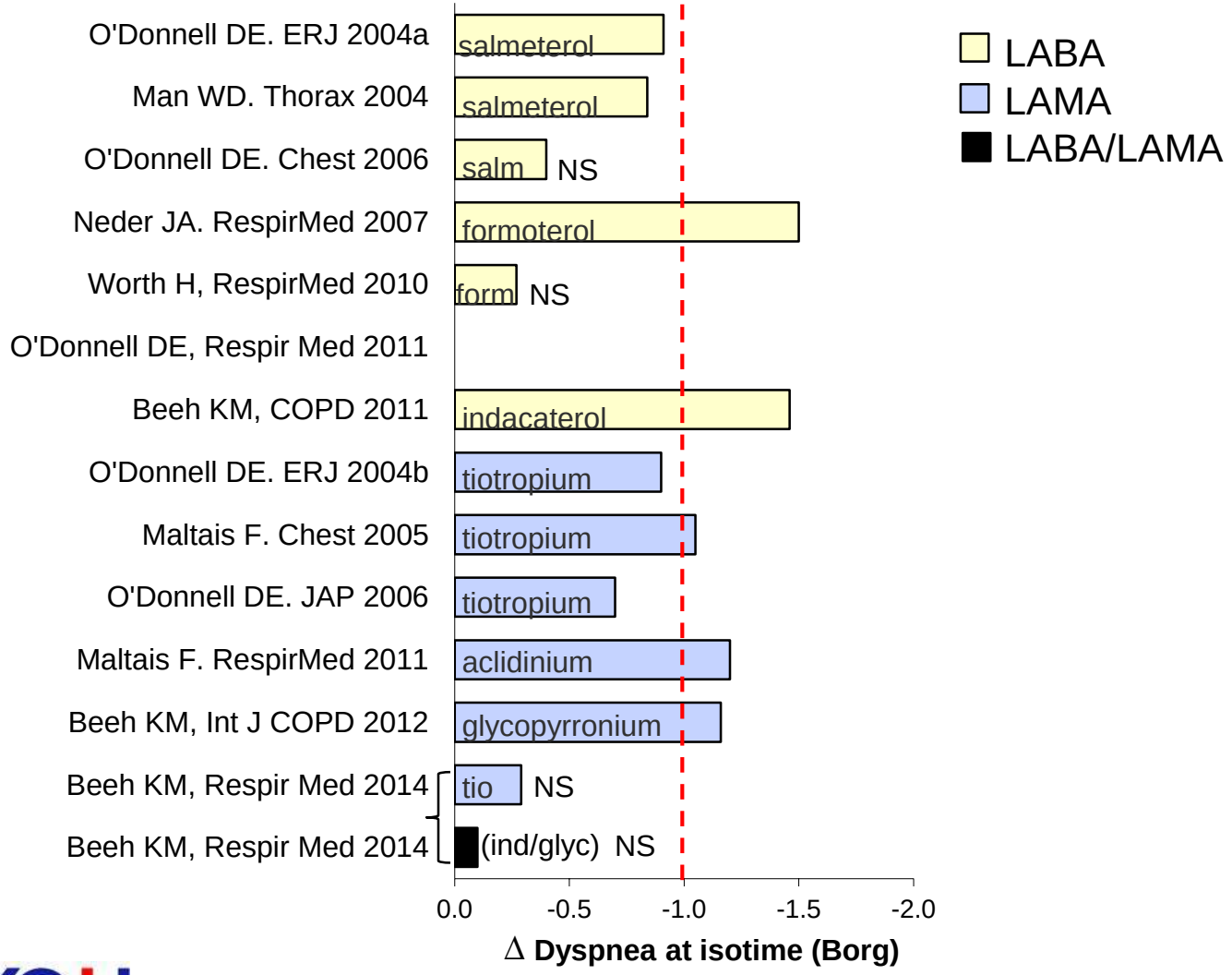
Measuring Dyspnea Intensity during Exercise



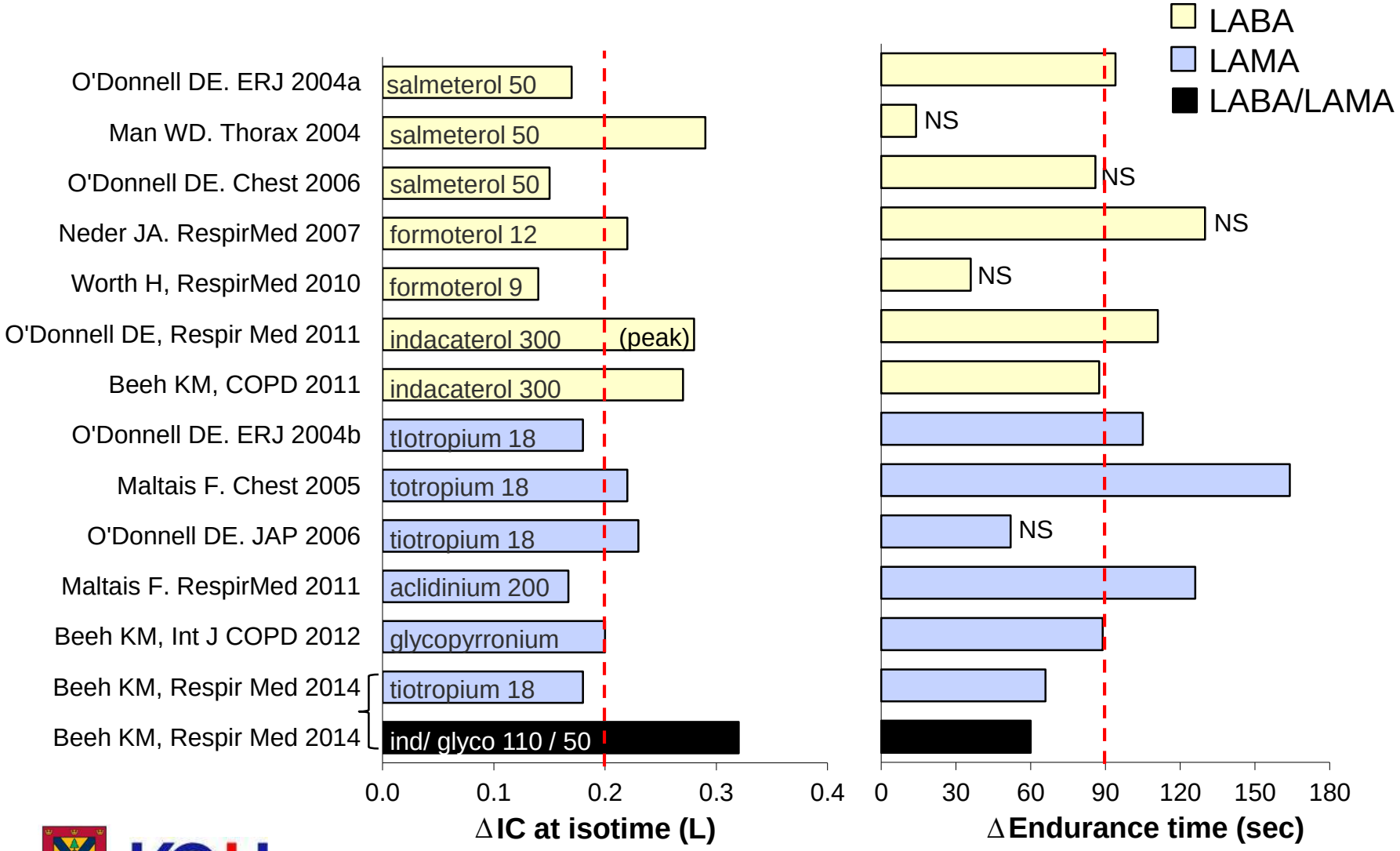
Symptom-limited Exercise Tests
(Incremental or Constant-load)



Improvements in Exertional Dyspnea



Responses to Bronchodilators in COPD



Langer D, et al. *Expert Rev Respir Med* 2014; 8(6): 731-49.

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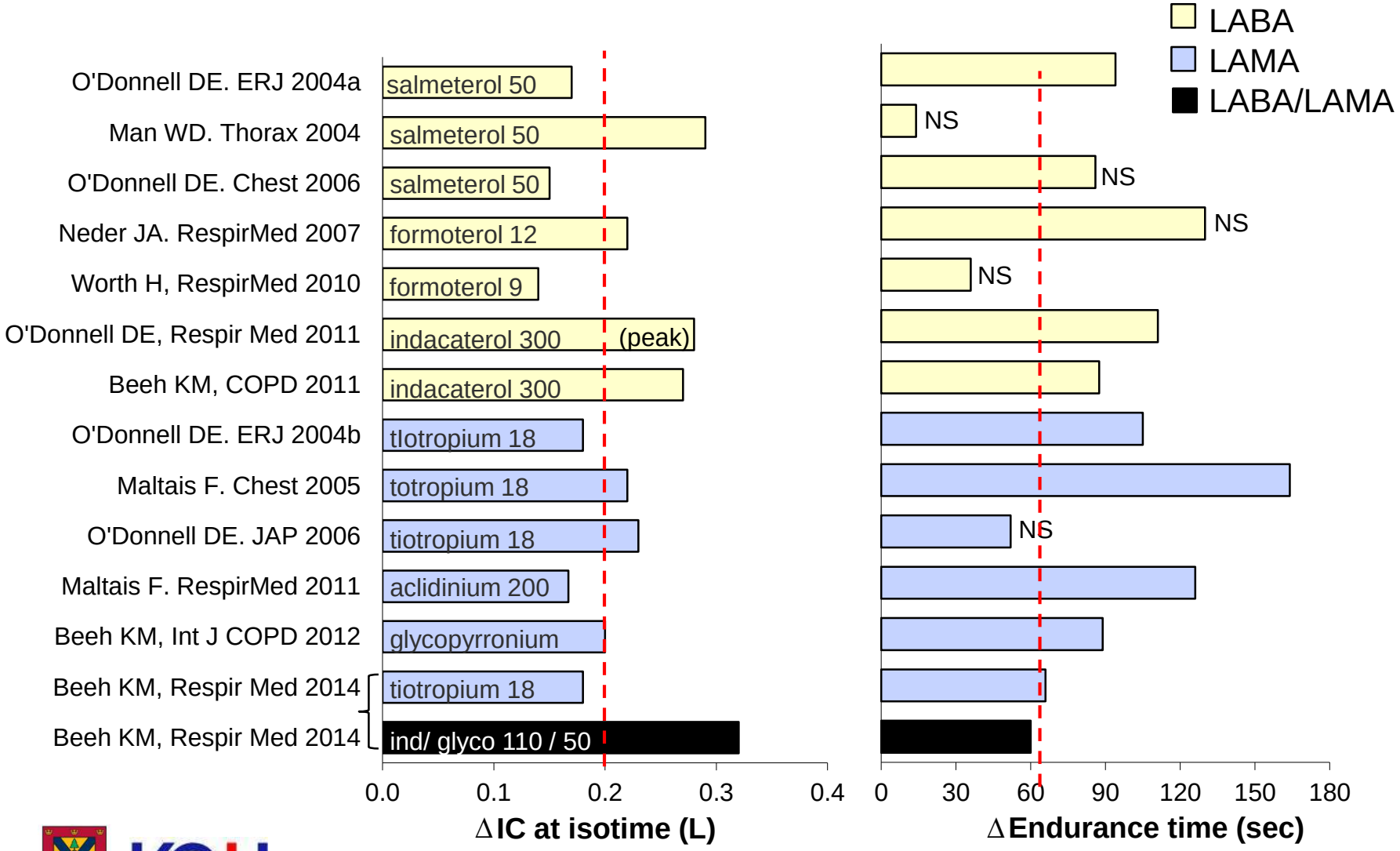
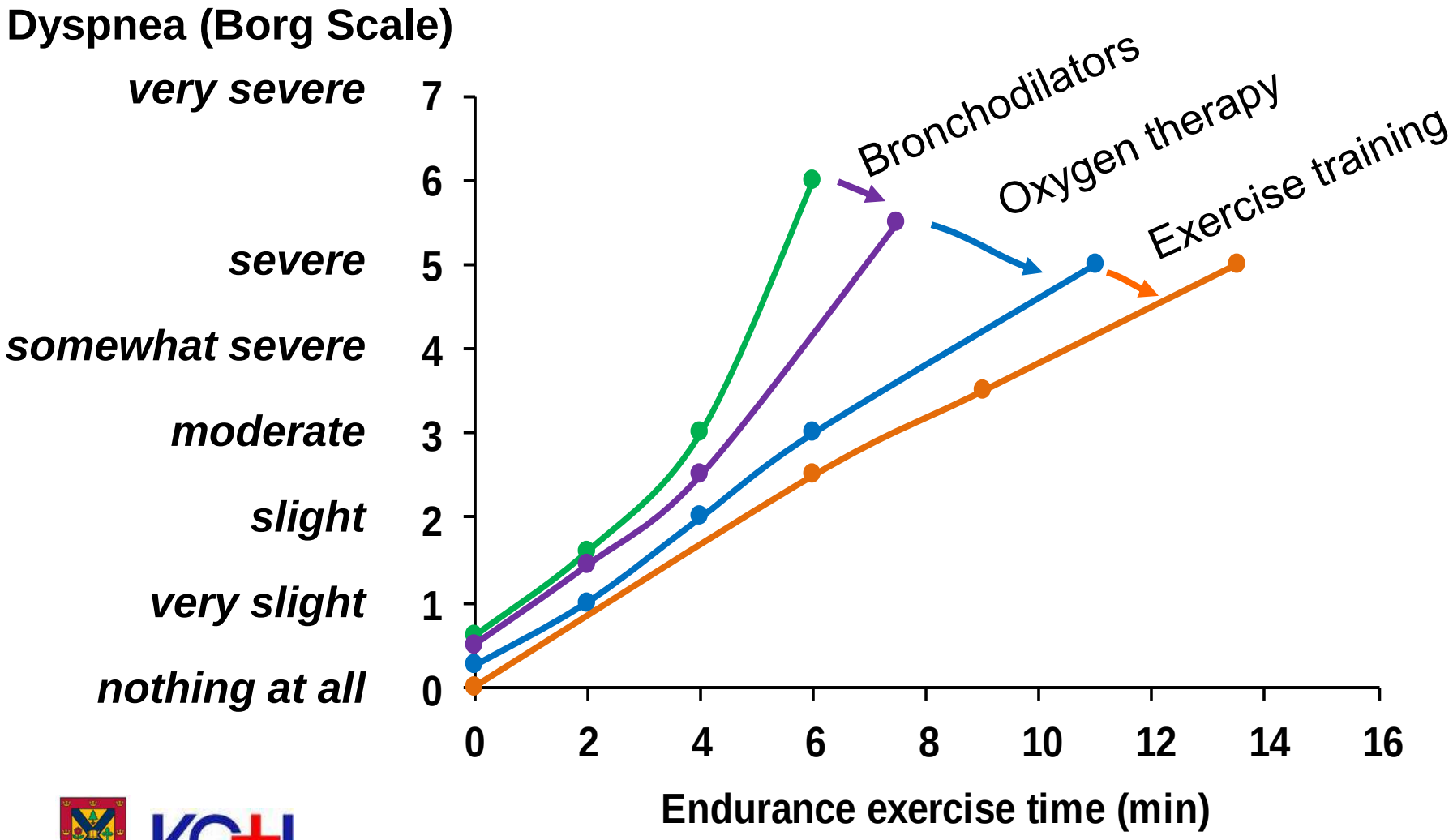


Langer D, et al. *Expert Rev Respir Med* 2014; 8(6): 731-49.

Lack of Improvement in Exercise Performance: Interpretation

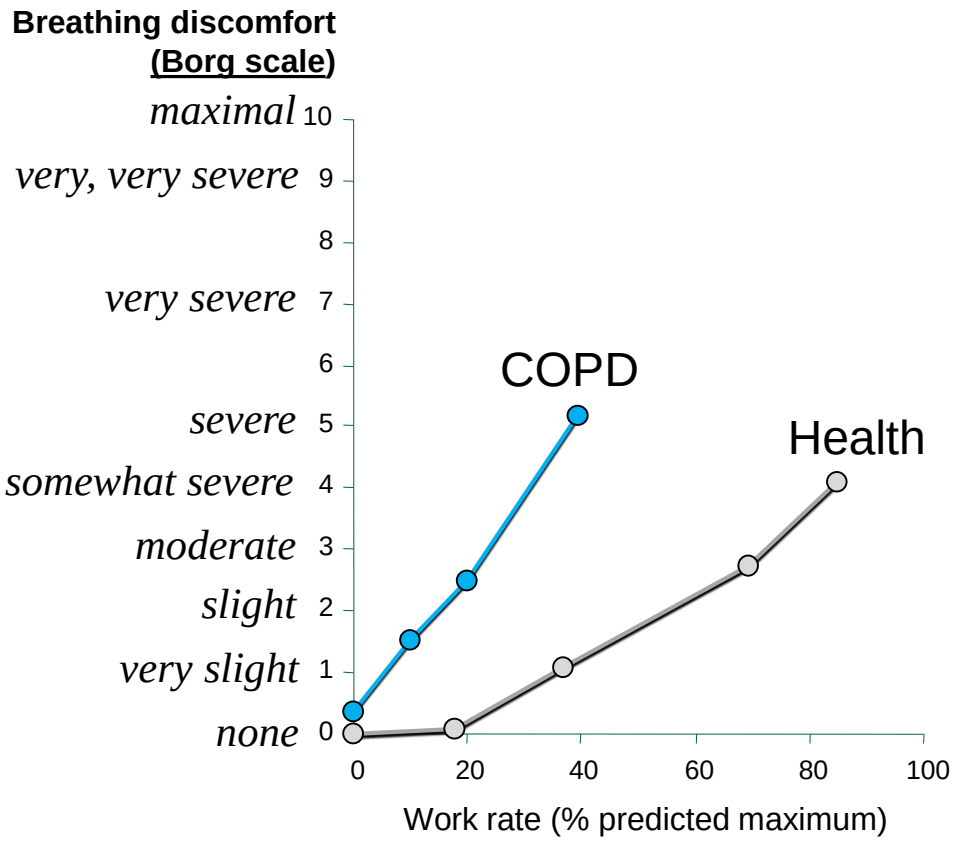
- Proximate exercise limiting factor not dyspnea or ventilatory constraints
- Dyspnea may improve while walking distance or endurance time do not
- Inter-subject, day-to-day variability in bronchodilator responses in COPD
- Methodological limitations:
  - Inadequate study sample
  - Testing protocol: training, encouragement, pre-test bronchodilators

Stepwise Approach to Therapy

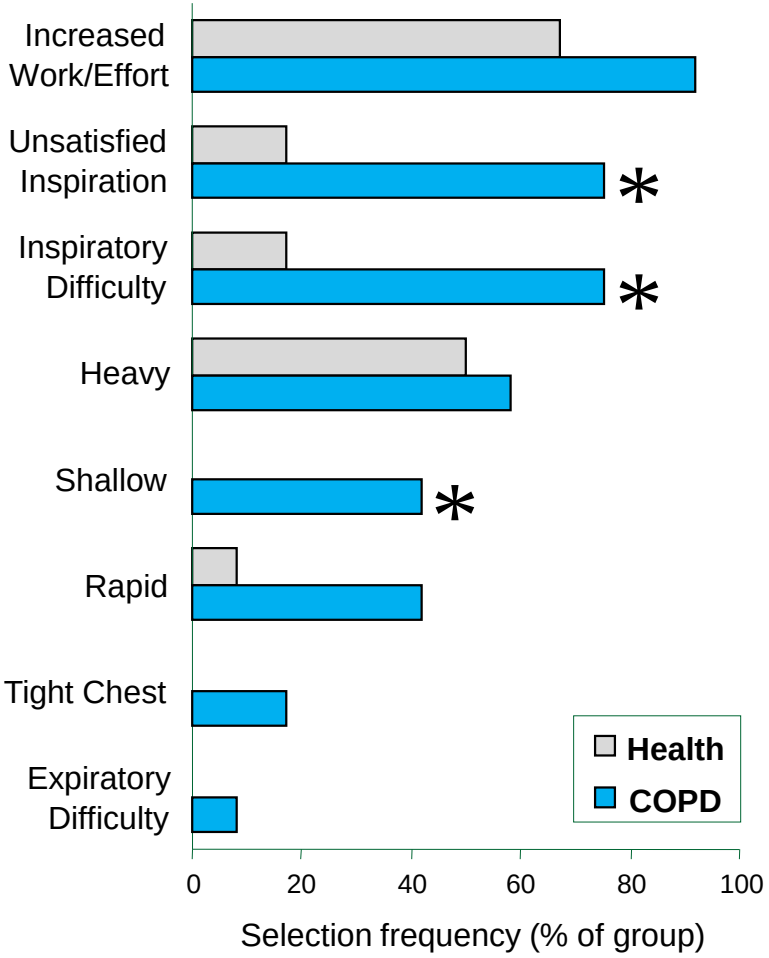


O'Donnell DE. *Med Sci Sports Exerc* 2001;33:S647-S655.

Dyspnea Intensity-Work rate Relationships



Quality of Dyspnea during Exercise

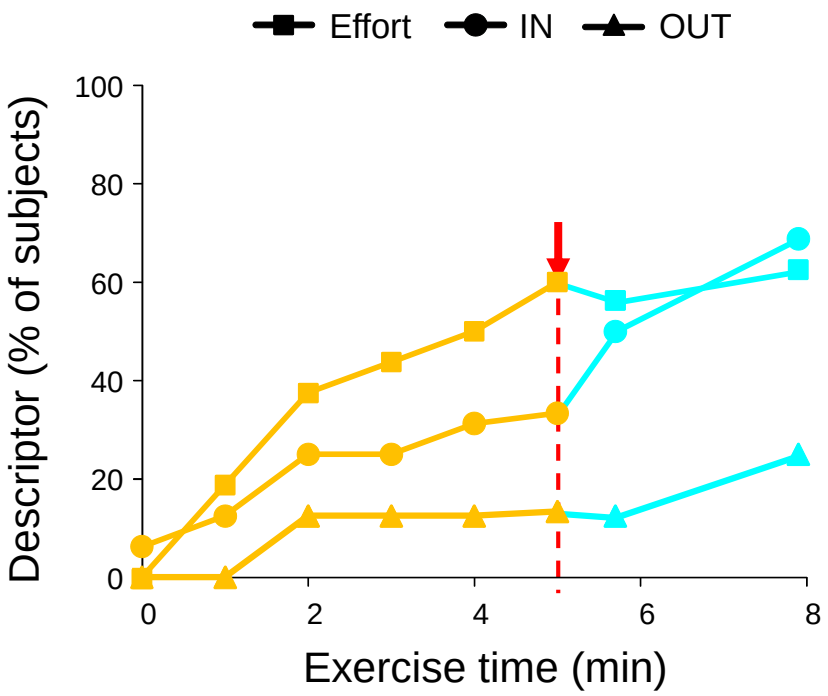


∗ $p<0.05$ *vs* Health

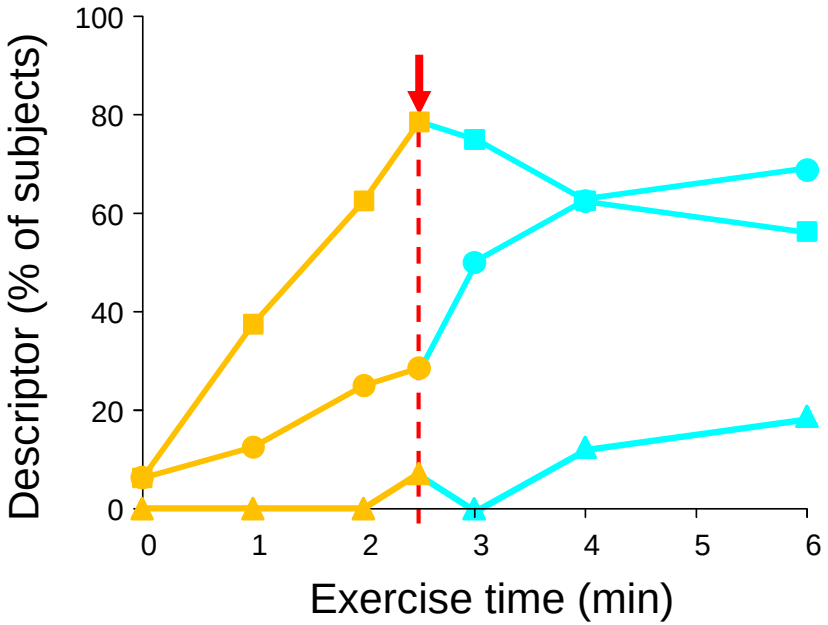
O'Donnell DE, et al. *AJRCCM* 1997;155:109-15.

Evolution of Dyspnea during Exercise in COPD

INCR exercise



CWR exercise



↓ = Critical ventilatory mechanical constraints (i.e., V_T/V_E inflection point)

Effort = "My breathing requires more work/effort"
IN = "I cannot get enough air in"
OUT = "I cannot get enough air out"

Laveneziana P, et al. *Am J Respir Crit Care Med* 2011.

Domains of Dyspnea Measurement (ATS 2012)

Domain	Definition	Measurement examples
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Affective distress	Measures of how distressing breathing feels, either immediate or evaluative	• COPD self-efficacy score • Anxiety intensity ratings (i.e., Borg scale, VAS) during exercise
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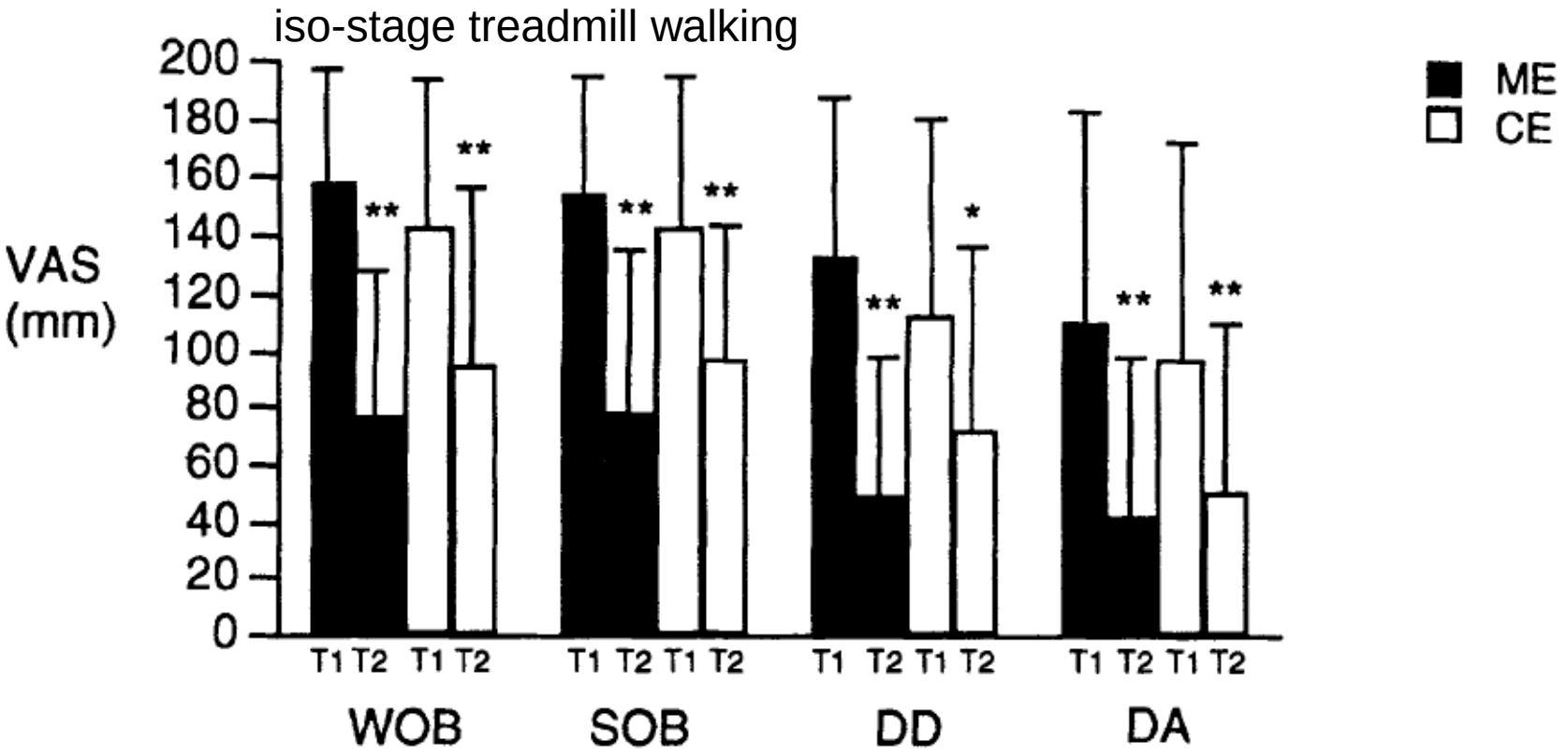
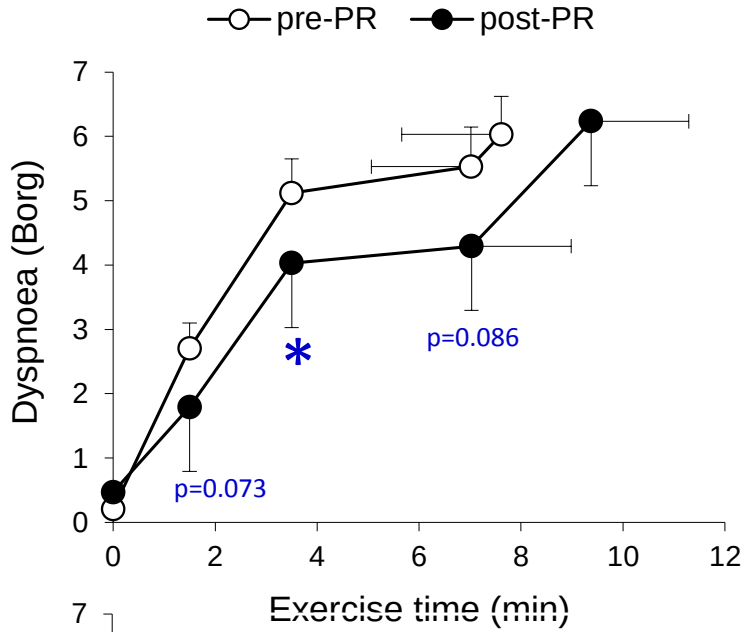
Exercise Training Decreases Dyspnea and its Affective Components in COPD

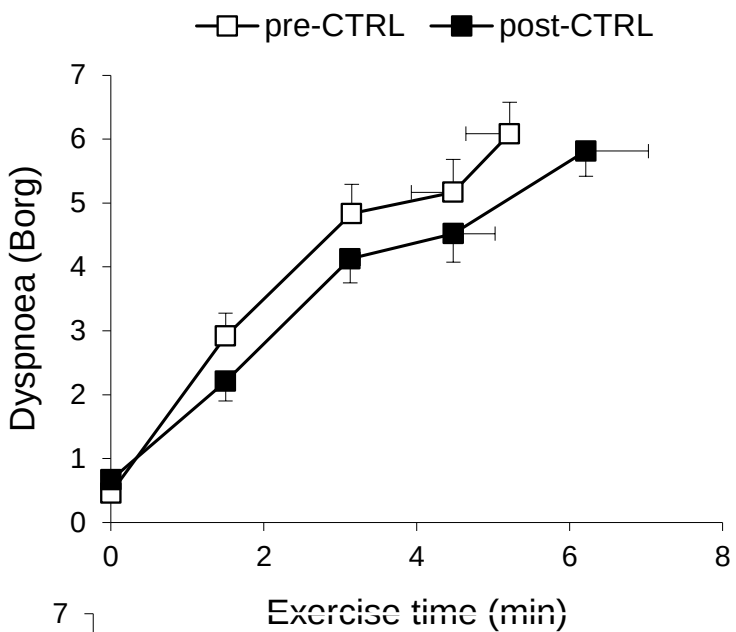


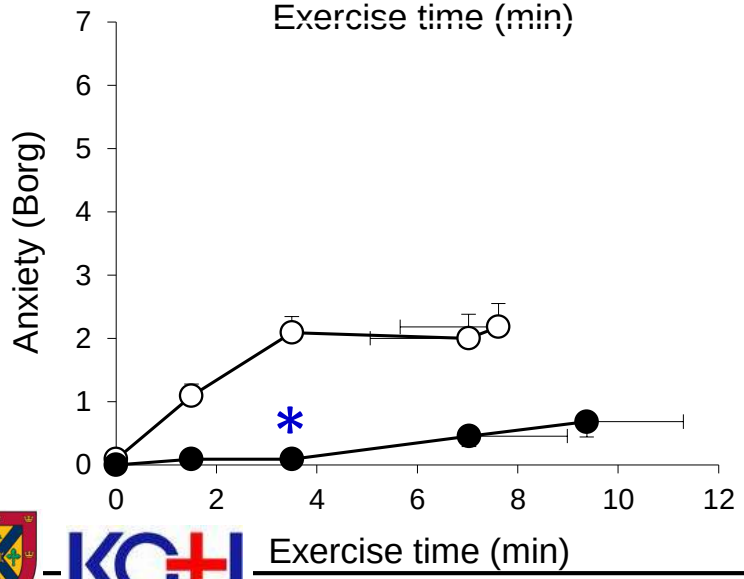
Intensity of dyspnea (SOB), work/effort of breathing (WOB), dyspnea-related distress (DD) and dyspnea-related anxiety (DA) decreased significantly after monitored-exercise (ME) or coached-exercise (CE) training.

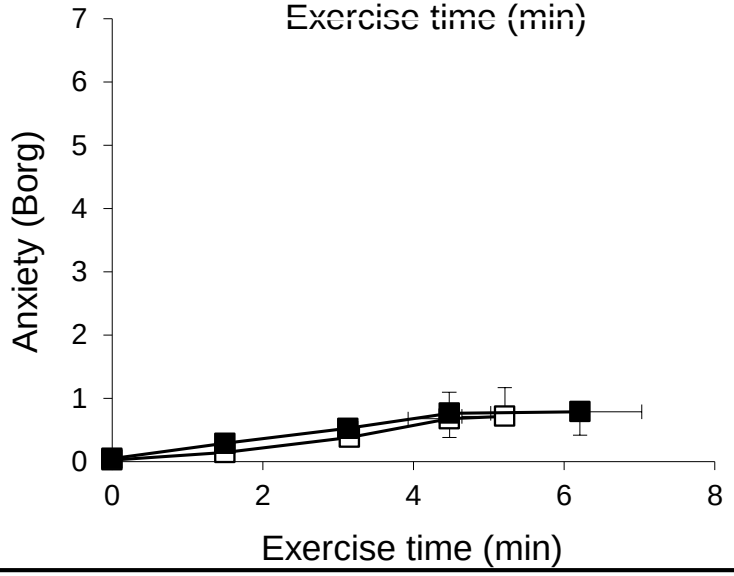
Carrieri-Kohlman V, et al. *Chest* 1996;110:1526-35.

Impact of Pulmonary Rehabilitation on Dyspnea-Related Anxiety in COPD









Wadell K, et al. *COPD* 2013;10:1425-35.

Symptom Impact or Burden

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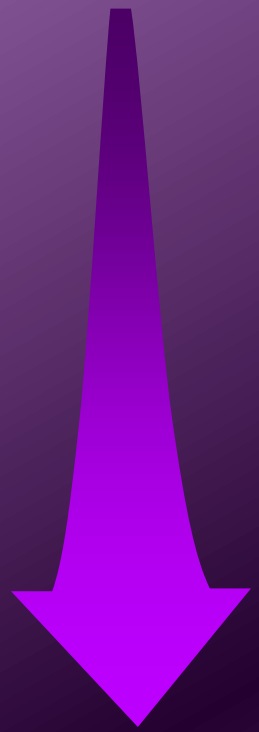
MRC Dyspnea Scale



Grade 1 Breathless with strenuous exercise

Grade 2 Short of breath when hurrying on the level or walking up a slight hill

Grade 3 Walks slower than people of the same age on the level or stops for breath while walking at own pace on the level

Grade 4 Stops for breath after walking 100 yards

Grade 5 Too breathless to leave the house or breathless when dressing

Fletcher CM, et al. *Br Med J* 1959;1:257-66.

Baseline & Transition Dyspnea Index

Functional Impairment

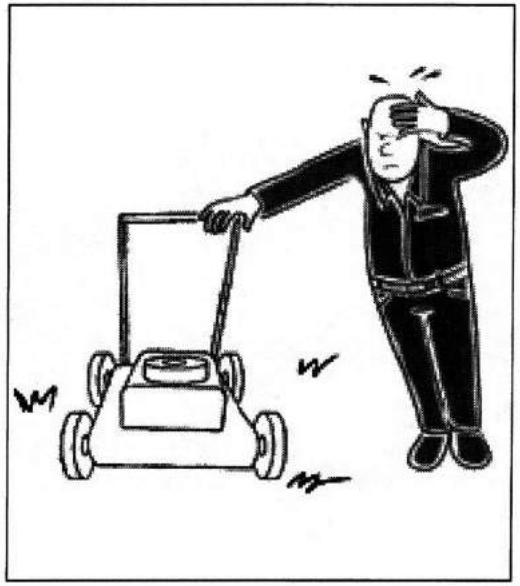
The extent to which activities are impaired because of shortness of breath

Magnitude of Task

The threshold task at which shortness of breath becomes evident

Magnitude of Effort

The vigor with which the maximum task can be performed



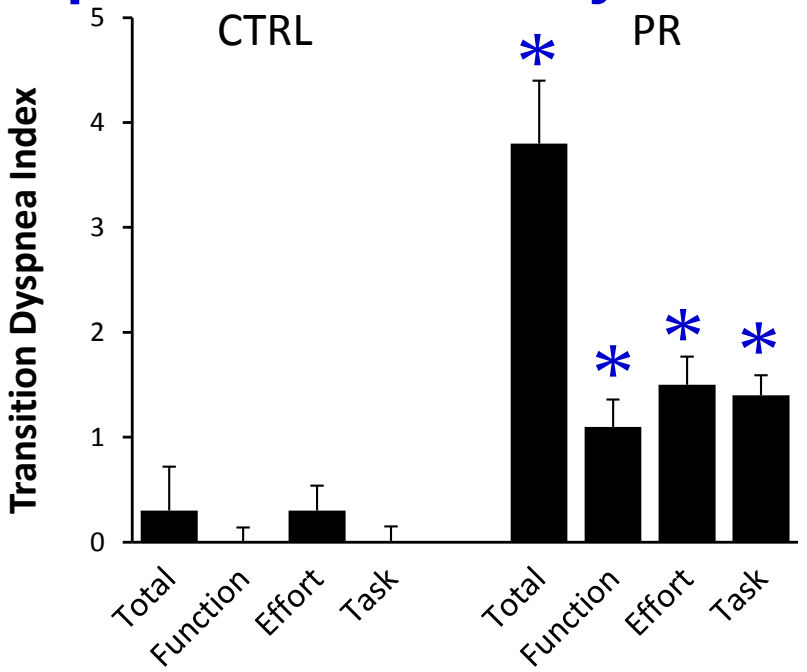
Baseline Dyspnea Index (BDI)

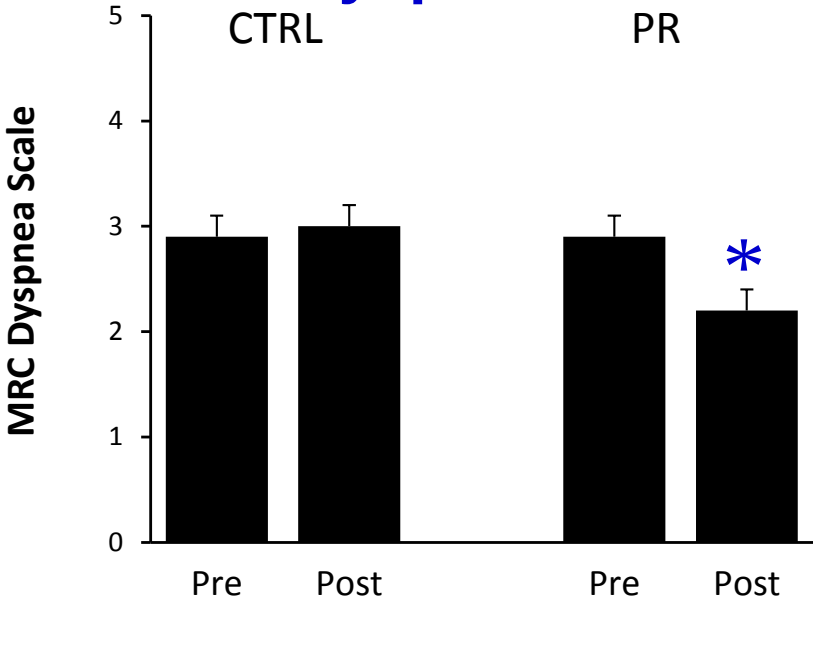
Score	Axis
0 - 4	Functional impairment
0 - 4	Magnitude of task
0 - 4	Magnitude of effort
0 - 12	Baseline focal score

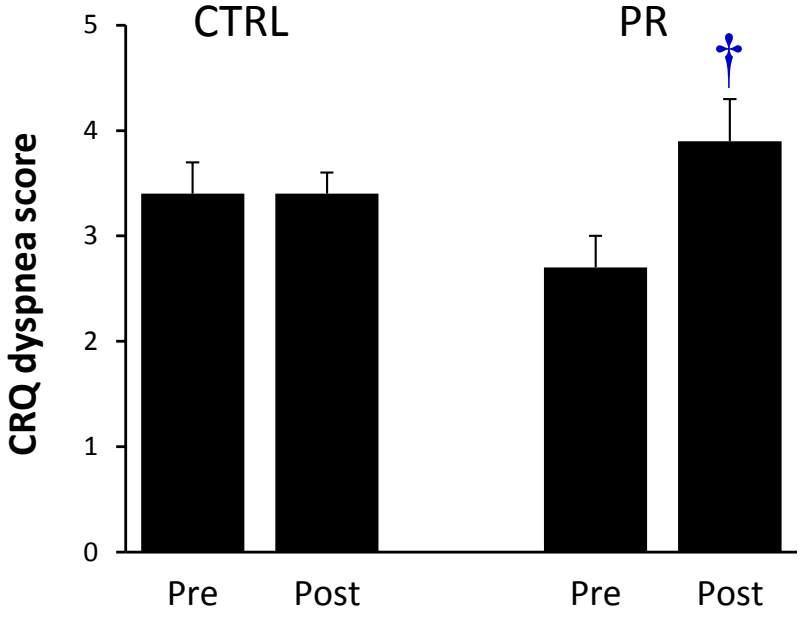
(0 = severe, 4 = unimpaired)

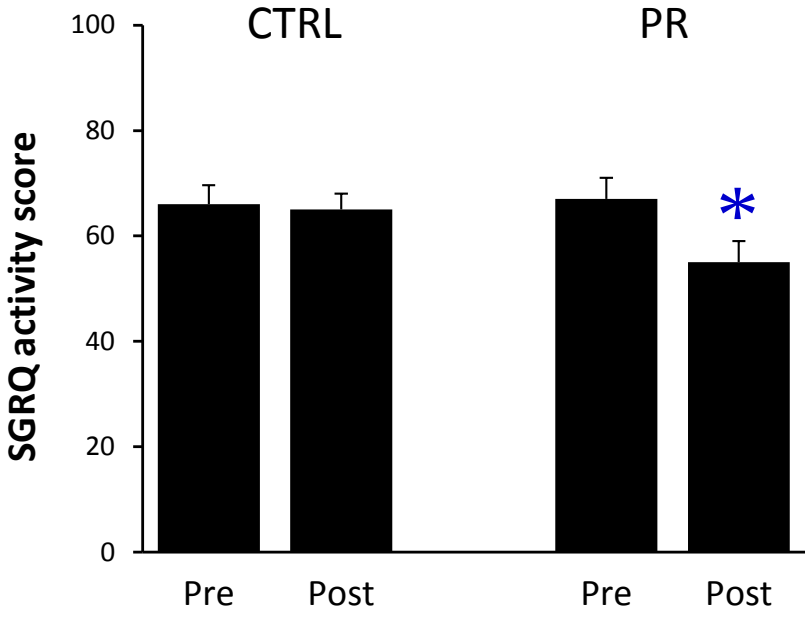
Mahler DA, *et al. Chest* 1984*; 85:* 751-758.

Impact of Pulmonary Rehabilitation on Dyspnea in COPD









Wadell K, et al. *COPD* 2013;10:1425-35.

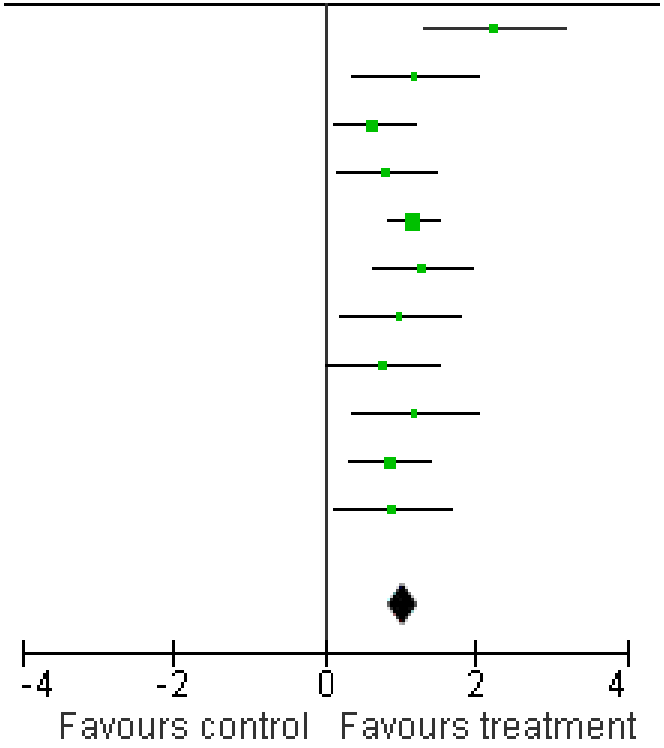
Benefits of Pulmonary Rehabilitation

CRQ dyspnea

	Rehab			Usual care				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Behnke 2000a	2.42	1.24	15	0.16	1.32	15	4.6%	
Cambach 1997	1.2	1.2	14	0	0.8	8	5.5%	
Goldstein 1994	0.68	1.14	40	0.02	1.3	39	11.8%	
Gosselink 2000	0.8	1.28	34	-0.02	1.32	28	8.6%	
Griffiths 2000	1	1.28	93	-0.18	1	91	24.3%	
Güell 1995	1.2	1.4	29	-0.1	1.1	27	8.5%	
Güell 1998	0.8	1.2	18	-0.2	1.2	17	6.0%	
Hernandez 2000	1.08	1.14	20	0.3	1.2	17	6.6%	
Simpson 1992	1.2	1.14	12	0	0.84	10	5.6%	
Singh 2003	0.96	0.88	20	0.08	0.84	20	12.1%	
Wijkstra 1994	0.86	1.02	28	-0.04	1.32	15	6.4%	
Total (95% CI)			**323**			**287**	**100.0%**	

Heterogeneity: Tau² = 0.02; Chi² = 11.60, df = 10 (P = 0.31); I² = 14%

Test for overall effect: Z = 10.13 (P < 0.00001)

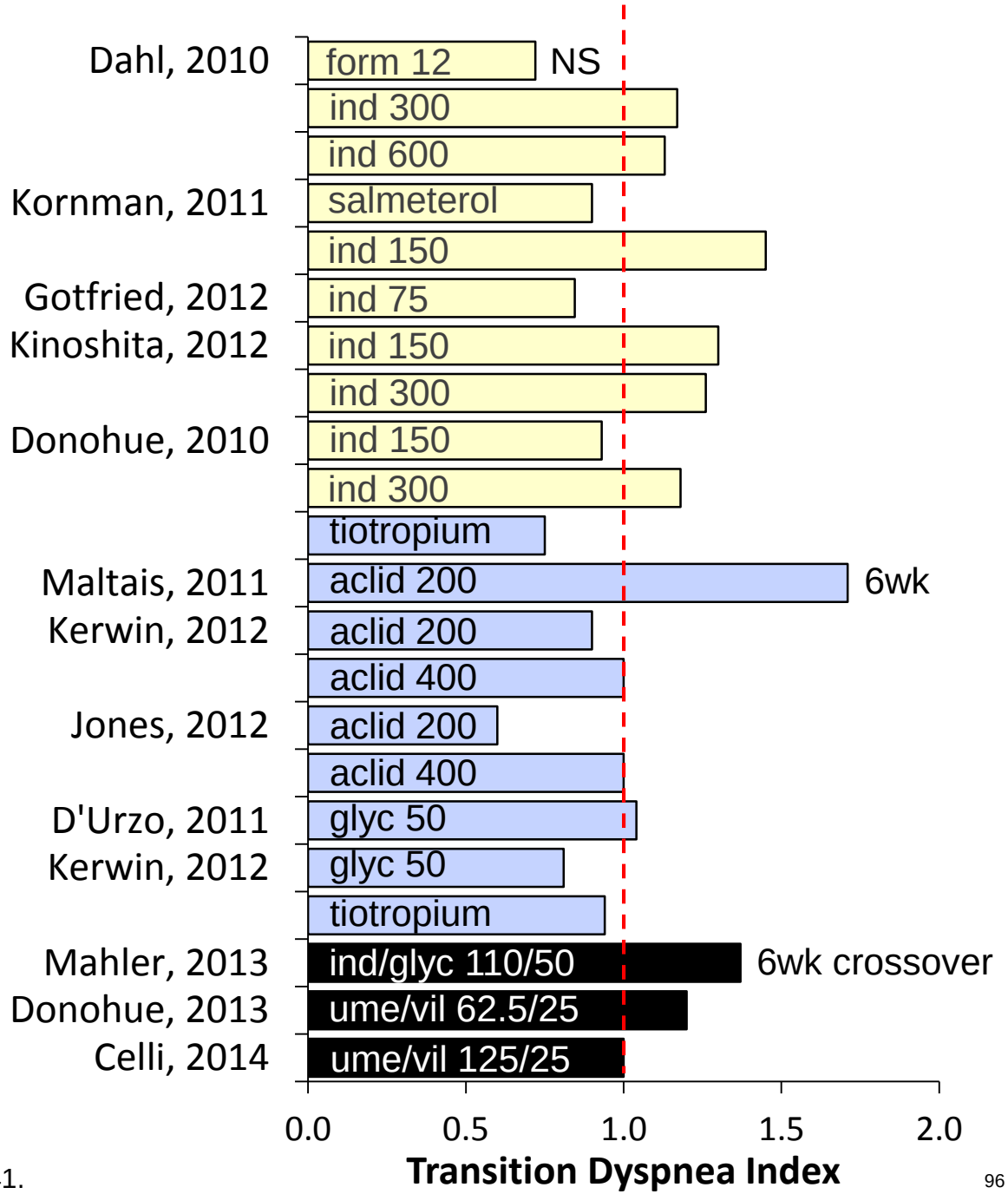


Lacasse Y, et al. *Cochrane Database Syst Rev* 2006; 4:CD003793.

TDI Response

- LABA
- LAMA
- LABA/LAMA

12-26 week studies
vs. placebo



Mahler & O'Donnell. *Chest* 2015; 147: 232-41.

TDI: Clinically Meaningful Difference

-3 Major Deterioration. Formerly working and has had to stop working and has completely abandoned some of usual activities due to shortness of breath.

-2 Moderate Deterioration. Formerly working and has had to stop working or has completely abandoned some of usual activities due to shortness of breath.

-1 Minor Deterioration. Has changed to a lighter job and/or has reduced activities in number or duration due to shortness of breath. Any deterioration less than preceding categories.

0 No Change. No change in functional status due to shortness of breath.

+1 Minor Improvement. Able to return to work at reduced pace or has resumed some customary activities with more vigor than previously due to improvement in shortness of breath.

+2 Moderate Improvement. Able to return to work at nearly usual pace and/or able to return to most activities with moderate restrictions only.

+3 Major Improvement. Able to return to work at former pace and able to return to full activities with only mild restriction due to improvement of shortness of breath.

TDI: Clinically Meaningful Difference

-3 Major Deterioration. Formerly working and has had to stop working and has completely abandoned some of usual activities due to shortness of breath.

-2 Moderate Deterioration. Formerly working and has had to stop working or has completely abandoned some of usual activities due to shortness of breath.

-1 Minor Deterioration. Has changed to a lighter job and/or has reduced activities in number or duration due to shortness of breath. Any deterioration less than preceding categories.

+1 Minor Improvement.
Able to return to work at reduced pace or has resumed some customary activities with more vigor than previously due to improvement in shortness of breath.

to return to most activities with moderate restrictions only.

+3 Major Improvement. Able to return to work at former pace and able to return to full activities with only mild restriction due to improvement of shortness of breath.

Key Messages

- Dyspnea is a complex multi-dimensional symptom
- Evaluation of dyspnea in the sensory, affective and impact domains is suggested
- Increase dyspnea intensity during activity in health and disease is related to increased inspiratory neural drive to the diaphragm
- The distressing sensation of “unsatisfied inspiration” is linked to neuromechanical uncoupling

Key Messages

- The distressing sensation of “unsatisfied inspiration” is linked to neuromechanical uncoupling.
- Interventions that relieve dyspnea intensity in COPD reduce central drive, improve respiratory mechanics/ muscle function and enhance neuromechanical coupling.
- Pulmonary rehabilitation (exercise training and education) consistently improves dyspnea in its intensity, affective and impact domains.

Exercise testing for the evaluation of muscle strength/endurance and pulmonary rehabilitation

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AIMS

- Demonstrate the clinical importance of muscle dysfunction in respiratory disease
- Present tools to evaluatie muscle strength and endurance in clinical practice

SUMMARY

Introduction

Dyspnea, impaired exercise tolerance and reduced quality of life are common complaints in patients with chronic respiratory disease. Several pieces of evidence point to the fact that these symptoms show only a weak relation to lung function impairment [1]. Prediction of exercise performance based solely on resting pulmonary function tests is inaccurate [2,3,4]. Other factors, such as peripheral and respiratory muscle weakness and deconditioning are now recognized as important contributors to reduced exercise tolerance [5,6]. Respiratory muscle weakness contributes to hypercapnia [7], dyspnea [5,8], weaning failure[9] and nocturnal oxygen desaturation [10]. A higher mortality rate was observed in patients with severe muscle weakness [11,12]. Assessment of skeletal muscle function contributes to the evaluation of impairment of COPD patients and thus to the assessment in rehabilitation in several ways. Skeletal muscle function is an independent marker of disease severity [12] since it contributes to the abovementioned clinically relevant issues. Recently, ICU acquired muscle weakness has gained increasingly interest and consequently the tools to diagnose muscle weakness [13]. Muscle function assessment enables to diagnose muscle weakness and thus to state the indication for rehabilitation. Indeed, isometric muscle testing seems helpful in selecting candidates for exercise training in healthy subjects [14] and in COPD patients [15]. COPD patients with muscle weakness seem to be better responders to rehabilitation 15. Measurement of isometric muscle strength and endurance was also found sensitive to detect changes in peripheral muscle function after rehabilitation [16-18].

Skeletal muscle strength is in general reduced in COPD. However, arm muscle strength is less affected than leg muscles and respiratory muscles [19,20], while proximal arm muscles were more affected than distal arm and hand muscles [19]. This information is helpful to optimize training prescription in a rehabilitation program. Allowing to target muscle training more specific to more impaired muscle groups.

Assessment of peripheral skeletal muscle function will be discussed from the point of view of both strength and endurance capacity of the muscles.

Respiratory Muscle Strength Testing

Clinically, respiratory muscle strength is measured as PImax and maximum expiratory pressure (PEmax). These pressures are measured using a small cylinder that fits to the patient's mouth with a circular mouthpiece. A small leak in the cylinder (two mm diameter and 15 mm length) prevents high pressures due to the contraction of the cheek muscles [21]. Standardizing the lung volume at which the pressures are measured is crucial [22]. To prevent chest wall and lung recoil pressures from contributing to the pressure generated by the inspiratory muscles, measurements are recorded at functional residual capacity (FRC). This lung volume, however, is difficult to standardize. In clinical practice, PImax is measured from residual volume whereas PEmax is measured at total lung capacity (TLC). At least five repetitions should be performed. Respiratory muscle testing is described in detail in a American Thoracic Society/European Respiratory Society position statement [23].

Several groups of investigators have published norms for PImax and PEmax [21,24,25]. Regardless of the norms used, the standard deviation is typically large. Therefore, weakness is not easy to define[26]. Inspiratory weakness is defined as a PImax lower than 50% of predicted [27] in the presence of clinical signs (e.g., dyspnea, impaired cough, and orthopnea) consistent with reduced respiratory muscle strength. Other methods, such as the sniff maneuver, have been developed as tools to quantify global respiratory muscle function [28]. The results of the sniff maneuver have been reported to be highly reliable in children with neuromuscular disease. More invasive methods such as electric or magnetic diaphragm stimulation can provide more accurate and detailed information on diaphragmatic function [29] and are useful in the diagnosis of diaphragmatic paresis. For most clinical applications, however, the assessment of inspiratory and expiratory mouth pressures is sufficient.

Limb Muscle Strength Testing

Muscle strength, or, more precisely, the maximum muscle force or tension generated by a muscle or (mostly) a group of muscles, can be measured in several ways and with different equipment.

Manual testing with the 0-5 scale from the Medical Research Council is often used in clinical practice, but very insensitive to assess differences in muscle strength of values above grade 3 (active movement against gravity) [30]. Therefore several equipment was developed to measure muscle strength more accurately:

1. One-repetition maximum (1-RM) weightlifting for isotonic muscle force is a dynamic method for measuring the maximum amount of weight lifted for one time during a standard weightlifting exercise. In elderly people, 1-RM can be calculated from sub maximal efforts [31]. For untrained persons the calculated 1-RM (kg) = 1.554 * (7-10RM weight,kg) -5.181. In COPD patients, the 1RM tests have been shown to be safe [32] and sensitive to measure changes after training [16]. However, to the best of our knowledge no normative data exist for the 1-RM tests, and the obtained values are largely dependent on the equipment used. Measurement of the 1-RM is often used to guide a muscle training program [33,34].

2. Dynamometry with mechanical or electrical equipment is used to measure isometric muscle force. In mechanical equipment mostly a steel spring is compressed, which moves a pointer on a scale, for example the handgrip dynamometer [35]. Handgrip dynamometry has been shown to be reliable and reference values are available [35,36]. It has been used in several studies in COPD patients [6, 37-39]. For other upper and lower extremity muscle groups handheld devices have been developed. This electrical equipment consists of an electronic force transducer connected to a computer. Two methods of isometric testing are described: the make-test and the break-test. In the make-test the maximal force of the subject is equal to the force of the observer. In the break-test, the force of the examinator exceeds the force of the patient slightly. Both tests are reproducible, but higher values were found during break-tests [40]. The hand-held dynamometry is a viable alternative to more costly modes of isometric strength measurements, provided the assessor's strength is greater than that of the specific muscle group being measured

[40,41]. References values are available, also for elderly healthy subjects [42]. Hand-held devices for muscle testing have been applied in COPD patients [19,43]

3. Computer-assisted dynamometers to measure isokinetic or isometric muscle strength have the advantage of measuring maximal muscle strength over a wide range of joint positions and velocities. This also takes into account also the force-velocity characteristics of the muscle contraction. However, the equipment is very expensive and not available to many practitioners. References values are available for isometric [11] and isotonic [44] muscle testing. In healthy subjects isometric and isokinetic measurements were well correlated [45,46]. Although direct comparison between these measures was not performed in COPD patients, two studies may suggest such a relationship also in COPD. Both isokinetic muscle strength [5,47] and isometric muscle strength [6,48] were significantly lower in COPD patients compared to healthy subjects.

The limitation of the use of maximal voluntary contractions is the potential to observe sub maximal contractions due to sub maximal cortical drive [49,50]. The use of superimposed electric or magnetic twitch contractions anticipates this potential variation in voluntary activation [49]. The technique of electrically superimposed twitch contractions was developed in 1954 by Merton [51]. Twitch stimulation, however, is not suggested for routine clinical evaluation of muscle force. When standardized, and maximal encouragement is given, isometric muscle strength results in reliable, and maximal data [50]. To answer specific research questions, however, magnetic or electrical nerve stimulation may be useful. Magnetic stimulation has nowadays become a validated research procedure. It is less painful than electrical stimulation, and the 'twitch' stimulations are relatively reproducible [52].

In addition, measurement of muscle mass with ultrasound has become increasingly popular as a reproducible and effort independent measure [13,53].

Limb Muscle Endurance Testing

The evaluation of lower limb muscle performance in patients with COPD has focused mainly on muscle strength. In addition to reduced muscle fiber cross sectional area [54] and muscle cross sectional area [20], changes in fiber type composition resulting in a decrement of fatigue-resistant slow fibers [54-56] and a reduction in oxidative enzymes [57-59] are the main morphological and histochemical alterations found in lower limb skeletal muscles. Following these morphological and histochemical alterations in muscle biopsies, it may be hypothesized that lower limb muscle endurance is decreased more than muscle strength in patients with COPD. Newell et al. [60] observed only a slight reduction in endurance capacity (torque reduction over 18 contractions) of elbow flexors in COPD patients compared to healthy subjects. The same was concluded for Triceps and Deltoid sustained contractions which were not different between healthy subjects and patients with mild COPD [47]. Along the same lines endurance (time to maintain 80% of peak torque) of the quadriceps muscle in hypoxemic COPD patients was normal [61]. In contrast, others found a mean reduction of 50% in quadriceps muscle endurance at sub maximal (20-40% of peak) torque) in patients with moderate to severe COPD [62,63].

Isolated muscle endurance can be measured in several ways. First, the time of a sustained maximal isometric muscle contraction until 60% of the initial maximal strength is left can be measured [64]. During this test blood supply is profoundly reduced and muscle contraction is very much dependent on anaerobic metabolism. Second, the decline in maximal force after a fixed number (18) of repetitive contractions with a fixed contraction (10sec) and relaxation time (5sec) can be assessed [65]. A third protocol consists of repeated contractions of 20% of the maximal voluntary contractions at a pace of 12 contractions per minute up to exhaustion [63,66]. The latter two are probably more related to oxidative capacity, as these dynamic muscle contractions at a low percentage of peak torque do not induce closure of capillaries in the muscle and thus do not deprivate the muscle from oxygen supply.

After a specific muscle endurance training program, significant improvements in the number of repetitions of loaded and unloaded isotonic contractions of upper and lower extremities over a 30 second

period were observed [67]. Although no data were shown on the reproducibility of this measurement, control subjects performed fairly reproducible results at their second visit after 12 weeks [67].

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63. Serres, I., V. Gautier, A. Varray, and C. Prefaut. 1998. Impaired skeletal muscle endurance related to physical inactivity and altered lung function in COPD patients. Chest 113:900-905.
64. Gandevia, S. C., D. K. McKenzie, and I. R. Neering. 1983. Endurance capacity of respiratory and limb muscles. Respir.Physiol. 53:47-61.
65. McKenzie, D. K. and S. C. Gandevia. 1987. Influence of muscle length on human inspiratory and limb muscle endurance. Respir.Physiol. 67:171-182
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67. Clark, C. J., J. E. Cochrane, and E. Mackay. 1996. Low intensity peripheral muscle conditioning improves exercise tolerance and breathlessness in COPD. Eur.Respir.J. 9:2590-2596.

EVALUATION

1. Limb muscle weakness is present in
   a. Only patients with COPD GOLD stage 3 and 4
   b. All COPD GOLD stages
   c. Mainly in COPD GOLD stage 4
   d. COPD patients on supplemental oxygen

2. Assessment of limb muscle strength is applicable (more answers might be correct)
   a. Only in hospitals with research facilities
   b. In exercise physiology laboratories
   c. In outpatient clinics
   d. In primary care settings

3. The diagnosis of limb muscle weakness has clinical implication for (more answers might be correct):
   a. The content of the rehabilitation program
   b. Prognosis
   c. Identification of the severity of airflow obstruction
   d. The start of non invasive ventilation

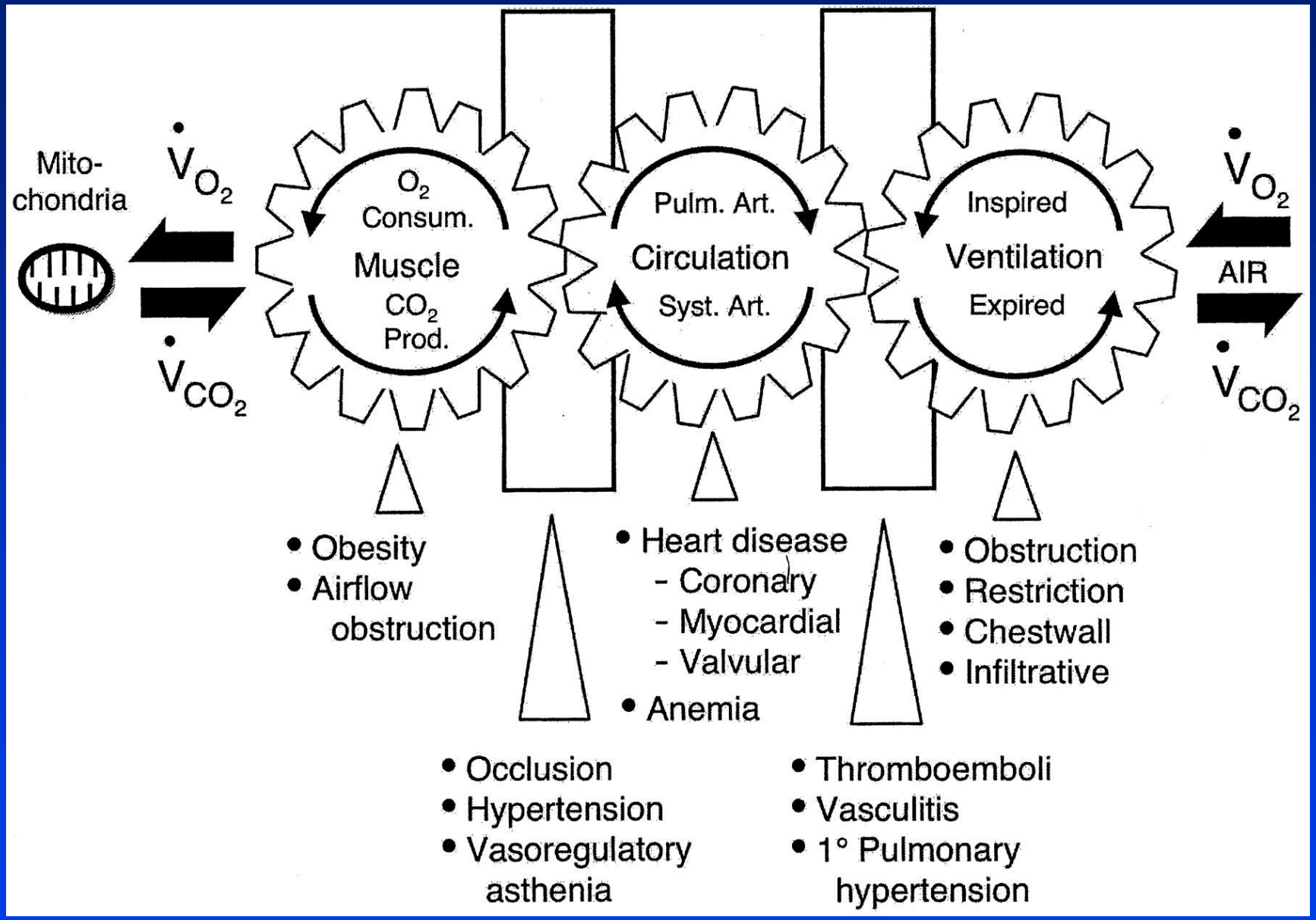
ERS EUROPEAN RESPIRATORY SOCIETY
every breath counts

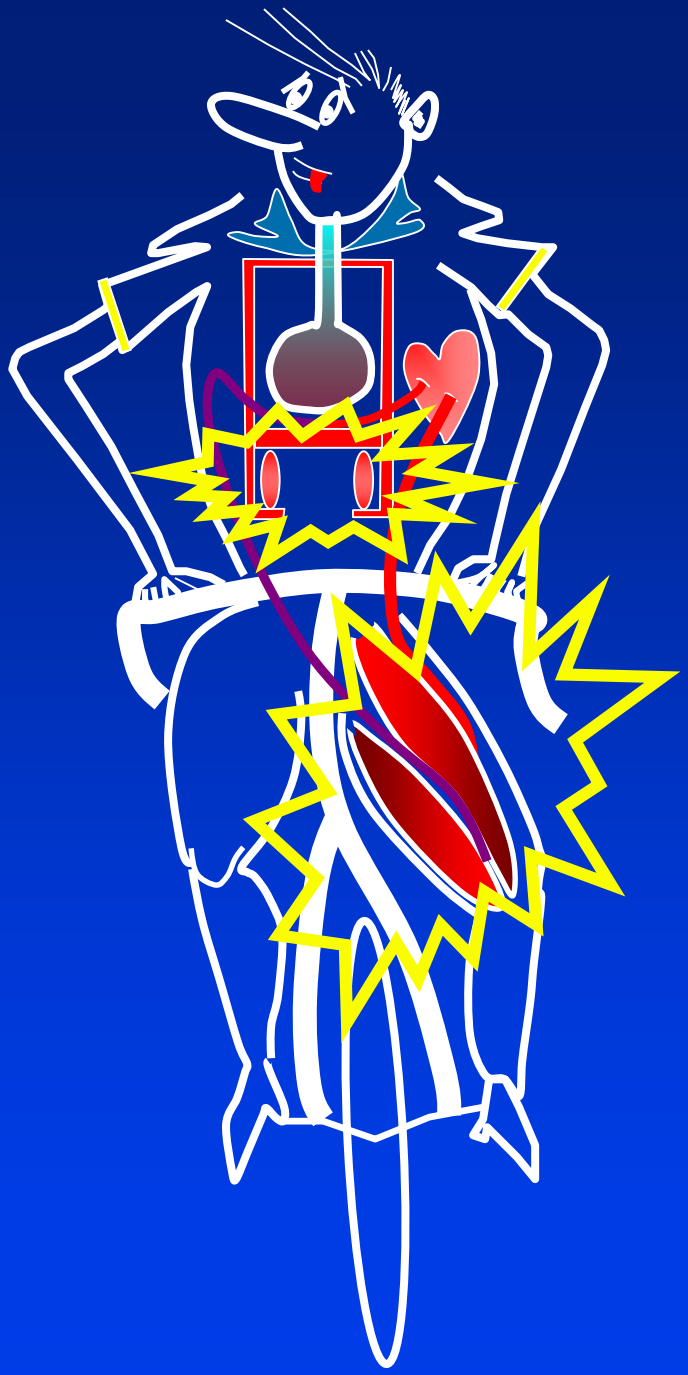
EXERCISE TESTING FOR THE EVALUATION OF MUSCLE STRENGTH/ENDURANCE AND PULMONARY REHABILITATION

Rik Gosselink, PT,PhD
Department Respiratory Rehabilitation
University Hospitals Leuven
Faculty of Kinesiology and Rehabilitation Sciences
University of Leuven Belgium

KU LEUVEN

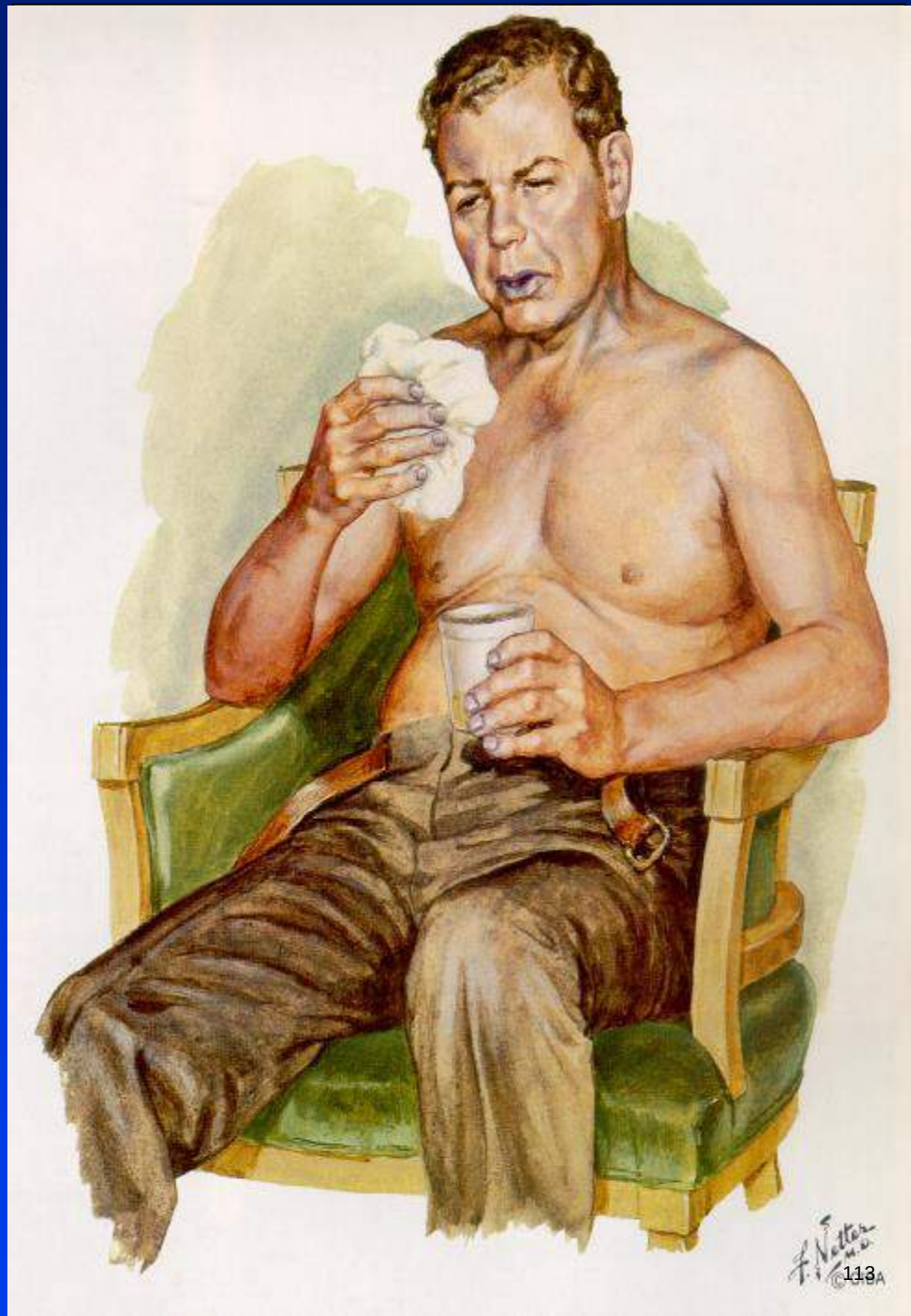
Faculty disclosure: none


Mito-
chondria
$\dot{V}_{O_2}$
$\dot{V}_{CO_2}$
O_2
Consum.
Muscle
CO_2
Prod.
Pulm. Art.
Circulation
Syst. Art.
Inspired
Ventilation
Expired
$\dot{V}_{O_2}$
AIR
$\dot{V}_{CO_2}$
• Obesity
• Airflow obstruction
• Heart disease
- Coronary
- Myocardial
- Valvular
• Anemia
• Obstruction
• Restriction
• Chestwall
• Infiltrative
• Occlusion
• Hypertension
• Vasoregulatory asthenia
• Thromboemboli
• Vasculitis
• 1° Pulmonary hypertension

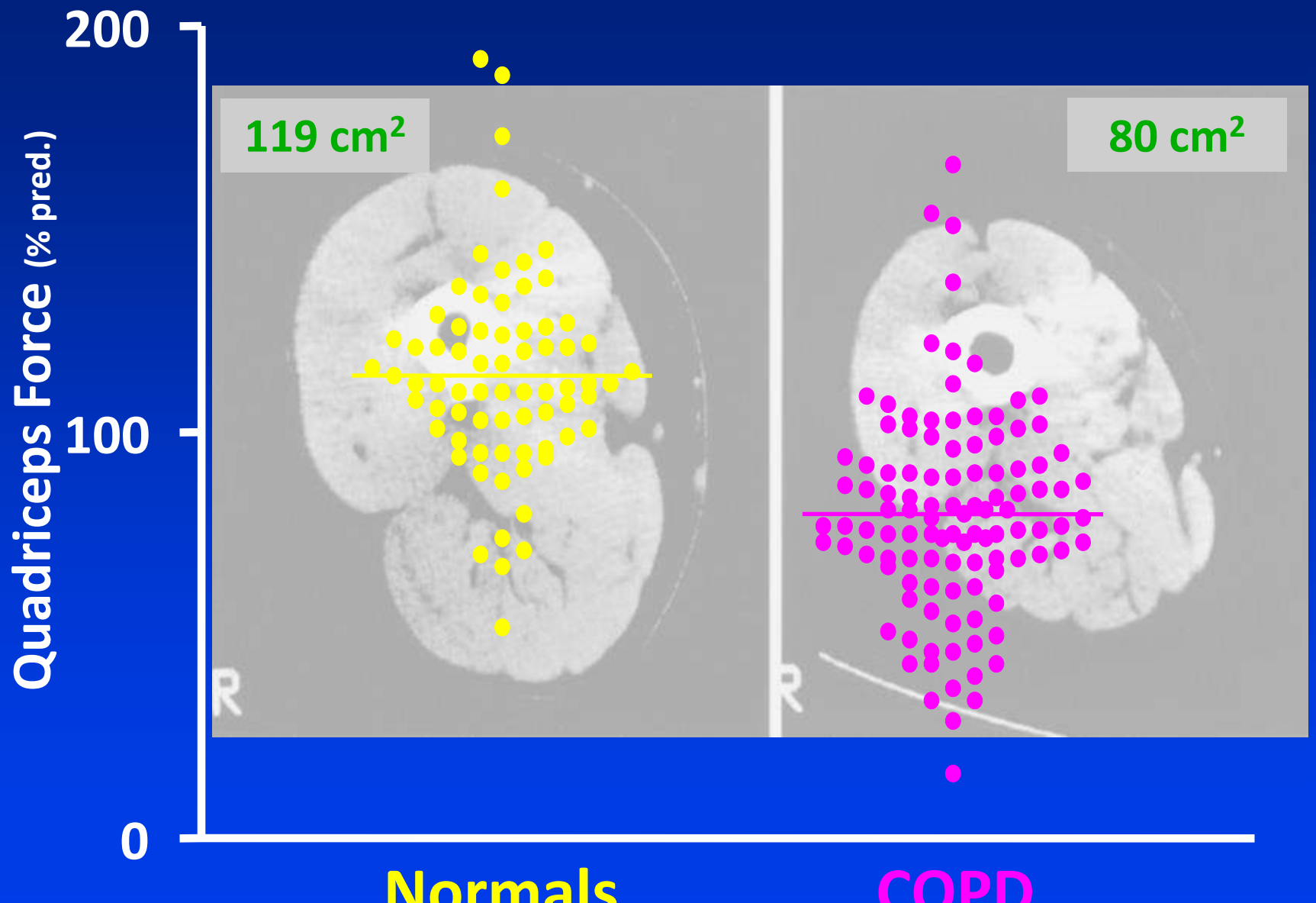


Aims

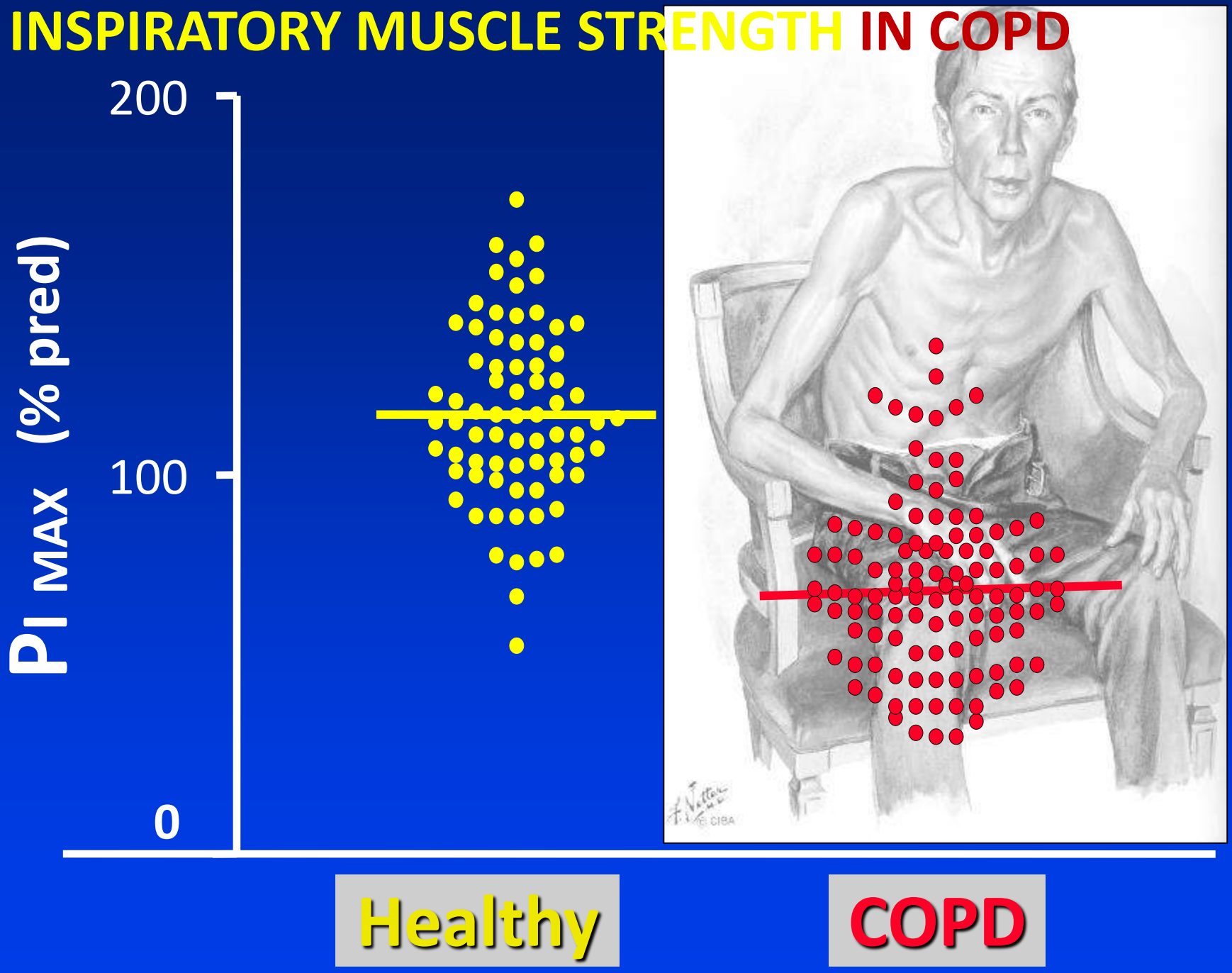
- Is muscle weakness present in cardiorespiratory diseases
- Causes of muscle weakness
- Is muscle weakness clinically relevant?
- How to assess muscle strength



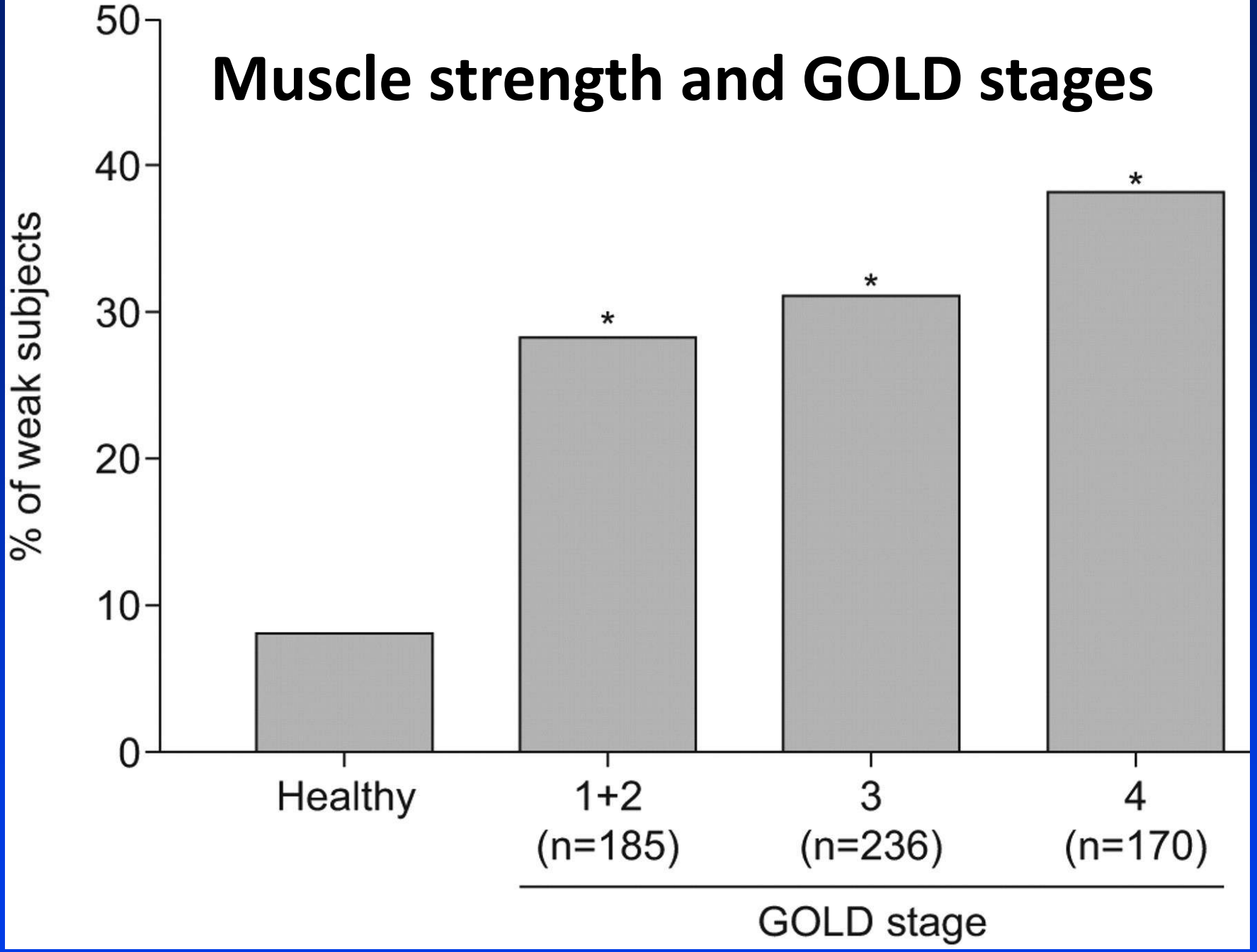
MUSCLE STRENGTH IN COPD



INSPIRATORY MUSCLE STRENGTH IN COPD

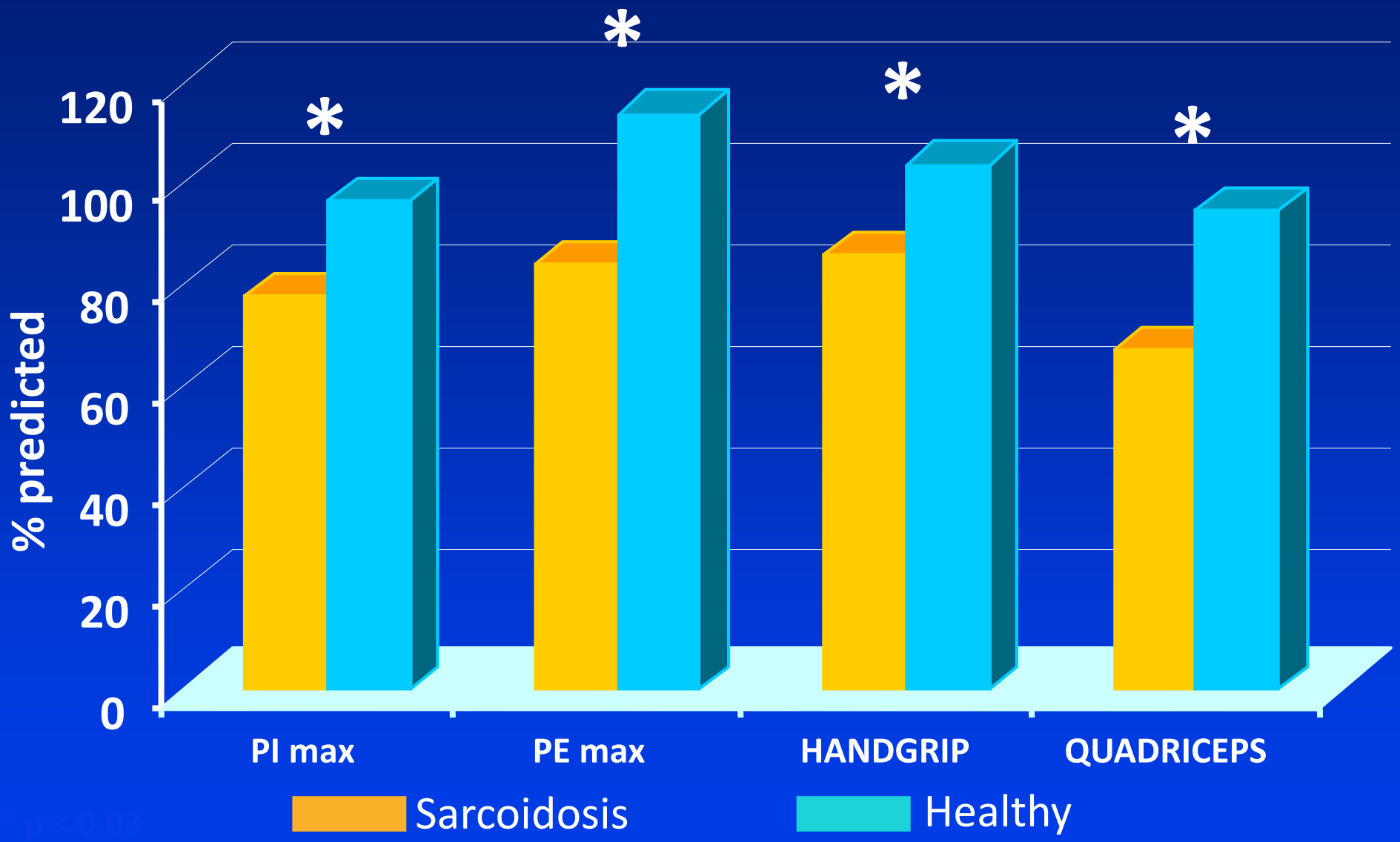


Muscle strength and GOLD stages

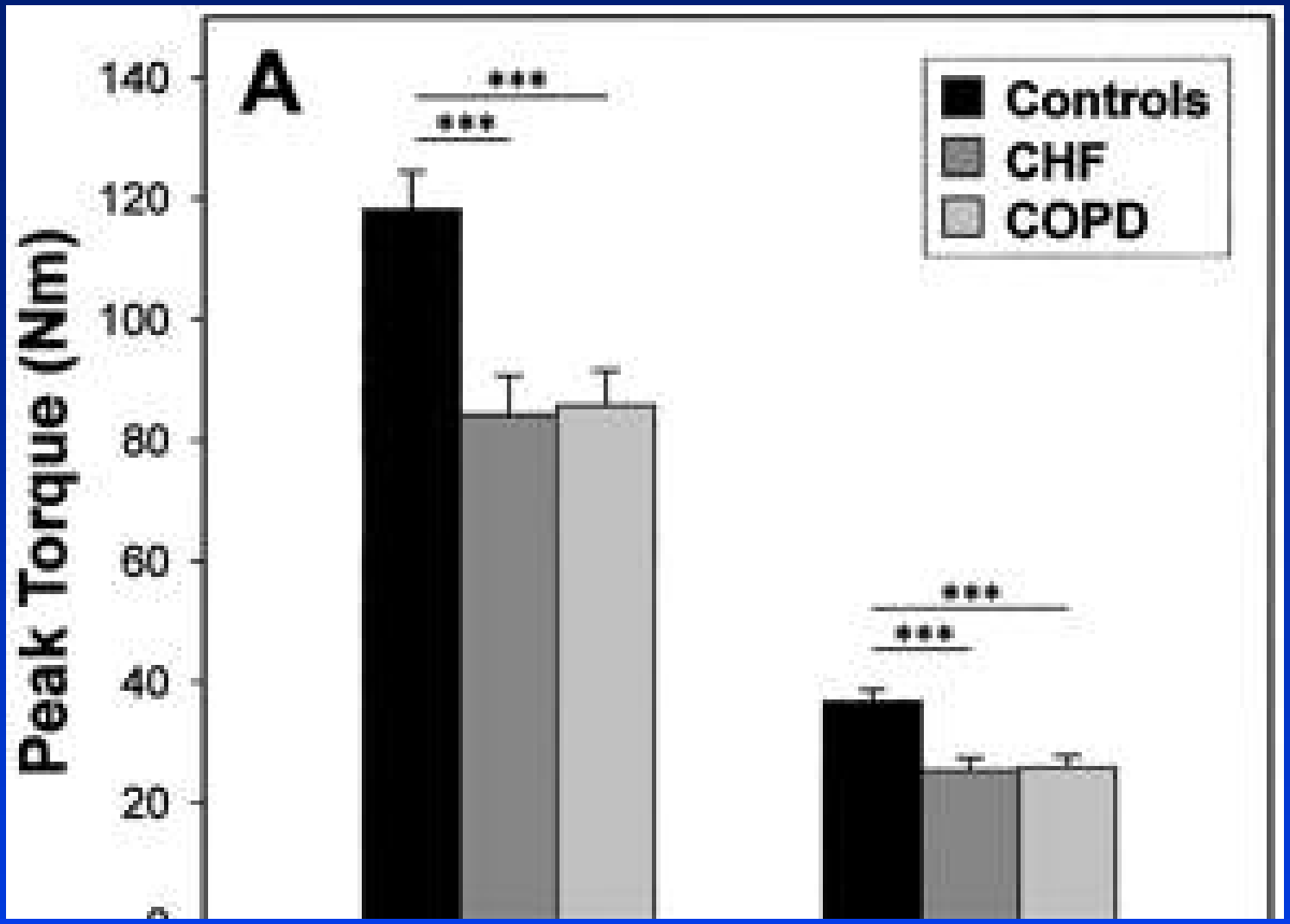


Seymour et al. ERJ 2010; 36:81-88

MUSCLE STRENGTH IN SARCOIDOSIS

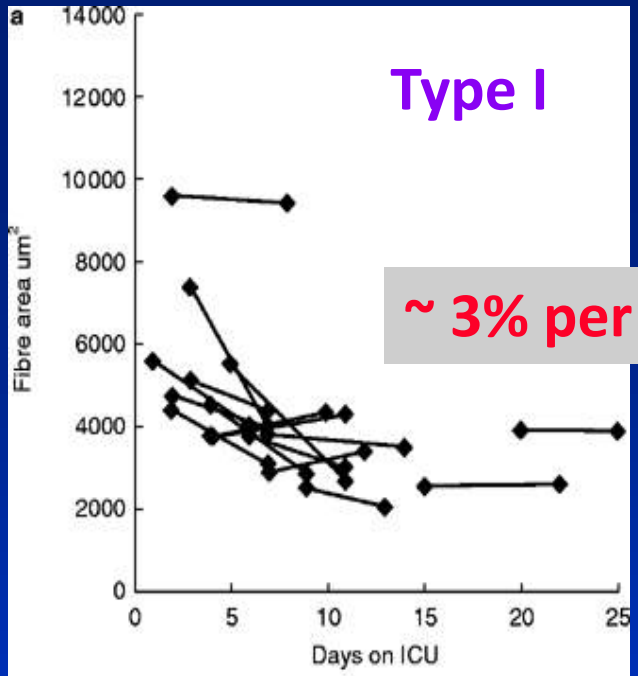


Spruit et al. Thorax 2005; 60:32

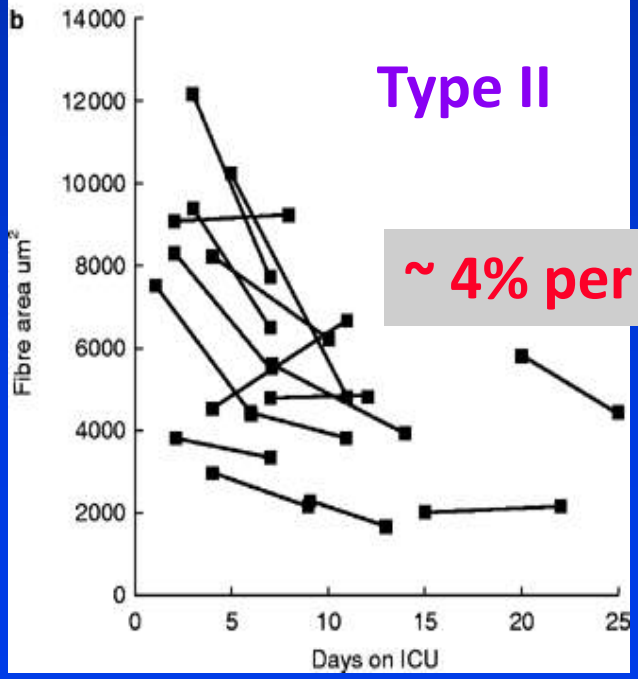


Gosker et al. Chest 2003;123:1416

Muscle weakness in critically ill patients



~ 3% per day



~ 4% per day

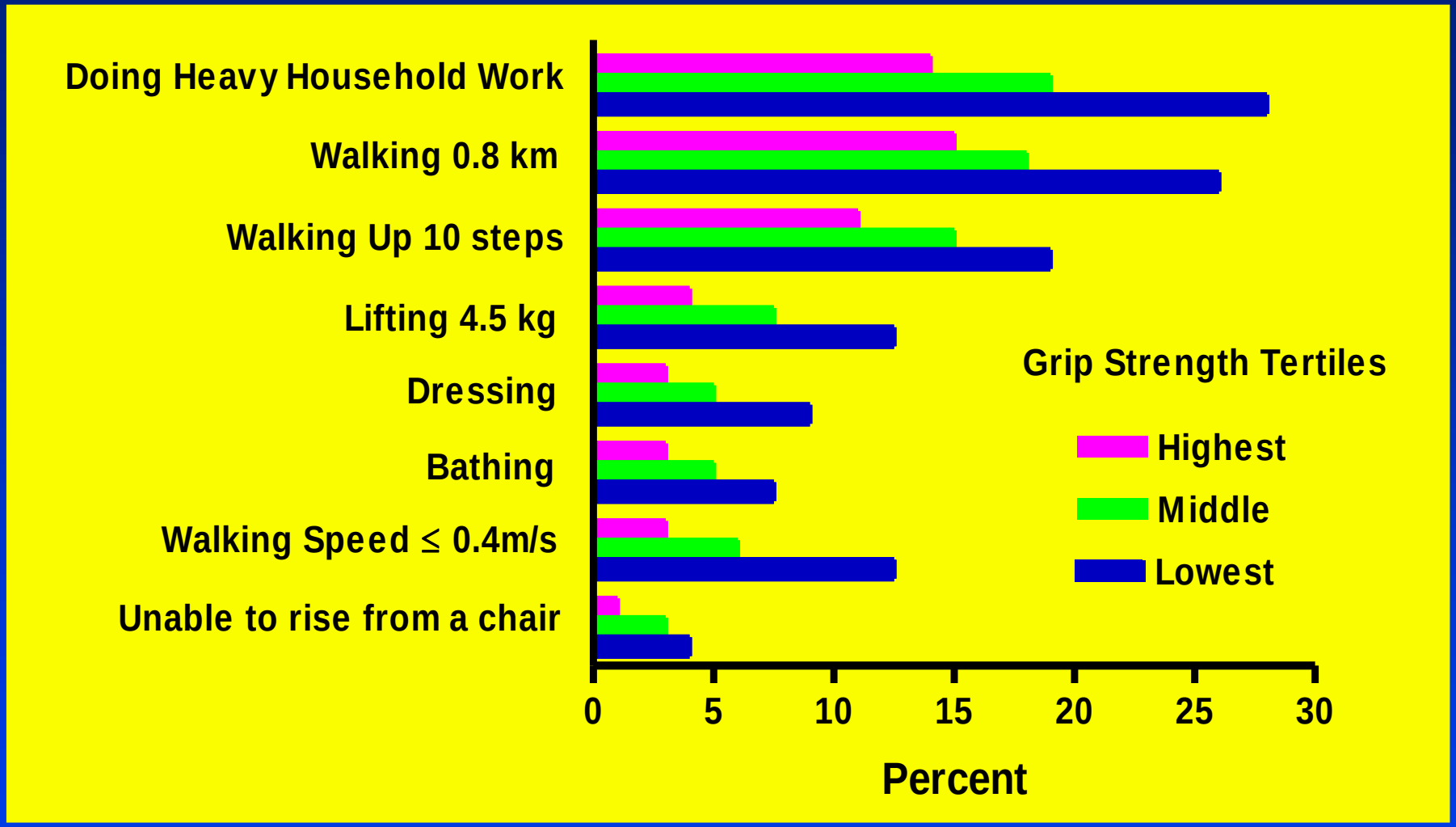
Helliwell et al. Neuropathology and Appl Neurobiol. 24, 507-517, 1998.

CAUSES OF MUSCLE WEAKNESS

- HYPERINFLATION
- HYPOXAEMIA
- HYPERCAPNIA
- DETRAINING - INACTIVITY
- MALNUTRITION
- DRUGS (STEROIDS, ANTIBIOTICS)
- INFLAMMATION - CYTOKINES
- CARDIAC FAILURE
- ELECTROLYTES DISTURBANCES

Is muscle weakness clinically relevant ?

FUNCTIONAL *LIMITATIONS* 25 YEARS AFTER ASSESSING HANDGRIP STRENGTH

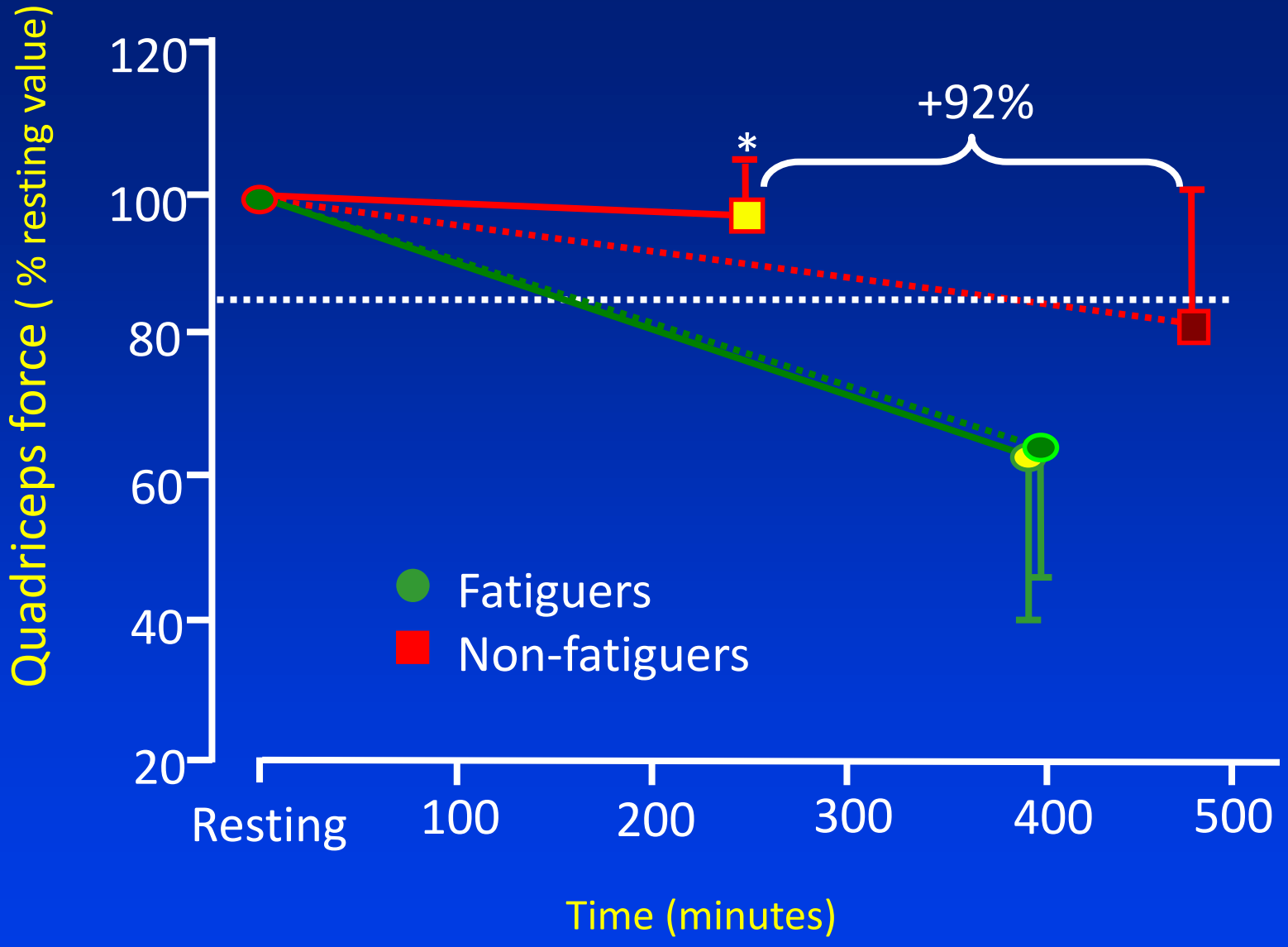


Ratanen et al. JAMA 281: 558-560, 1999.

Factors related to exercise limitation in COPD

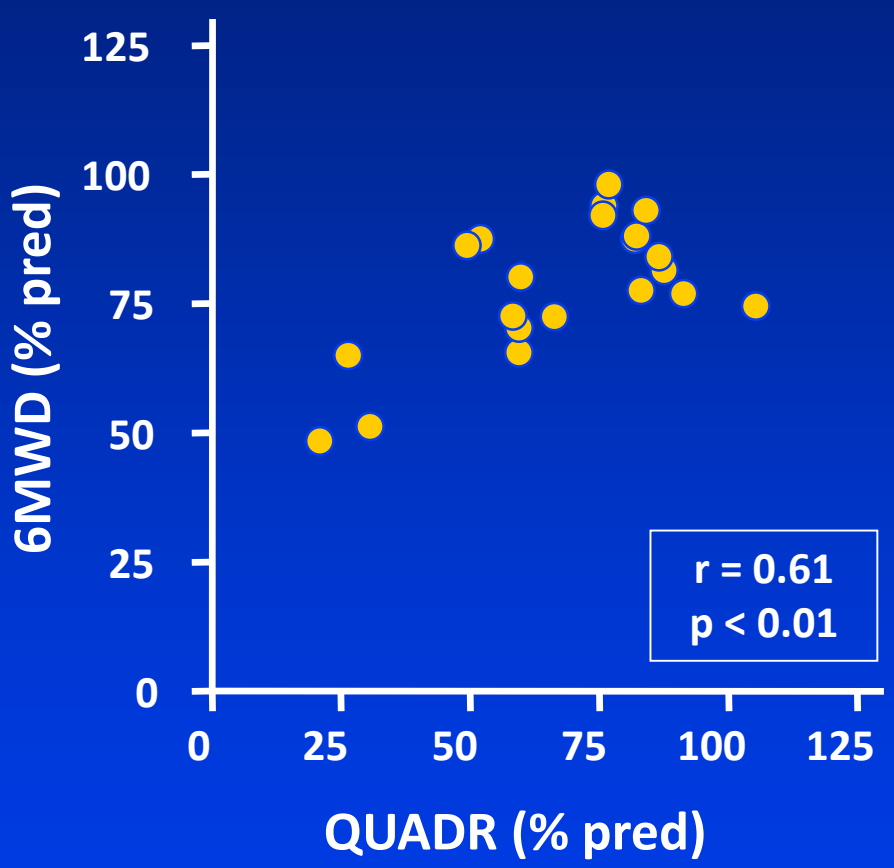
	$\dot{V}O_2max$	6MWD
$T_{L,CO}$	0.73*	NS
FEV_1	0.32	NS
QF	0.40*	0.64*
PImax	NS	0.24*

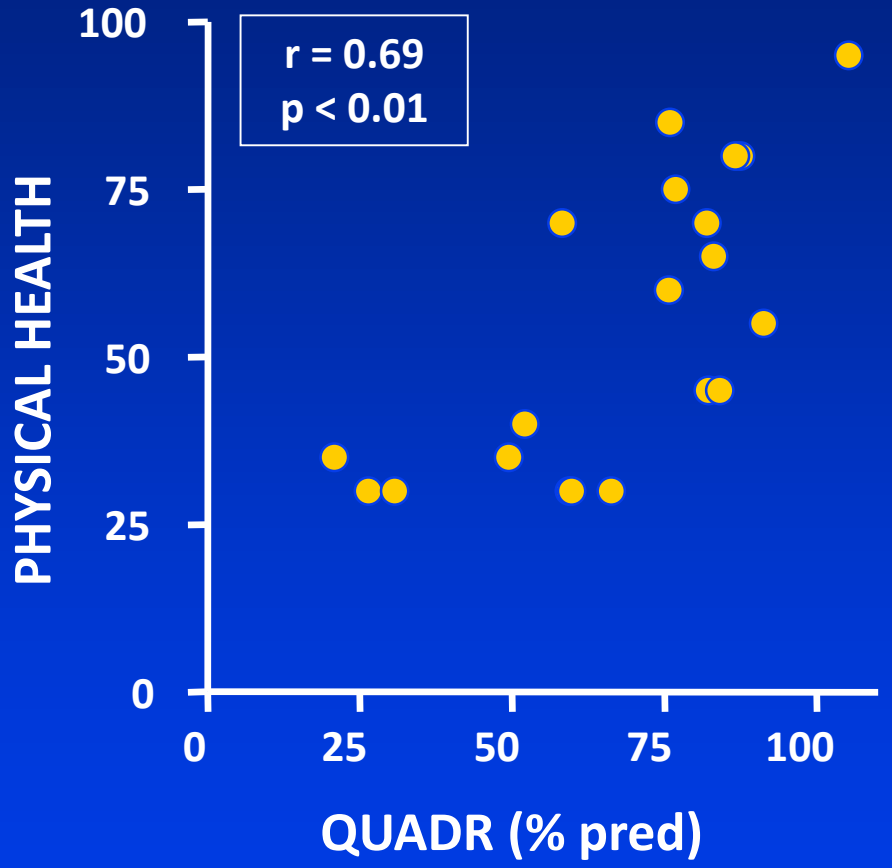
Gosselink et al Am J Respir Crit Care Med 153:976-980; 1996



Saey AJRCCM 2003

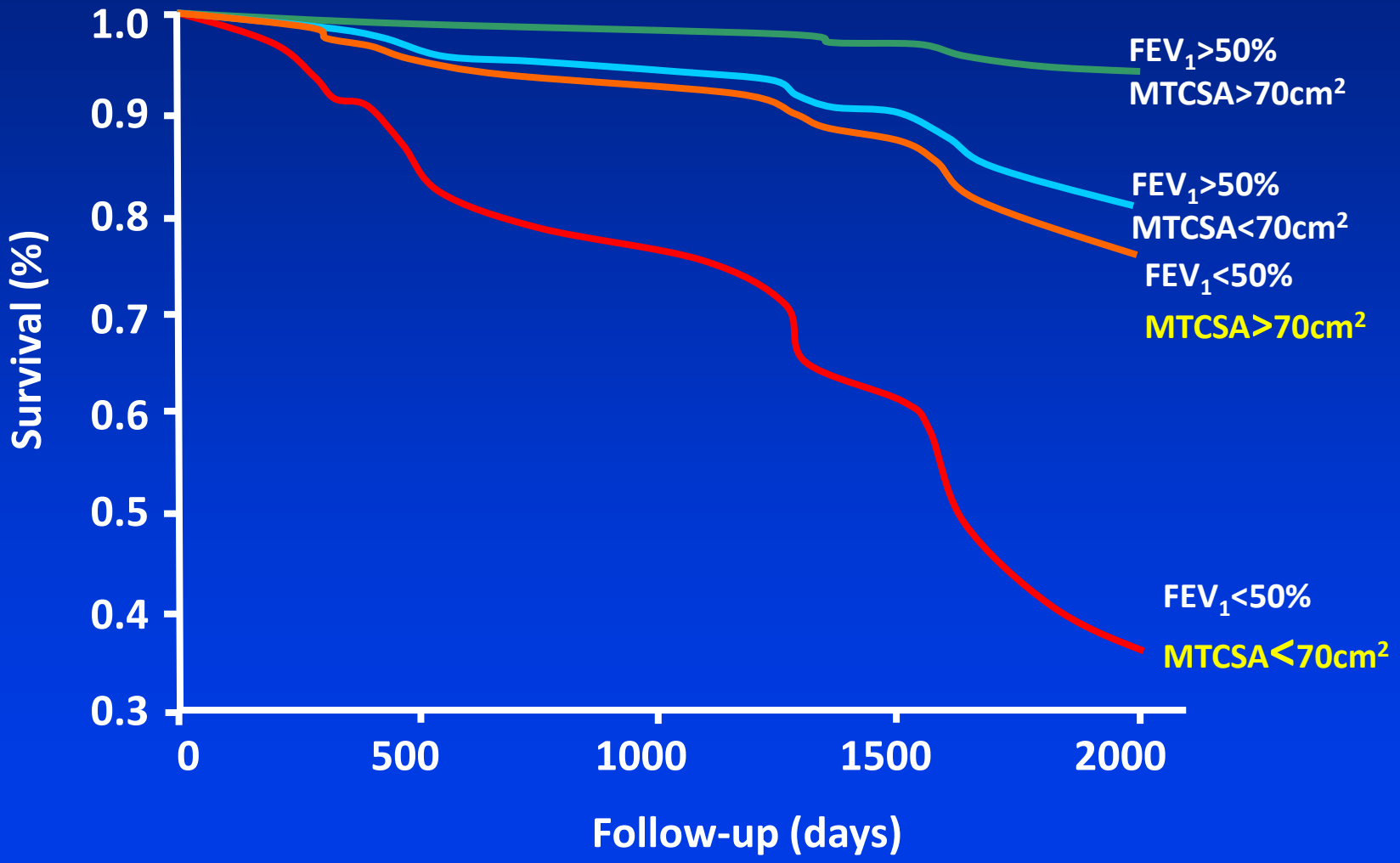
MUSCLE STRENGTH IN SARCOIDOSIS





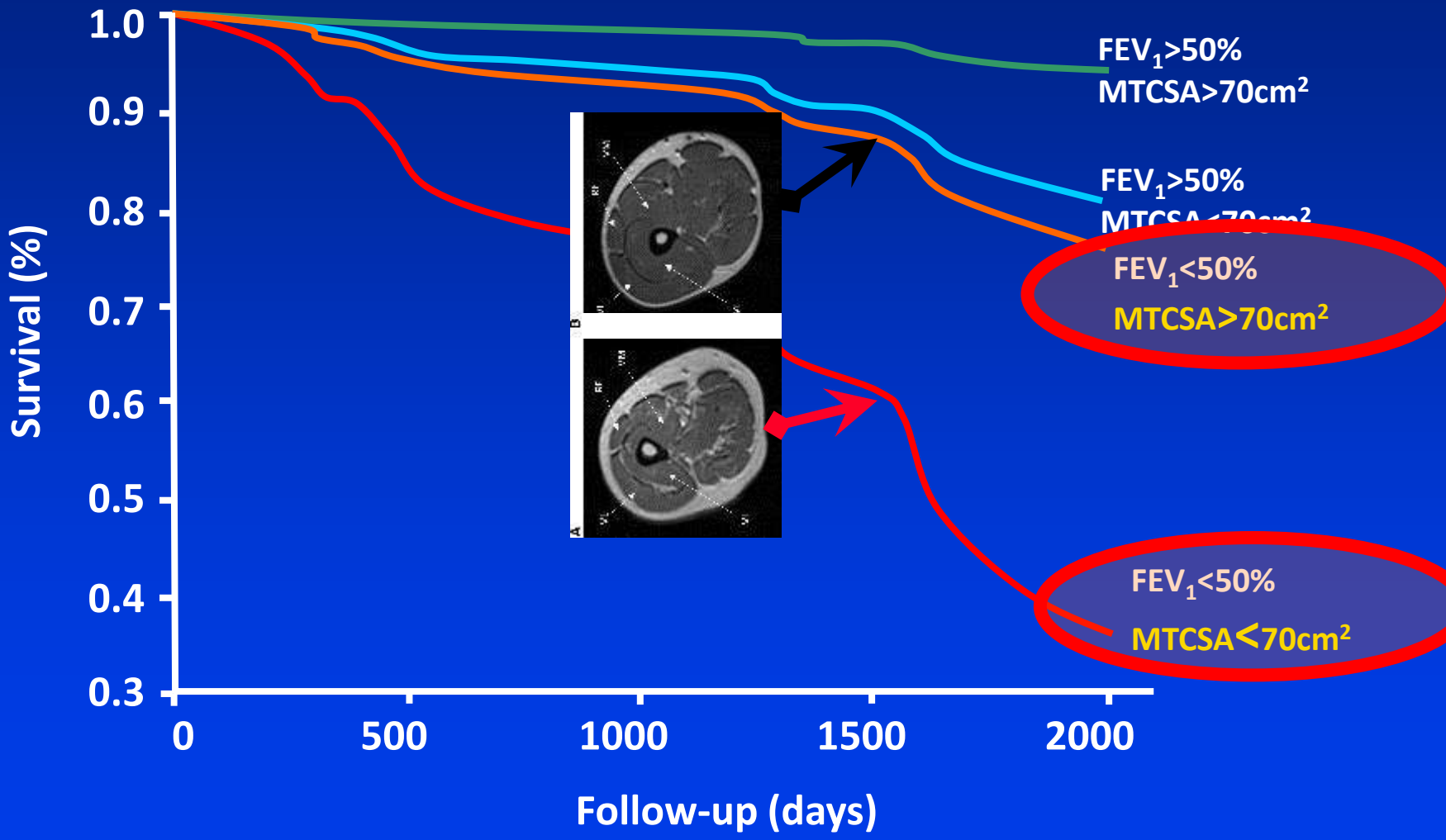
Spruit et al Thorax 2005; 60:32

Predictors of mortality



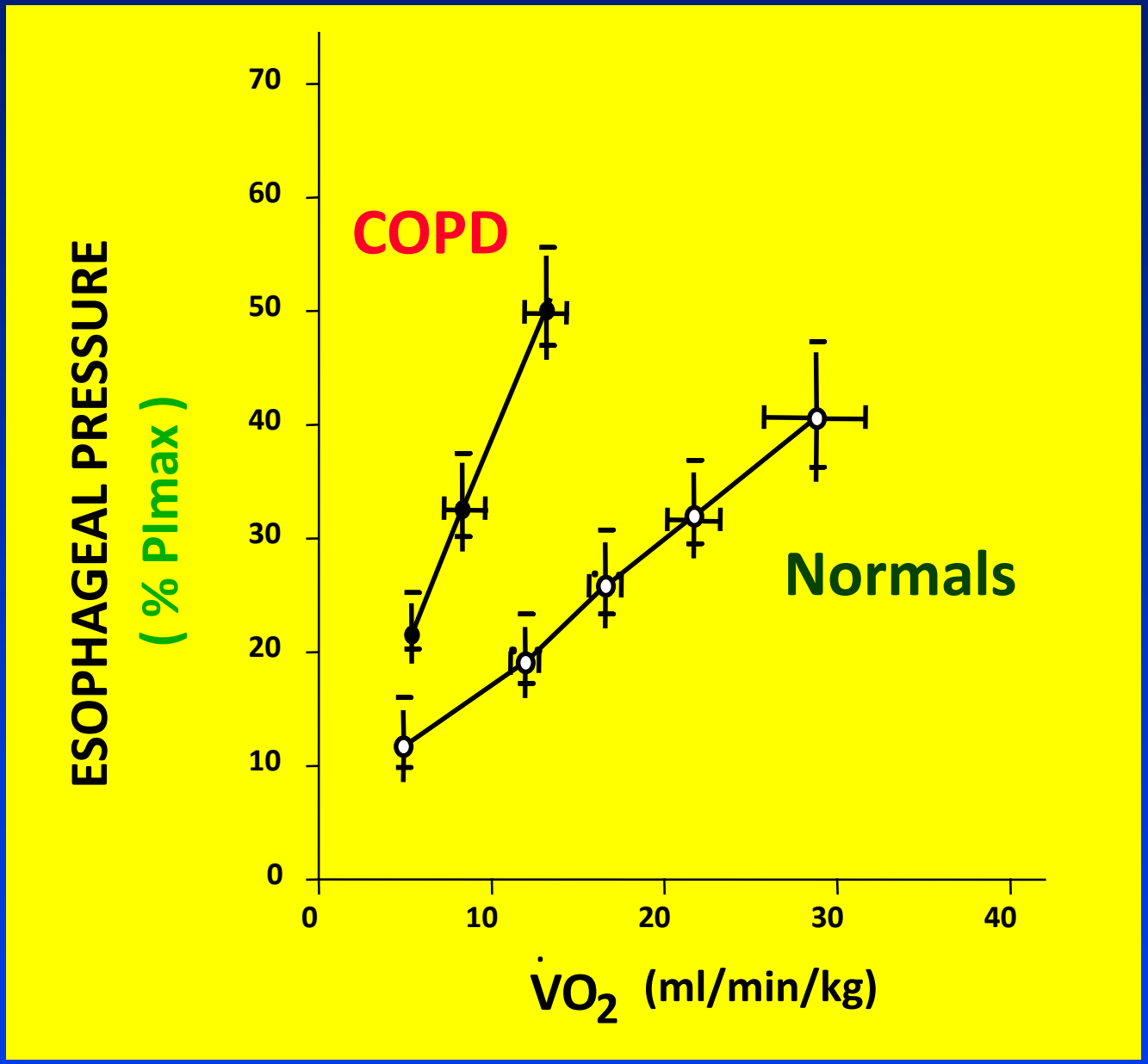
Marquis, AJRCCM 2002

Predictors of mortality



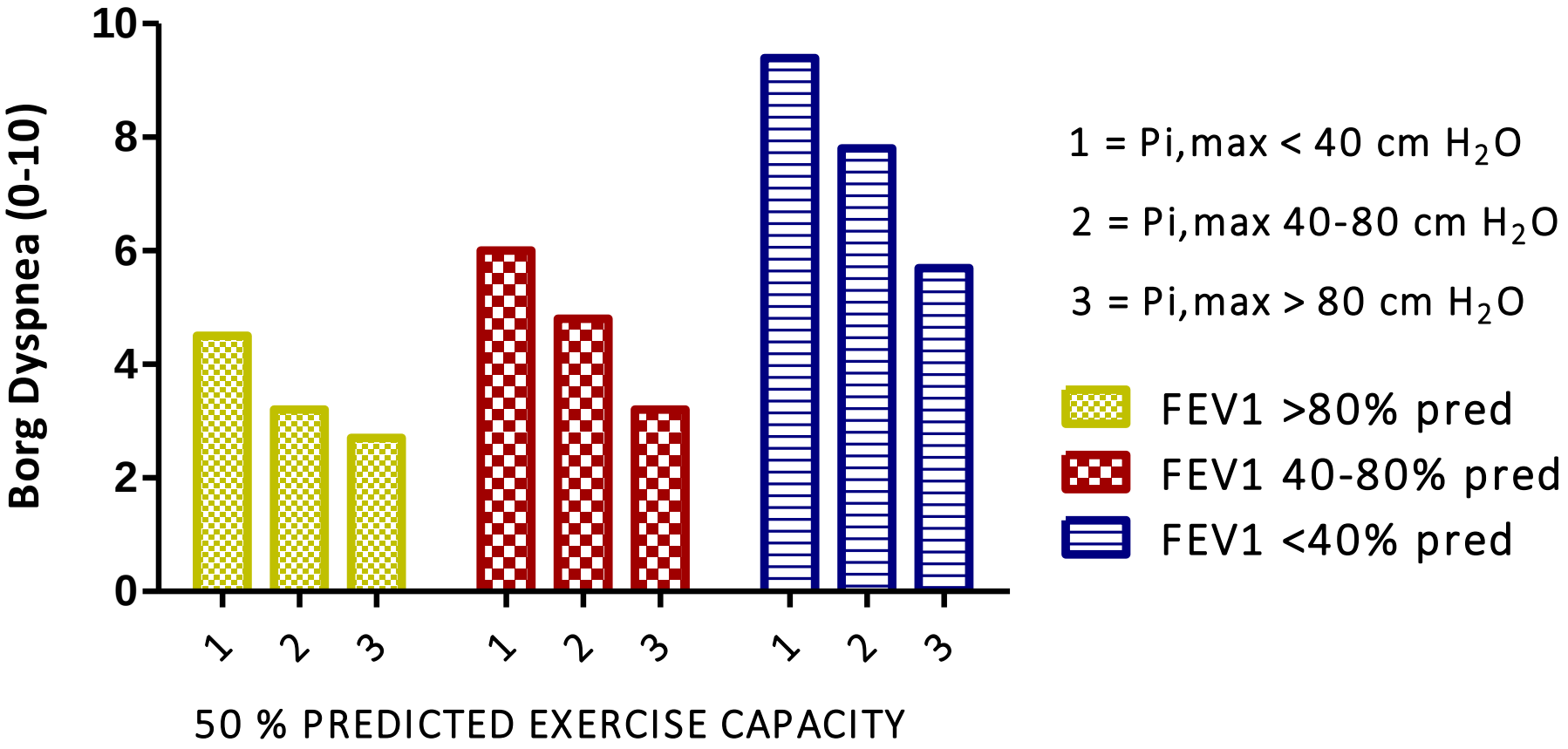
Marquis, AJRCCM 2002

Respiratory effort



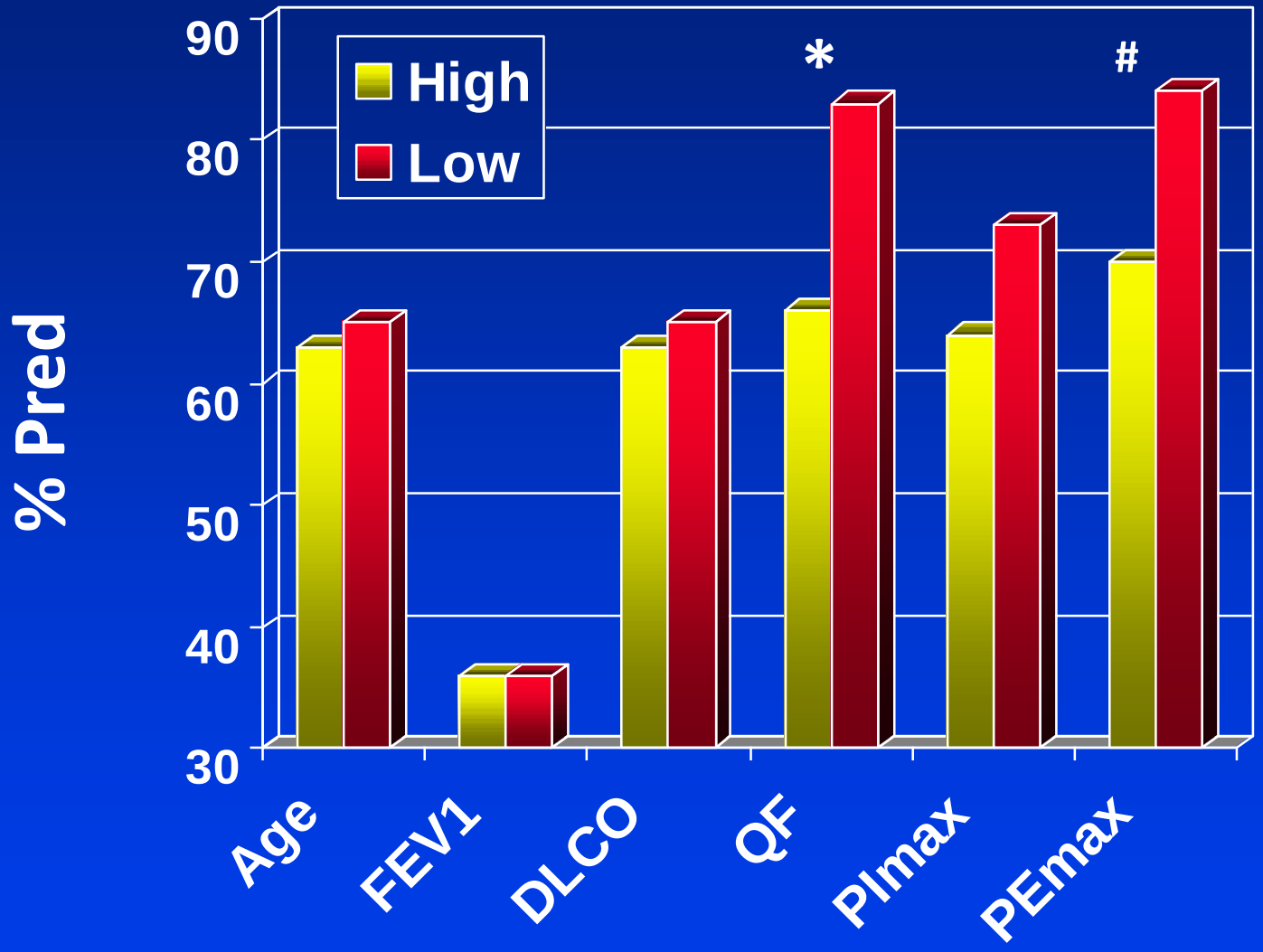
O'Donnell et al. Am J Respir Crit Care Med, 155: 109-115, 1997.

Dyspnea and Pimax



Killian KJ and Jones NL. Respiratory Muscles and Dyspnea. *Clinics in Chest Medicine.* 1988;9(2):237-47.

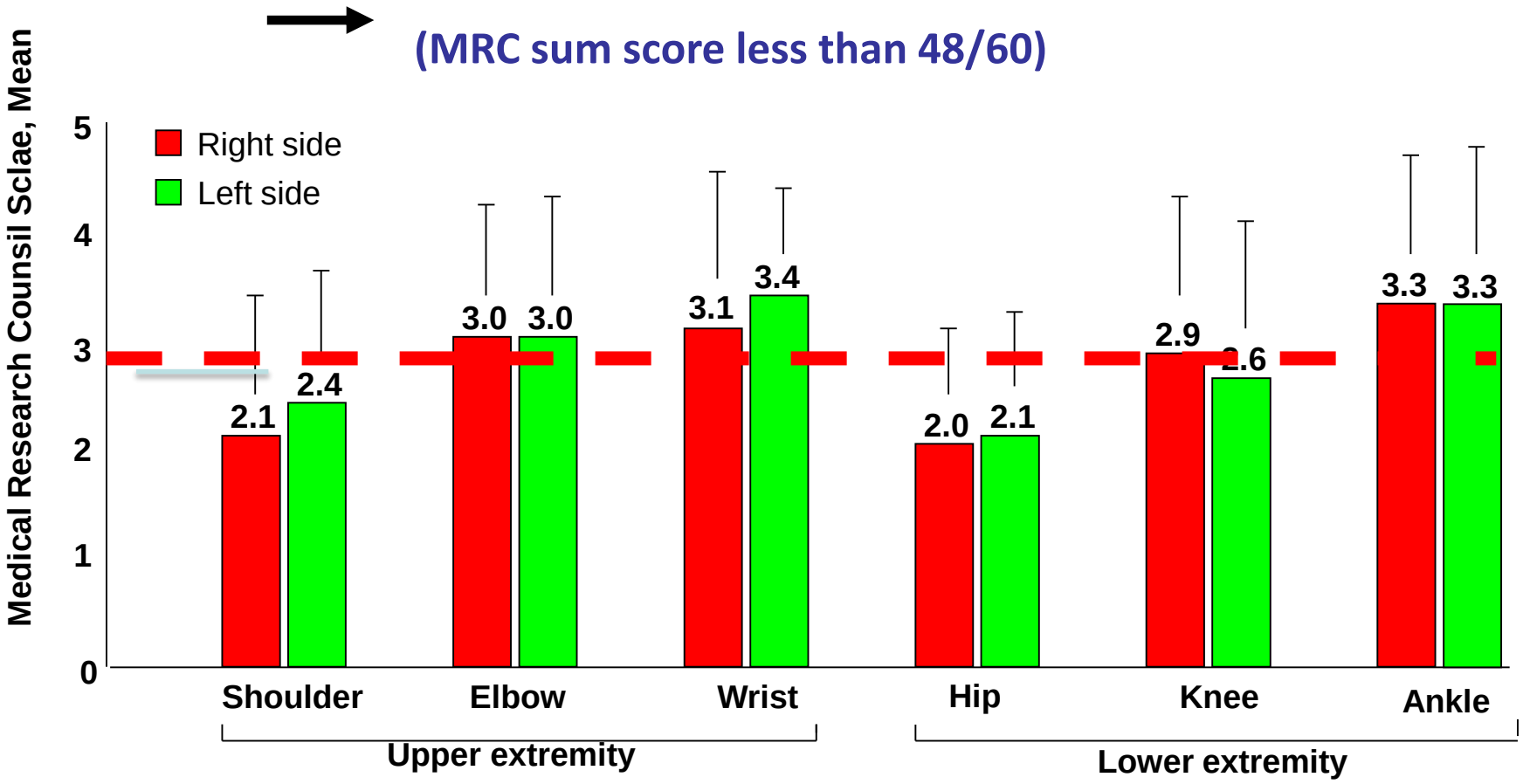
Utilisation Health Care Resources



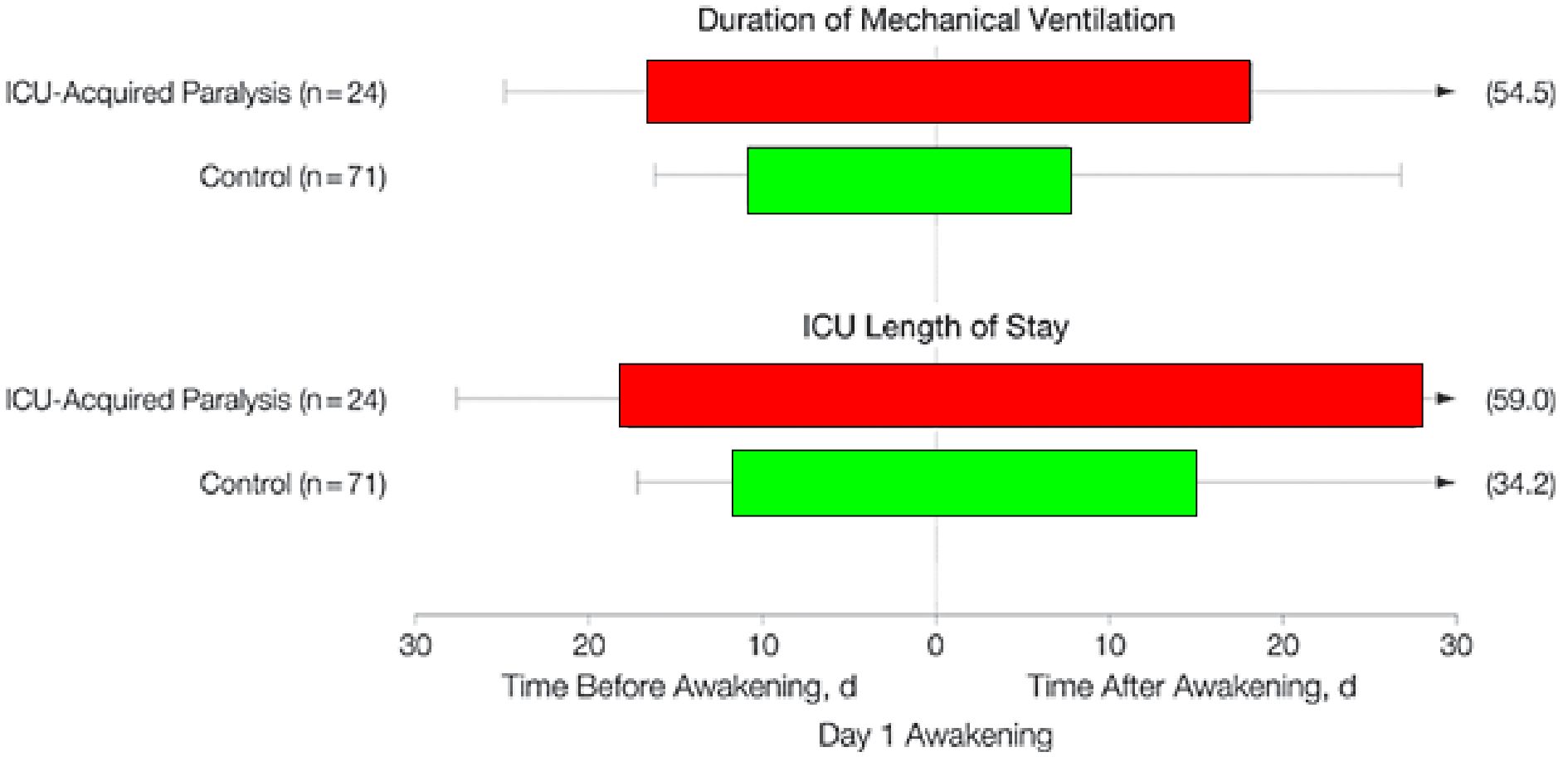
Decramer et al ERJ, 1997, 10, 417-423

95 surgical and medical **ICU patients**, mechanically ventilated for more than 7 days

25 % had significant **muscle weakness** at day 7 after awakening

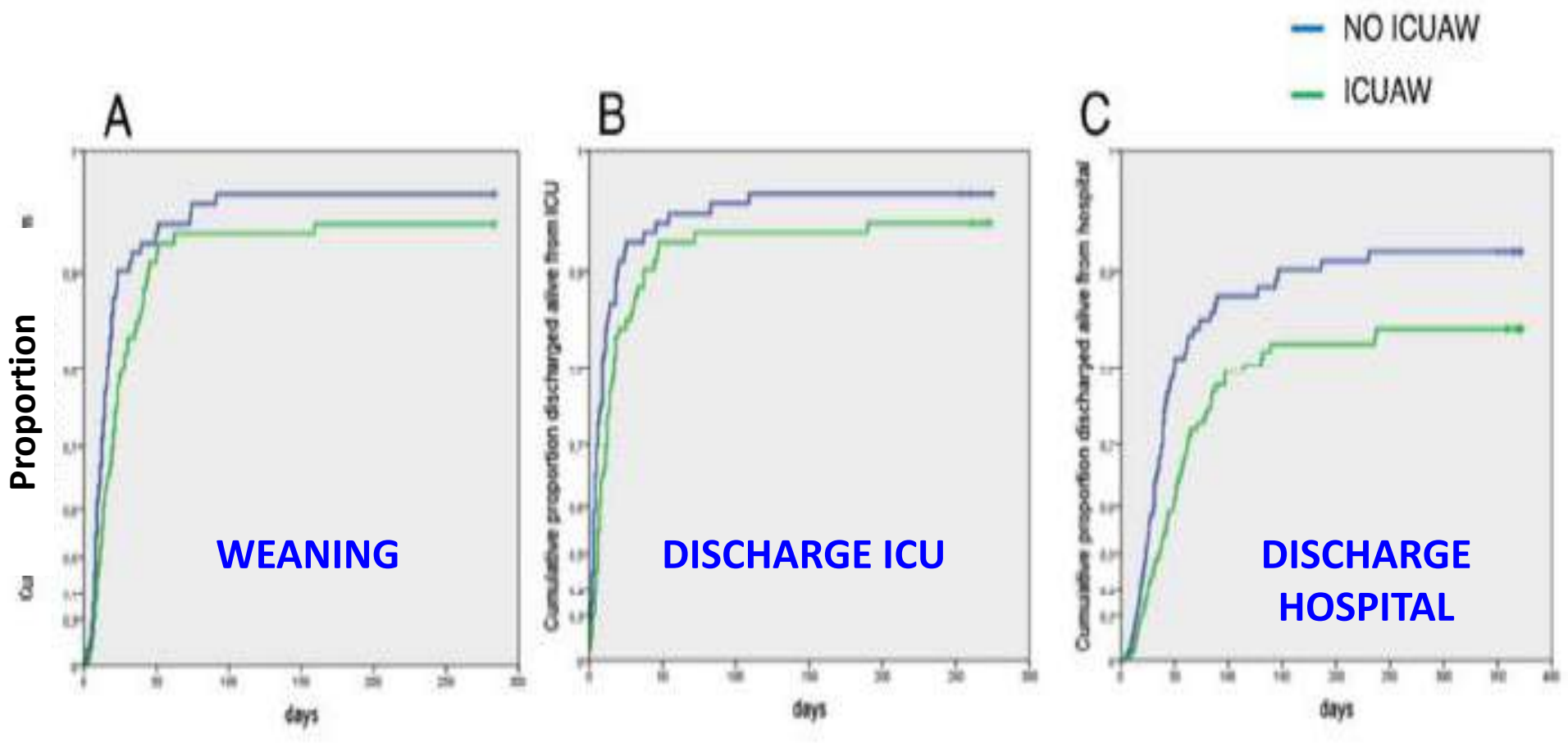


De Jonghe B, JAMA 2002



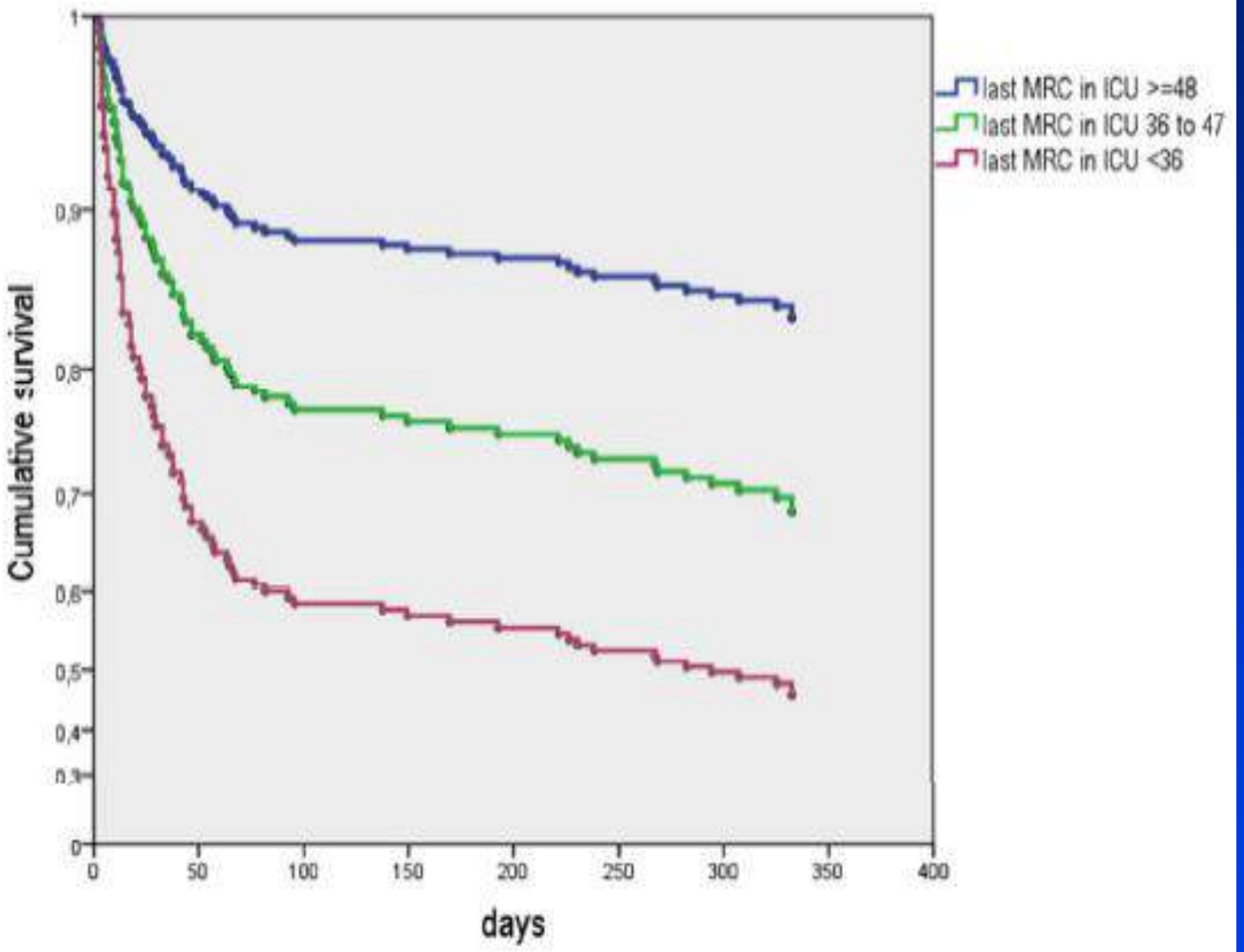
De Jonghe B, JAMA 2002

MUSCLE WEAKNESS AFFECTS CLINICAL OUTCOME IN CRITICALLY ILL



Hermans et al. AJRCCM 2014

MUSCLE WEAKNESS AND SURVIVAL



Hermans et al. AJRCCM 2014; in press

An Official American Thoracic Society and European Respiratory Society Statement; Update on Limb Muscle Dysfunction in COPD: 2013 Update

François Maltais, Marc Decramer, Esther Barreiro, Yan Burelle, Richard Casaburi, Richard Debigaré, PN Richard Dekhuijzen, Frits Franssen, Ghislaine Gayan-Ramirez, Joaquim Gea, Harry Gosker, Rik Gosselink, Maurice Hayot, Sabah NA Hussain, Wim Janssens, Michael I Polkey, Josep Roca, Didier Saey, Annemie M. W. Schols, Martijn A. Spruit, Michael Steiner, Tanja Taivassalo, Thierry Troosters, Ioannis Vogiatzis, Peter D. Wagner

Major conclusions of the statement include :

- Limb muscle dysfunction is prevalent in COPD. Muscle atrophy and weakness carry important consequences such as diffiiculties in engaging in physical activity, exercise intolerance, poor quality of life and premature mortality. Metabolic alterations in relation to lower limb muscle structural changes within the lower limb muscle are also involved in exercise limitation.

- Limb muscle strength should be assessed routinely in patients with COPD.

Maltais et al. AJRCCM 2014 (in press)

An Official American Thoracic Society Clinical Practice Guideline: The Diagnosis of Intensive Care Unit–acquired Weakness in Adults

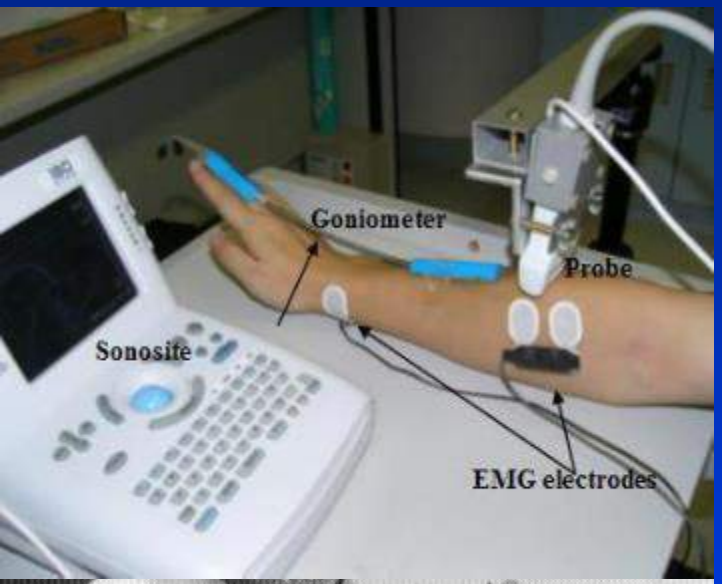
Eddy Fan, Fern Cheek, Linda Chlan, Rik Gosselink, Nicholas Hart, Margaret S. Herridge, Ramona O. Hopkins, Catherine L. Hough, John P. Kress, Nicola Latronico, Marc Moss, Dale M. Needham, Mark M. Rich, Robert D. Stevens, Kevin C. Wilson, Chris Winkelman, Doug W. Zochodne, and Naeem A. Ali; on behalf of the ATS Committee on ICU-acquired Weakness in Adults

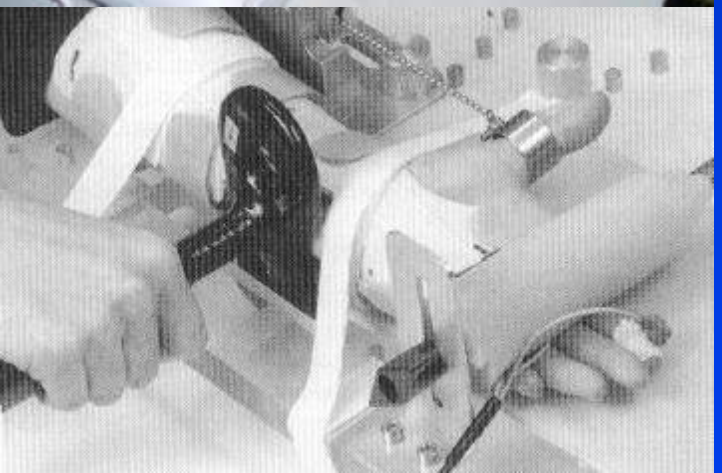
American Journal of Respiratory and Critical Care Medicine Volume 190 Number 12 | December 15 2014

their merits were discussed. The Medical Research Council (MRC) muscle strength score was used in the majority of studies reporting strength. As a result, in these guidelines, we consider the reference standard to be an average MRC muscle strength score of less than 4 across all muscles tested as determined by MMT (7).

How to assess limb muscle strength /endurance ?

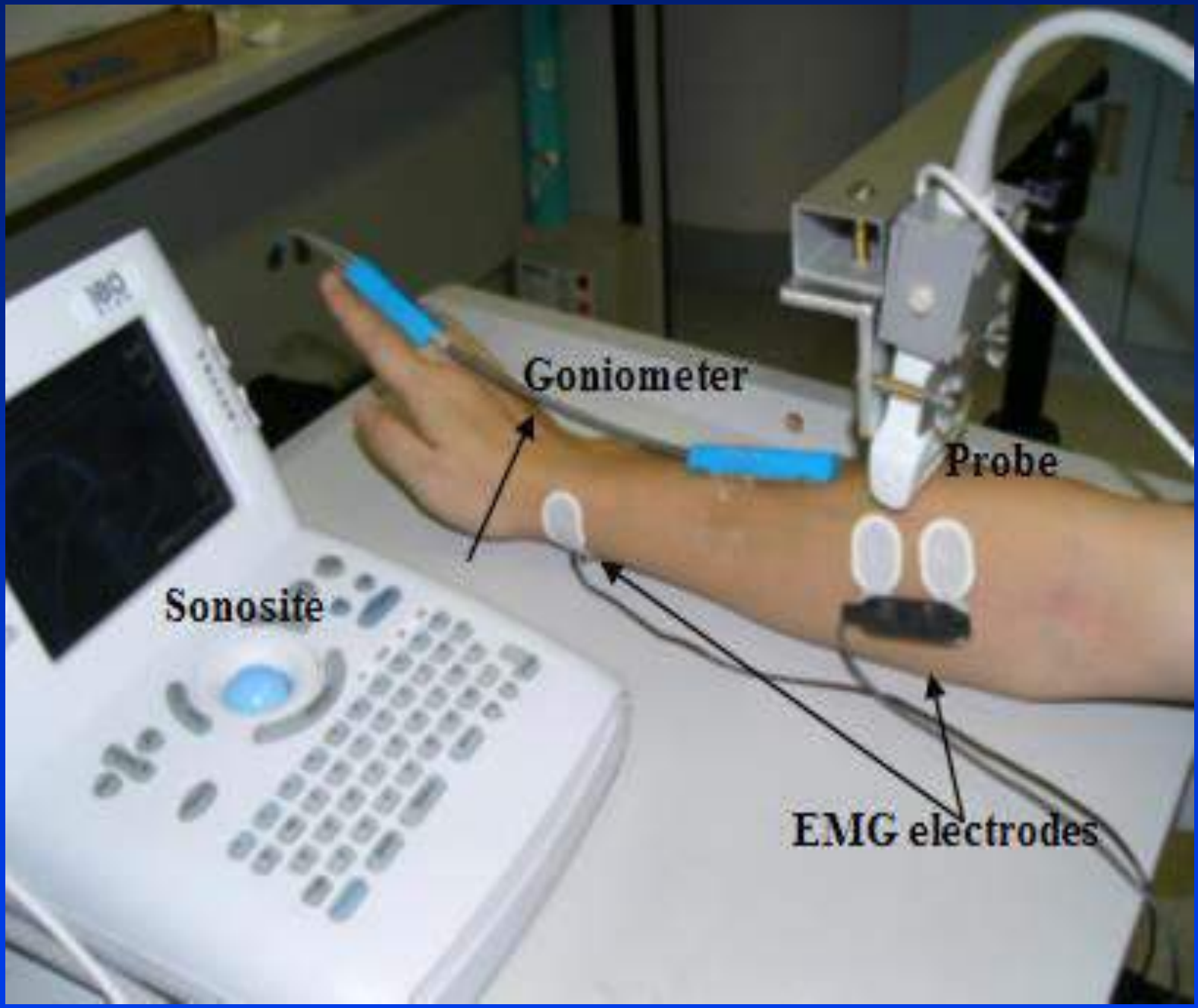
Clinical assessment of limb muscle strength

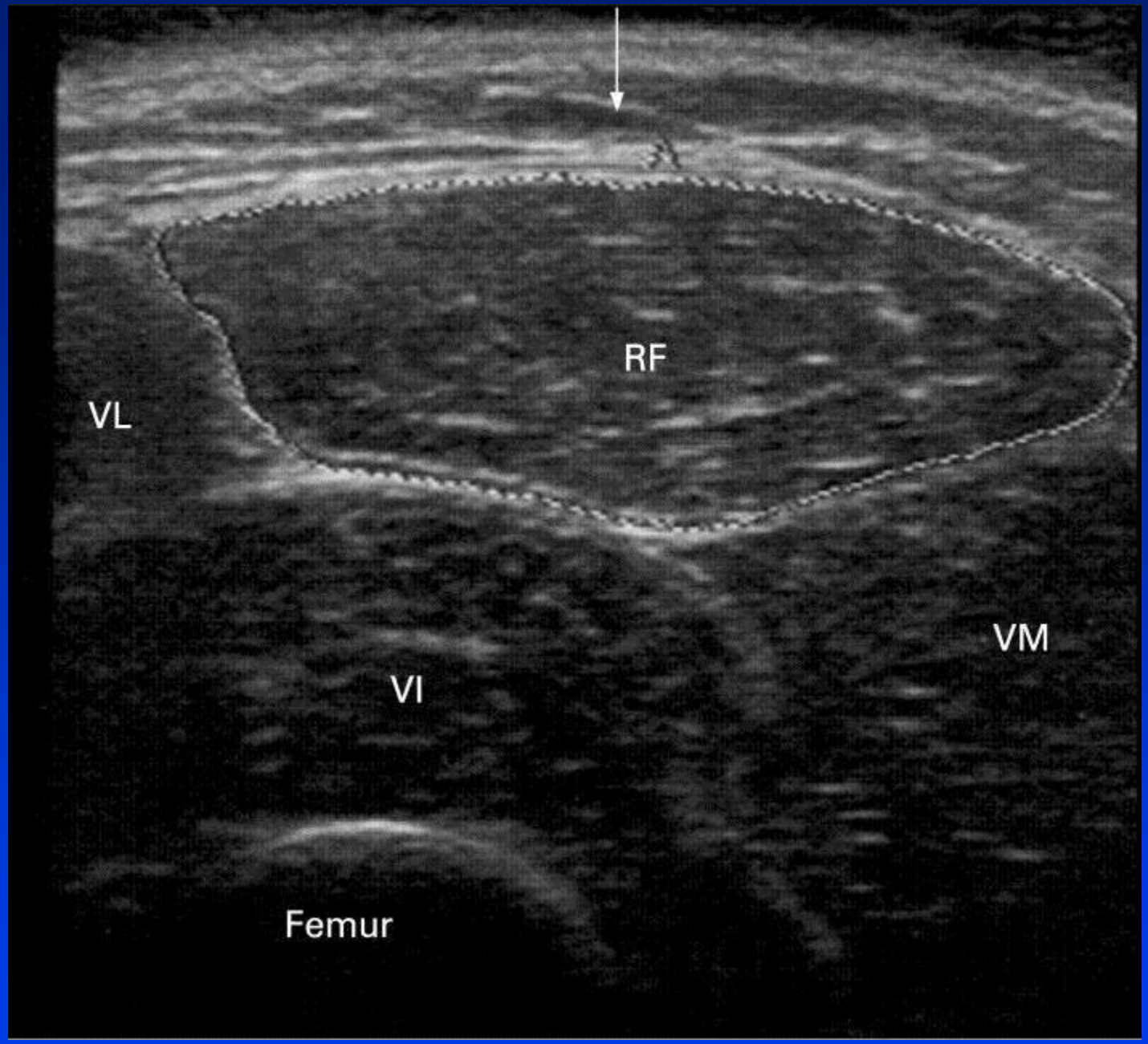




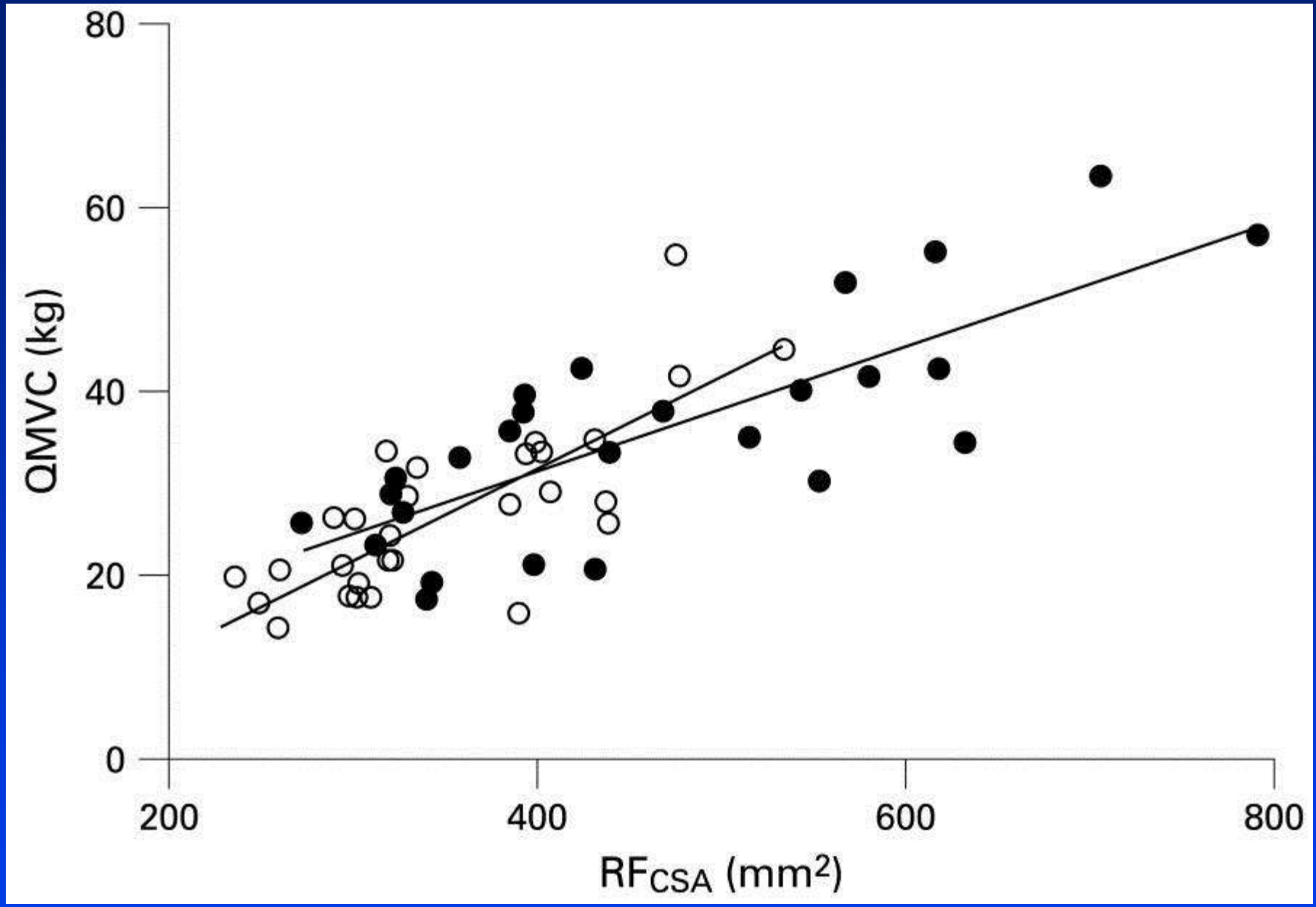
MUSCLE FUNCTION ASSESSMENT

- **VOLUNTARY MANEUVERS:**
  - **MANUAL MUSCLE TESTING: MRC 0-5**
  - **(HAND HELD) DYNAMOMETRY**
- ***INVOLUNTARY MANEUVERS***
  - ***MUSCLE TWITCH STIMULATION FORCE***
  - ***MUSCLE MASS (ULTRASOUND – CT/MRI)***


Goniometer
Probe
Sonosite
EMG electrodes

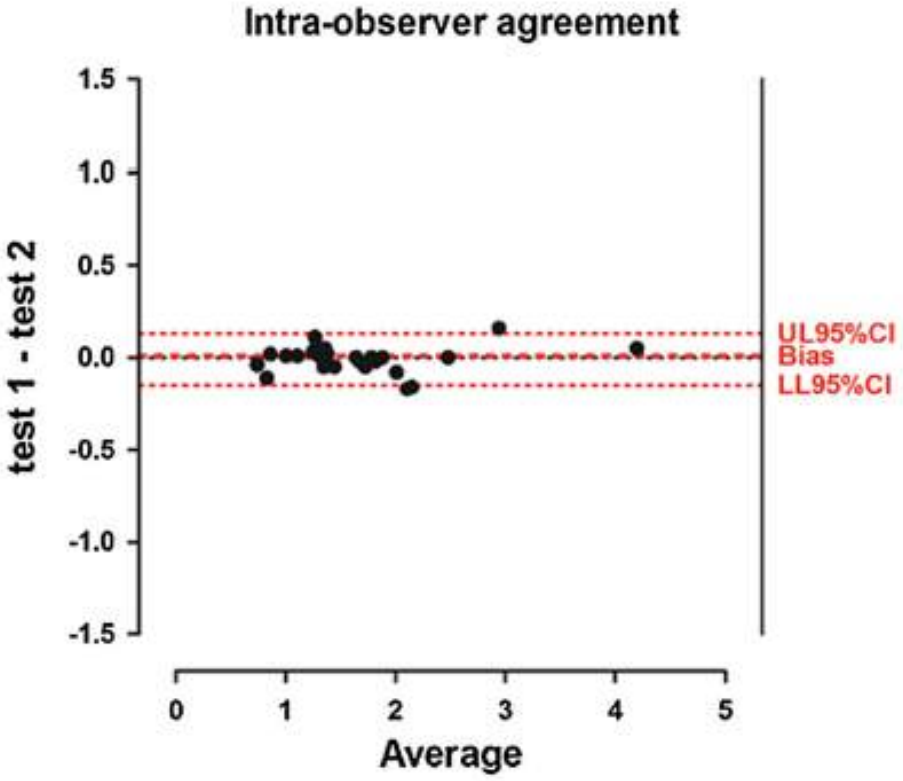


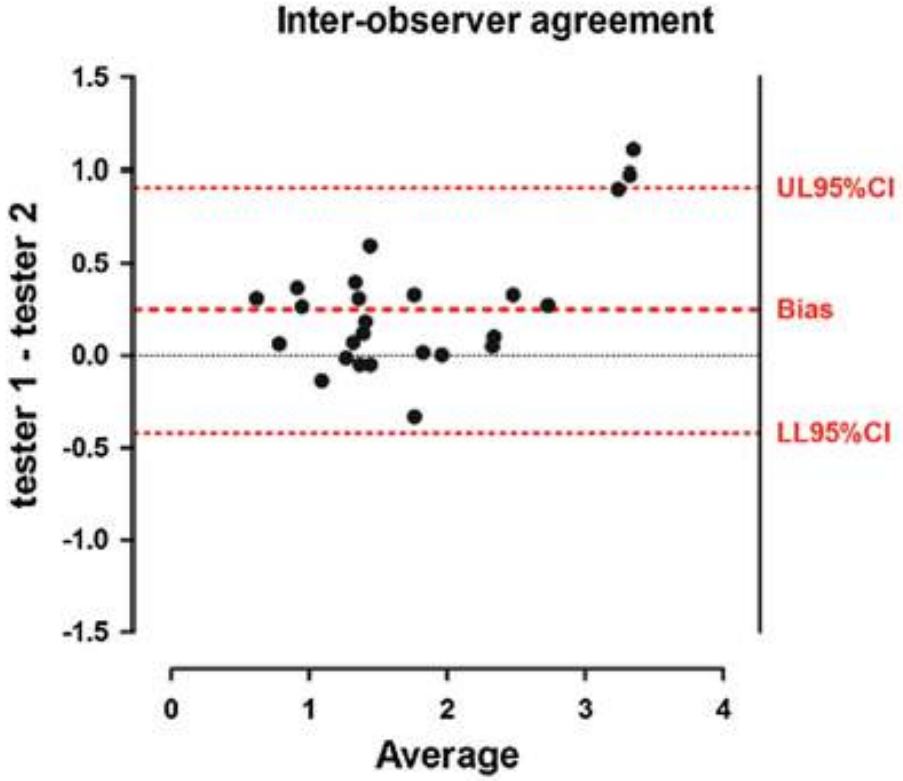
Seymour et al. Thorax 2009; 64: 418–23



Seymour et al. Thorax 2009; 64: 418-23

Thigh muscle thickness in ICU patients

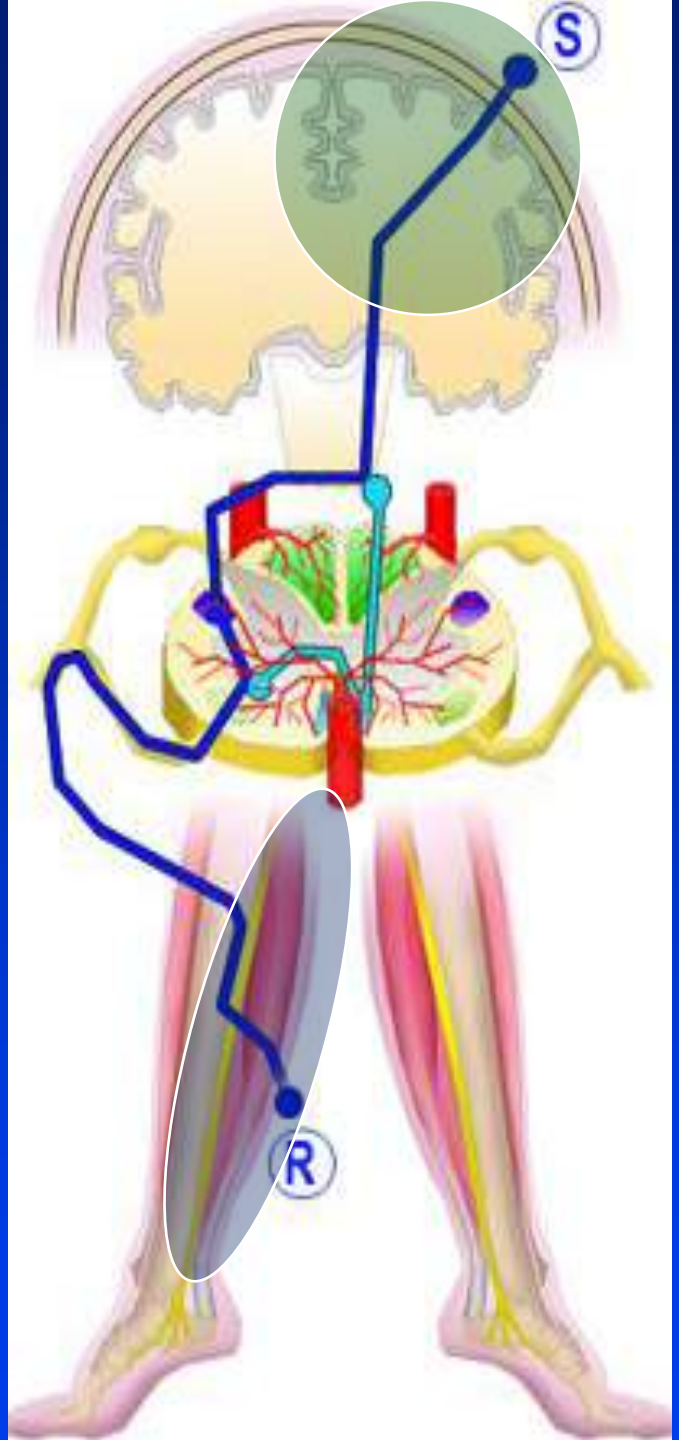




Segers et al. Int Care Med 2015

LIMB MUSCLE FUNCTION ASSESSMENT

- **VOLUNTARY MANEUVERS:**
  - ***MANUAL MUSCLE TESTING: MRC 0-5***
  - ***(HAND HELD) DYNAMOMETRY***
- **INVOLUNTARY MANEUVERS**
  - **MUSCLE TWITCH STIMULATION FORCE**
  - **MUSCLE MASS (ULTRASOUND – CT/MRI)**



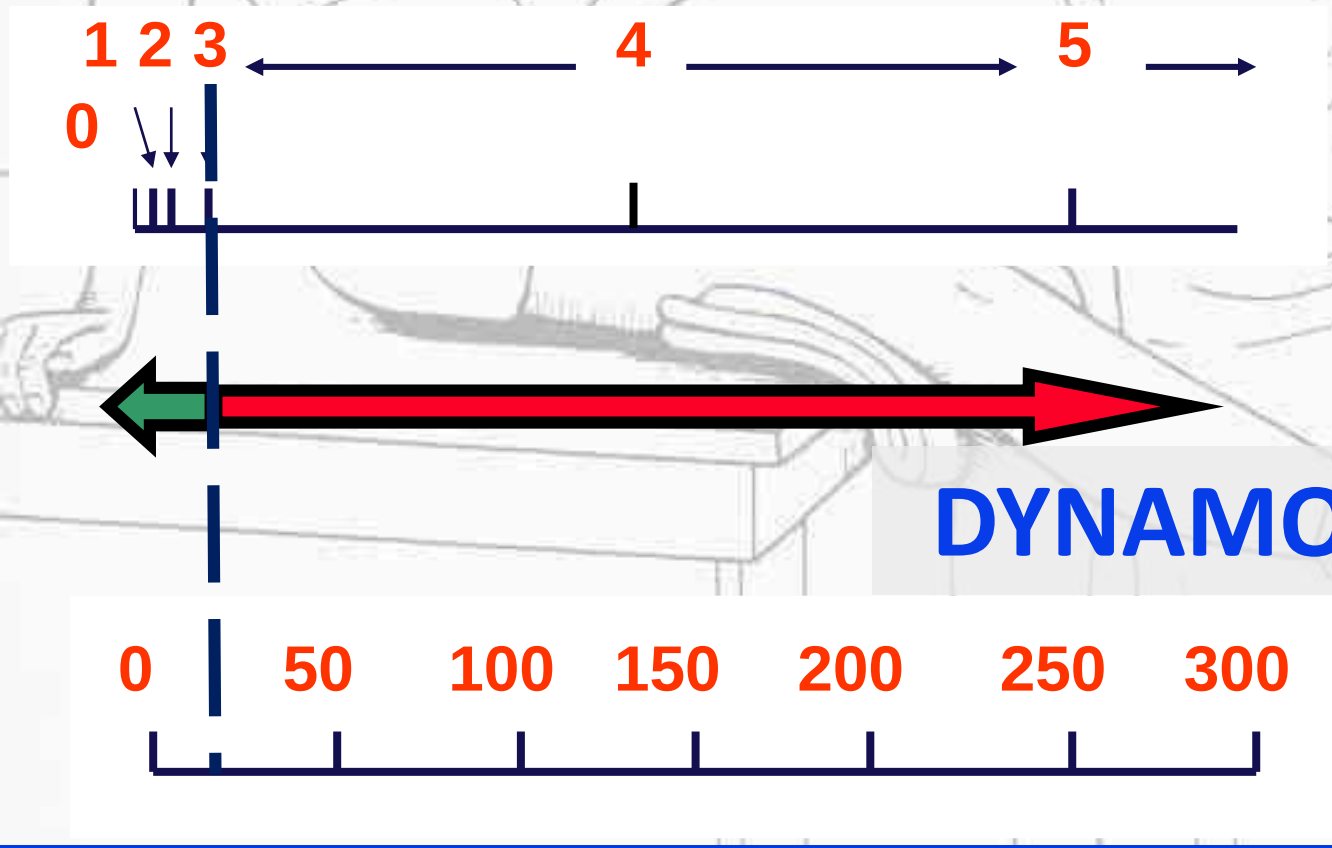
VOLUNTARY ACTIVATION:

FULL COOPERATION OF THE PATIENT IS REQUIRED!

Medical Research Council (MRC)

0 = no visible contraction
1 = flicker or trace of contraction
2 = active movement with gravity eliminated
3 = active movement against gravity
4 = active movement against gravity and resistance
5 = normal power

MUSCLE STRENGTH



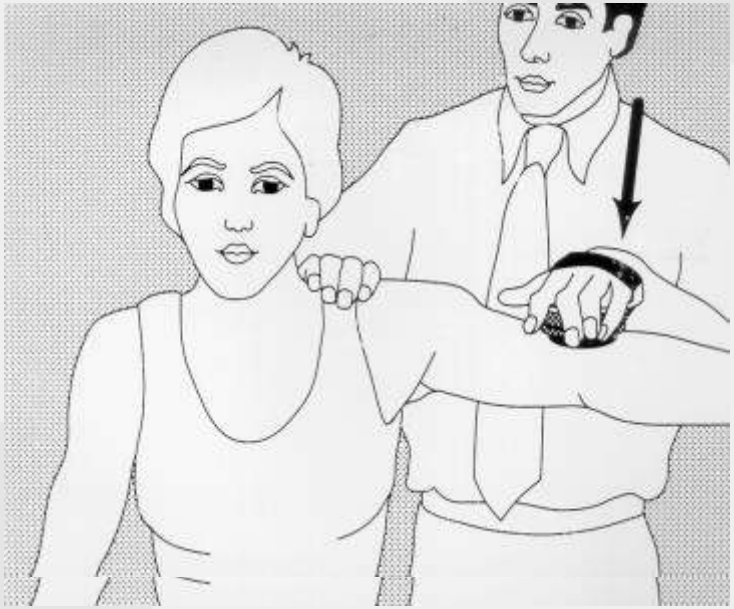
Objective muscle strength assessment

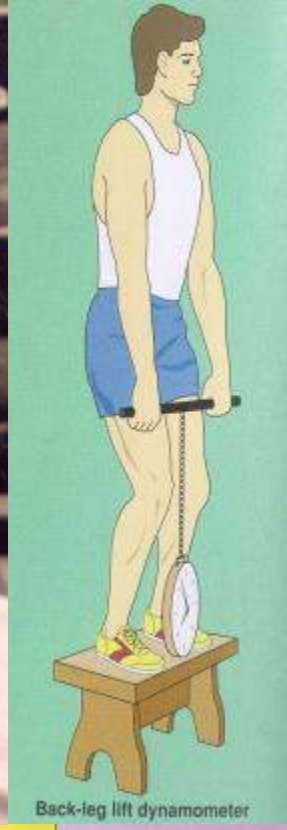
- 1-Repetition maximum load
- Dynamometry
  - Isometric muscle testing
  - Handgrip dynamometry

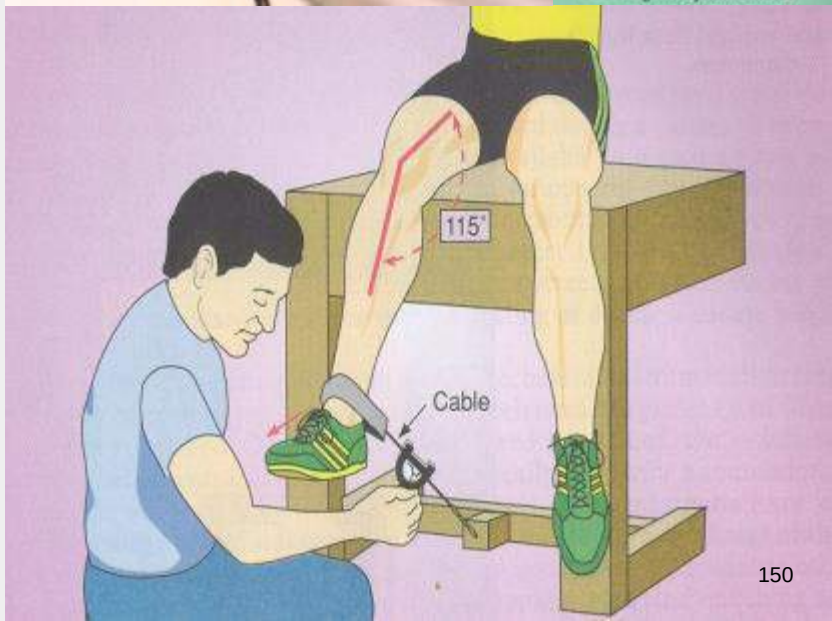
One repetition maximum load (1RM)

- Isotonic contraction
- 7-10 repetitions maximum
- No normative data
- Recommend for follow-up measurements and setting training intensity

Dynamometry

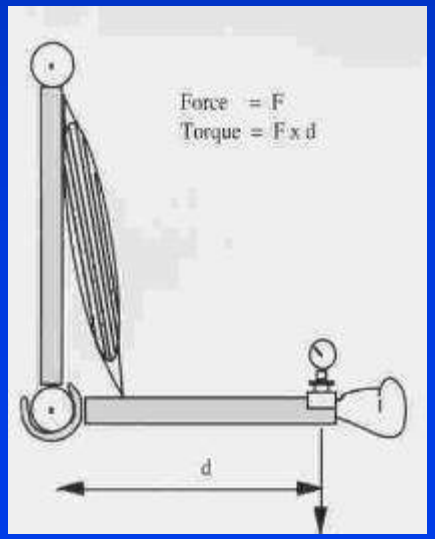


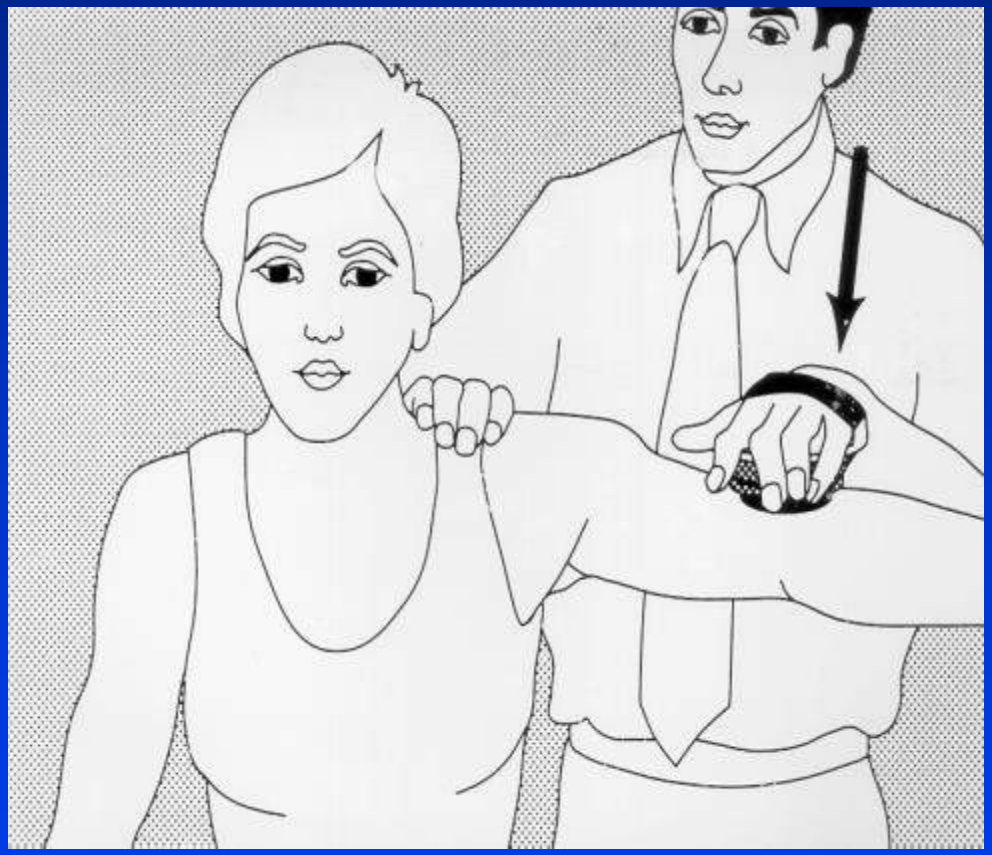


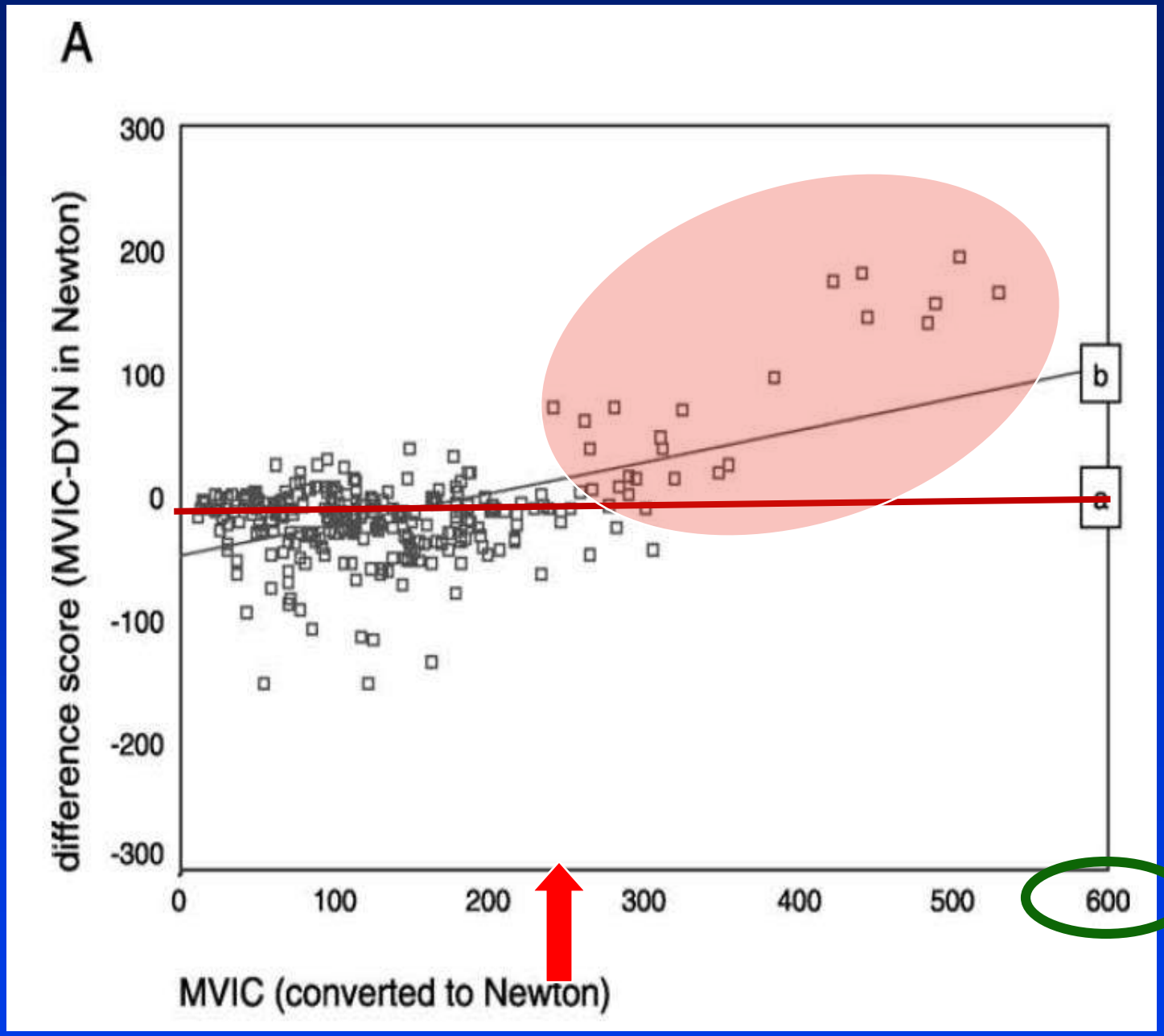


Hand-held Dynamometry

- Isometric contraction
- MAKE vs. BREAK test
- Electronic hand held device
- Normative data

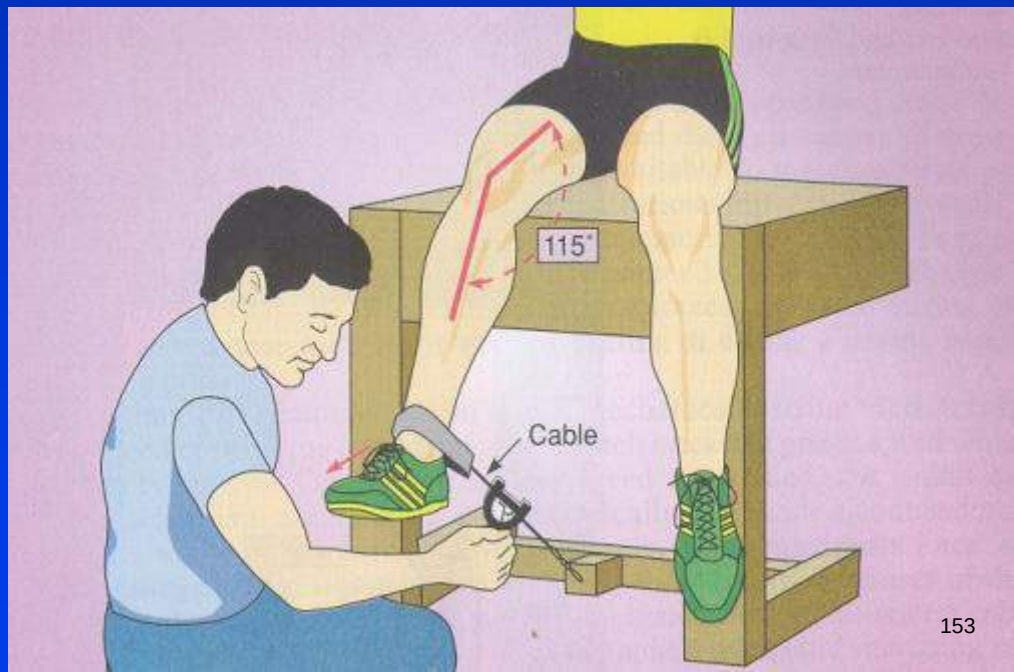






Visser et al. Neuromusc. Disorders 2003; 13:744-750

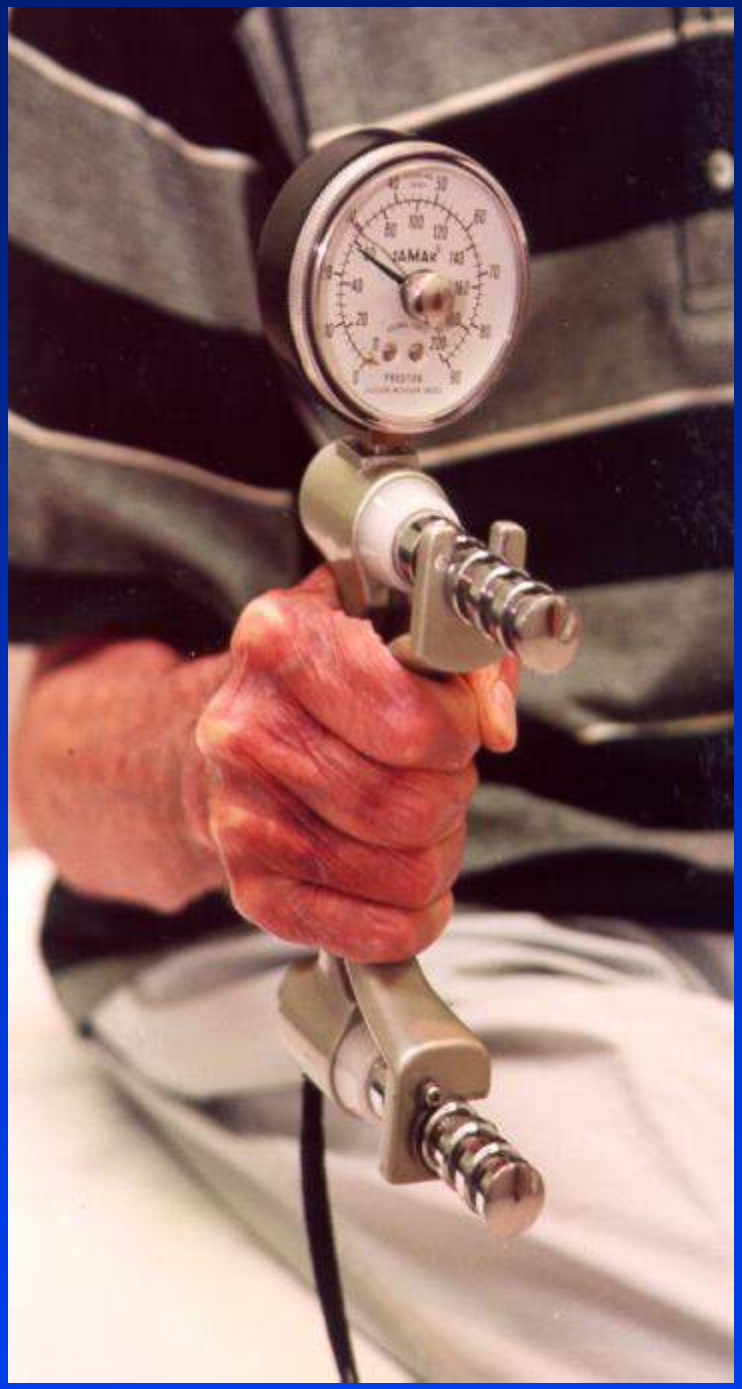

Strength (kg)
30.00
15.00
0.00
0.00
4.00
8.00
12.00
16.00
Time (seconds)

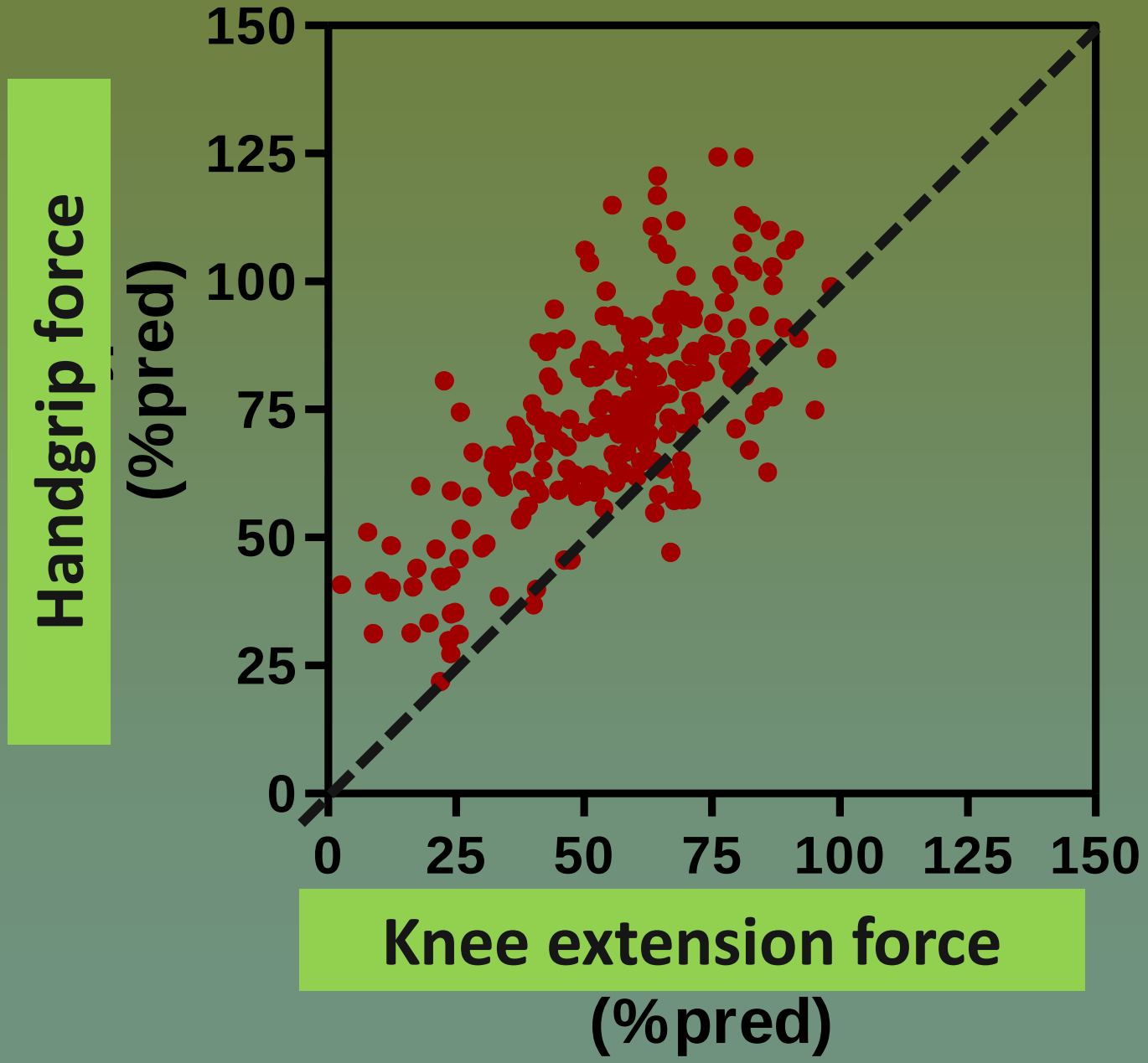

115°
Cable

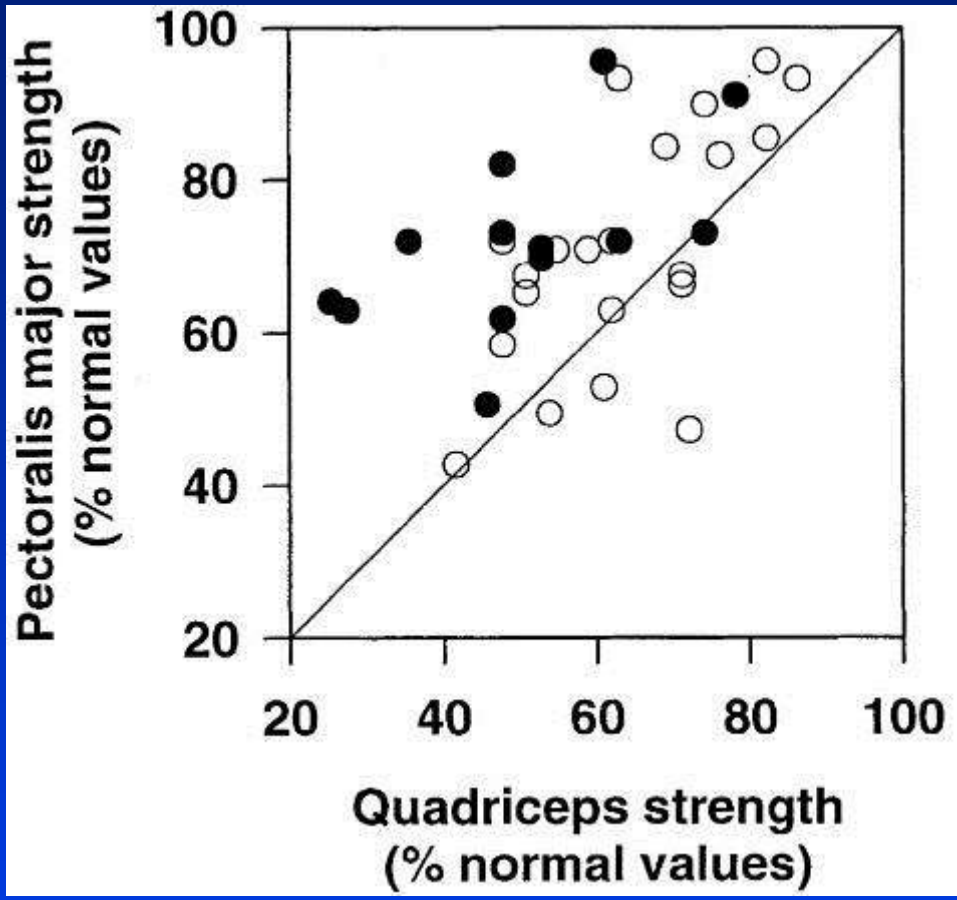
Which muscle group(s)?

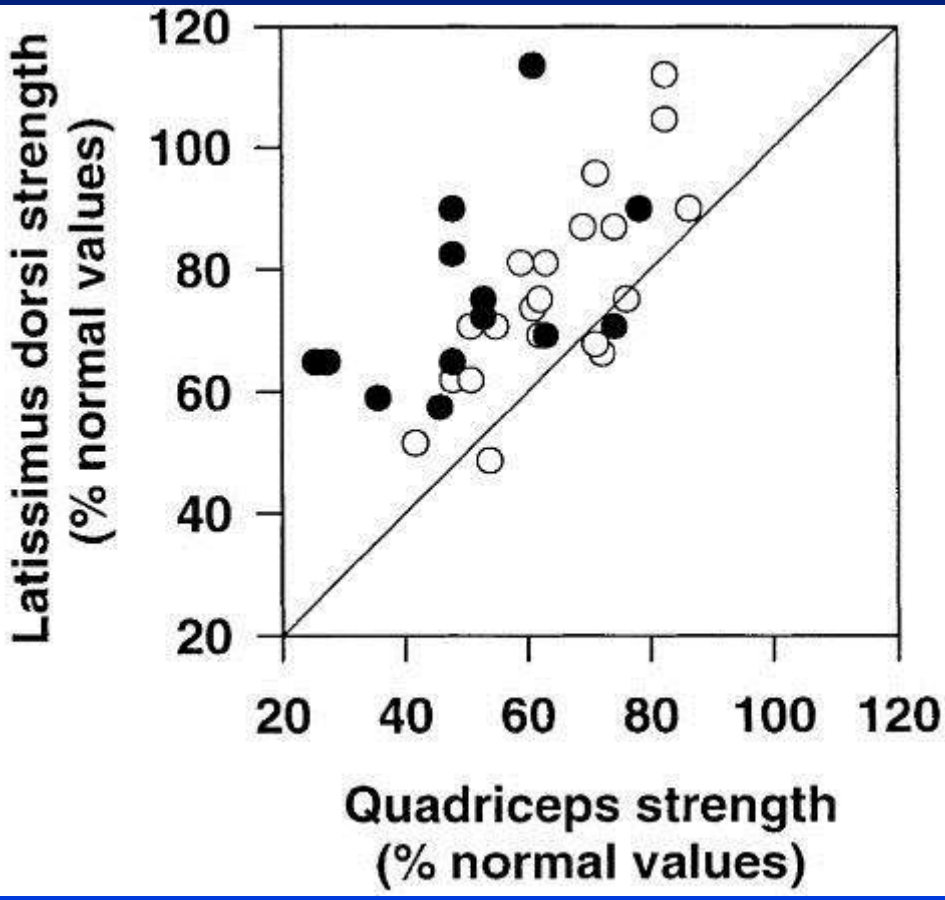
Is muscle weakness generalized?

- EASY - INEXPENSIVE
- REPRODUCIBLE
- REFERENCE VALUES
- VALIDITY AS INDICATOR OF GENERAL MUSCLE FORCE ?

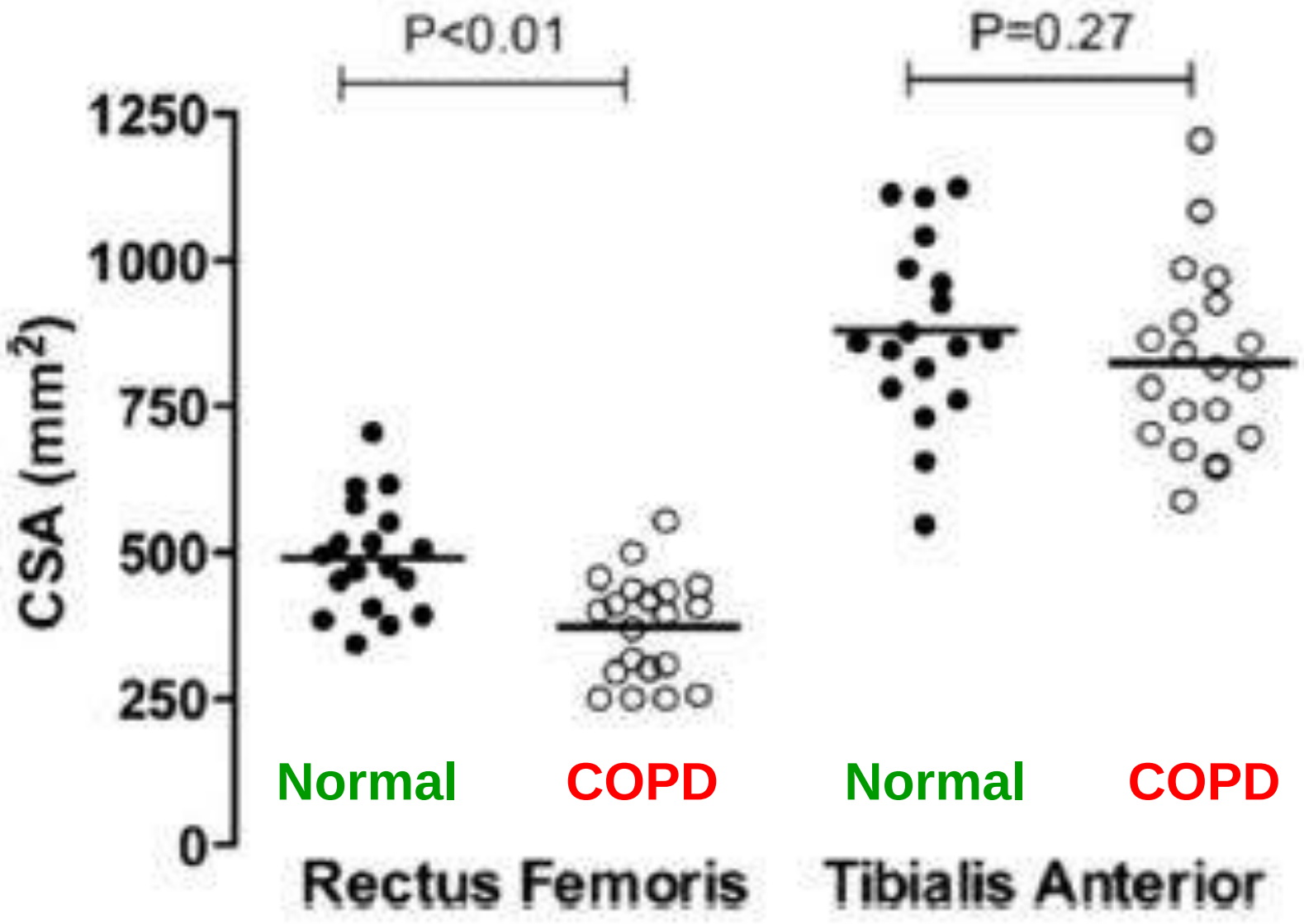



Handgrip force
(%pred)
150
125
100
75
50
25
0
0
25
50
75
100
125
150
Knee extension force
(%pred)





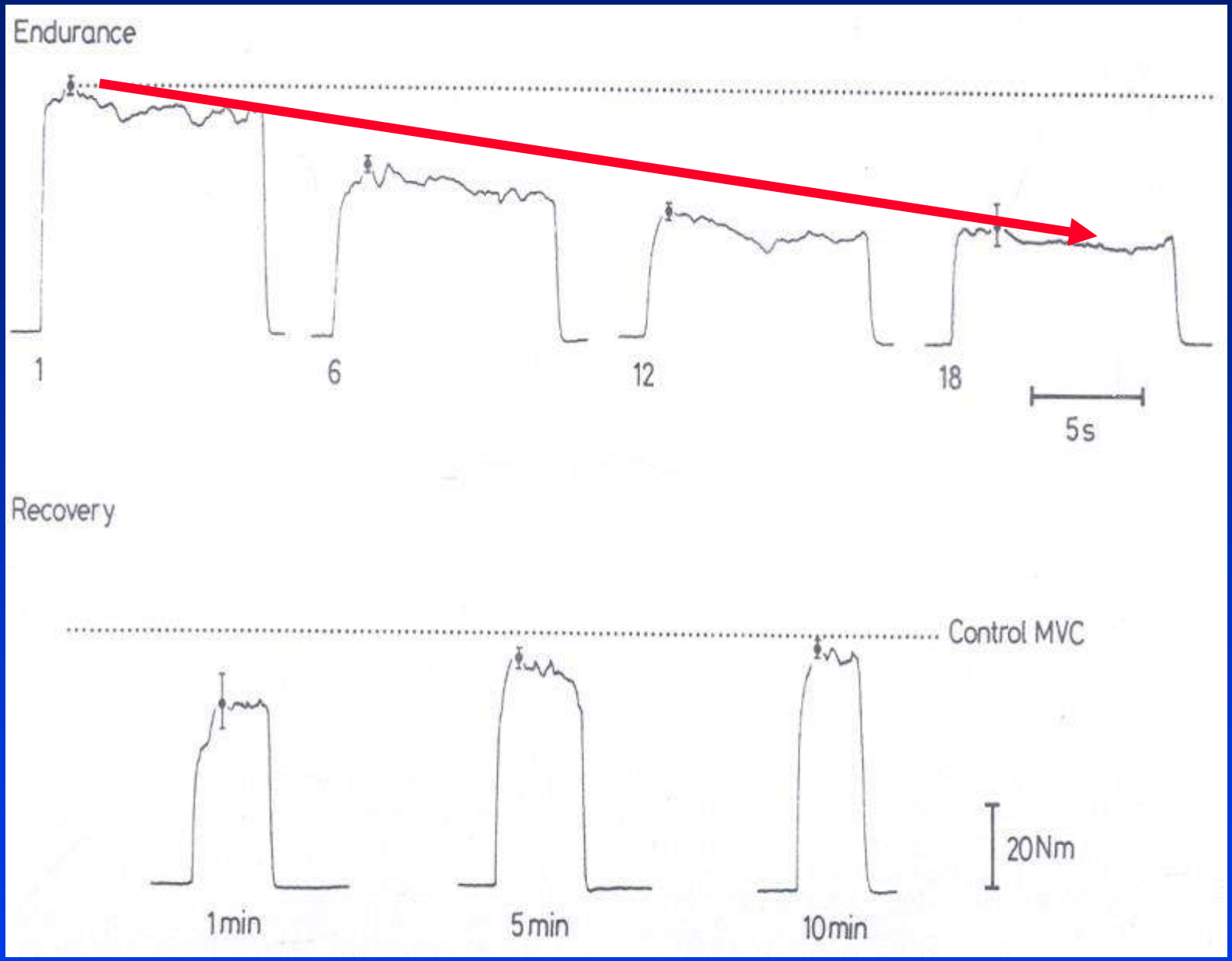
Bernard et al. Am J Respir Crit Care Med, 158, 629, 1998.



Seymour et al. Muscle and Nerve, 47, 548, 2012.

Modalities of muscle endurance assessment

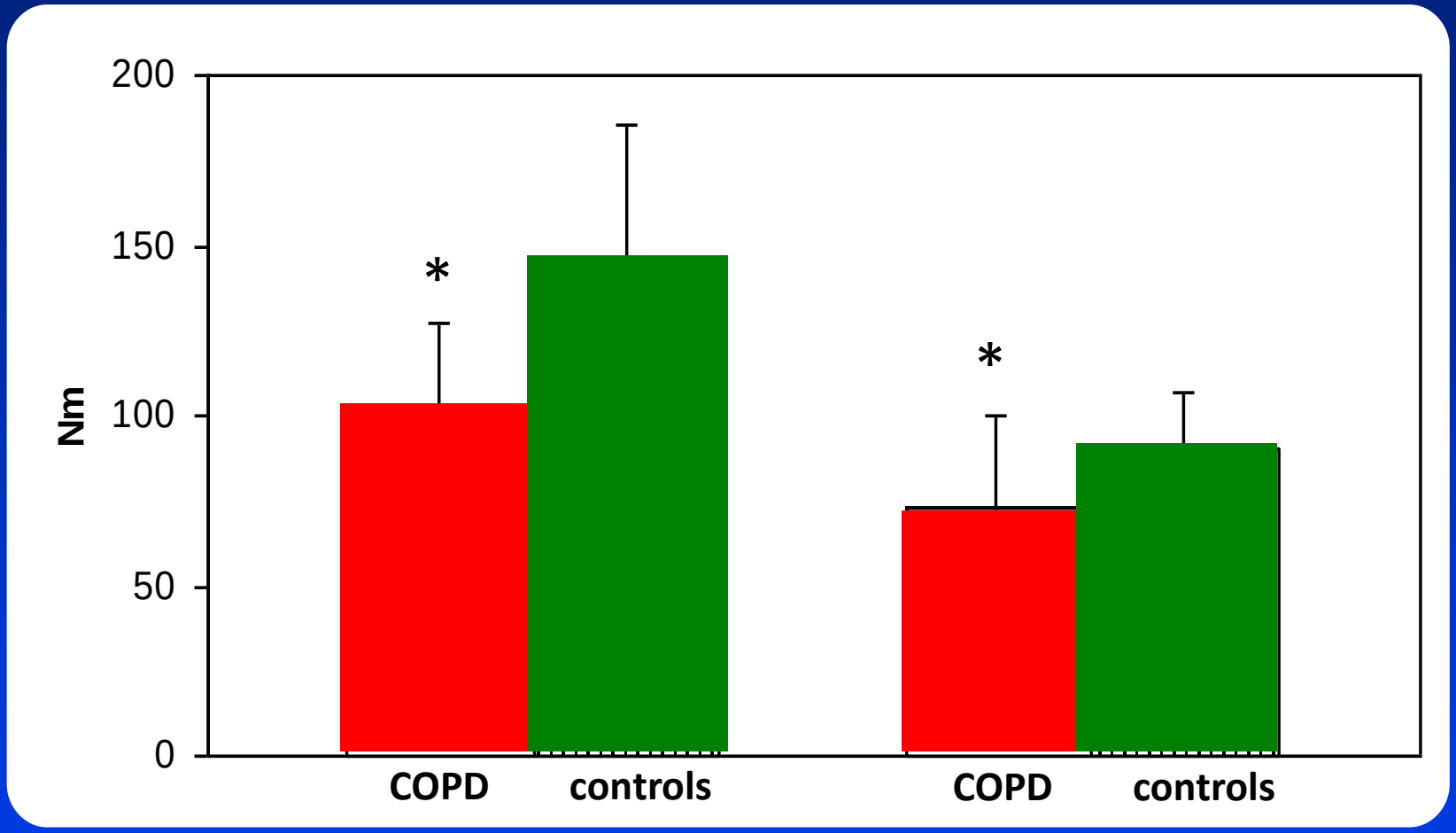
- Sustained maximal isometric contraction
- Repetitive isotonic or isometric contractions
- Muscle fatigue assessment by twitch stimulation



Lloyd et al. J. Neurol Neurosurg Psychiatry 1988, 51:1316-1322

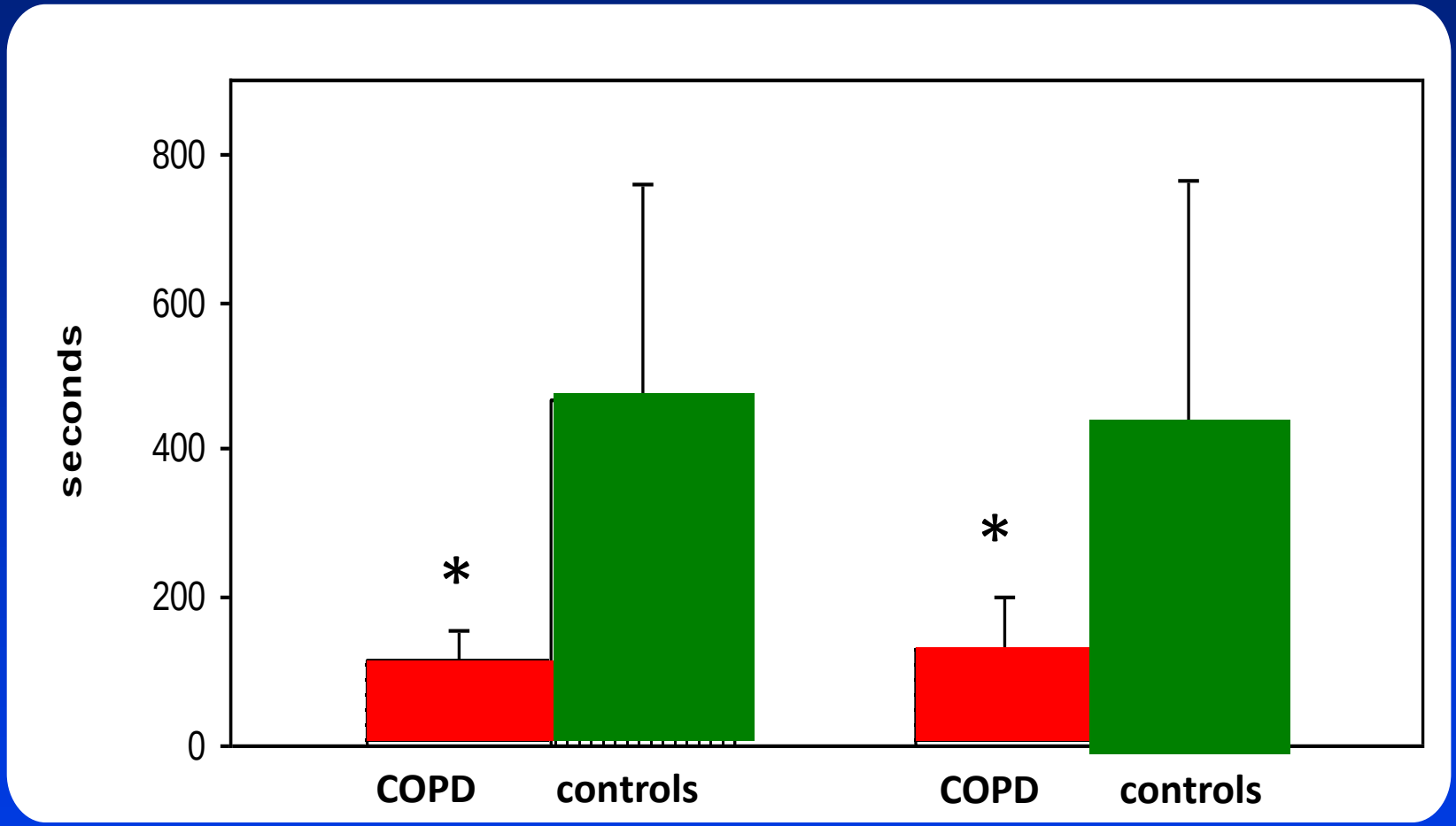
Assessment of quadriceps endurance with low resistance (20% MVC) contractions (30/min)

Quadriceps Force



Van 't Hul et al Muscle and Nerve 2004; 29:267.

Quadriceps Endurance

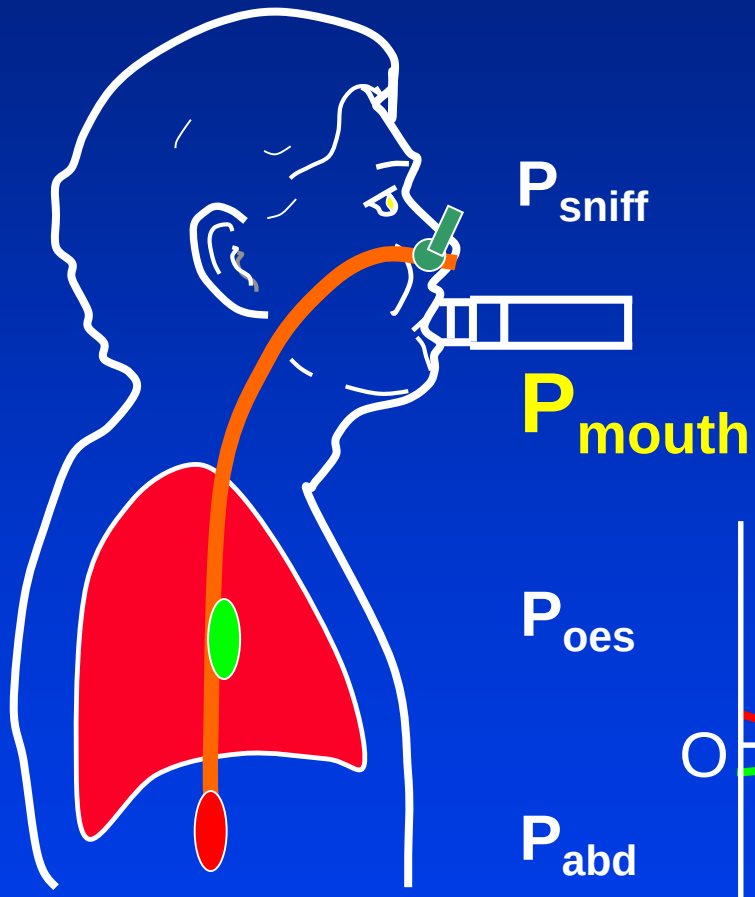


Male **Female**

Van 't Hul et al Muscle and Nerve 2004; 29:267.

How to assess respiratory muscle strength ?

Measurement of respiratory muscle strength

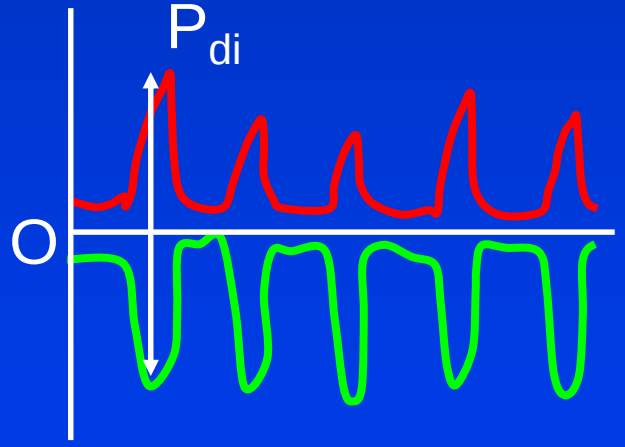


Maximal voluntary contractions

Pressures during twitch stimulation of the phrenic nerve

Electrical

Magnetic



Inspiratory muscle strength

Maximal static pressures at the mouth

- Measurement of pressure generated by all in- or expiratory respiratory muscles AND passive elastic recoil
- Advantages :
  - ✓ simple and quick
  - ✓ well tolerated
  - ✓ non-invasive
- Disadvantages
  - ✓ effort dependent
  - ✓ global measurement
  - ✓ result dependent on technique, and equipment used

PI_{max} is the mean pressure sustained over *one* second of a maximal and quasi static inspiration

Inspiratory muscle endurance

Conclusions

- Muscle weakness is present and clinically relevant in cardio-respiratory diseases
- Muscle strength and endurance assessment are ***accessible*** and ***reliable tools*** in the clinical evaluation of ***functional impairment*** of patients with cardiorespiratory disease

Lung function tests in preschool children

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AIMS

- To highlight the difficulty of measuring lung function in preschool children.
- To show the main technical aspects of the most common lung function tests for preschool children.
- To show their clinical applications in preschool children.

SUMMARY

Measuring lung function in preschool children (2-5 year old) is a difficult task, because they are physiologically different from older children and have a very short attention span [1]. Nevertheless, several techniques have been developed during the past century that allow the evaluation of lung function while the subject is breathing at tidal volume. This characteristic makes these tests extremely attractive for the assessment of lung function in "partially collaborating" subjects, i.e. preschoolers. Spirometry can also be attempted in preschoolers as long as the appropriate (i.e.: modified) acceptability criteria are used [1]. The feasibility of any lung function test in preschoolers, however, strongly depends on the capability of the operator of initiating a good relationship with the child and keeping him/her quiet and focused [1]. This is a very important aspect of measuring lung function in preschool children.

The American Thoracic Society/European Respiratory Society (ATS/ERS) Working Group on Lung Function in Young Children has published technical recommendations for most preschool techniques [1] and has more recently reviewed their clinical applications [2]. The ERS Task Force on Monitoring Asthma in Children has also very recently reviewed their role in the management of paediatric asthma [3]. This lecture will focus on the most used techniques for the assessment of lung function in preschool children.

Preschool Spirometry

Since preschool children are physiologically different from older children, many of the acceptability criteria used for spirometry in older children and adults are simply unrealistic in preschoolers [4]. For example, their lungs tend to empty in less than 1 s during a forced expiratory manoeuvre, so that not only the criterion of a 3-6 s expiration can obviously not be met, but also the forced expiratory volume in one second (FEV_1) can often not be measured in preschool children. Also, because of their poor attention span, the adult spirometry reproducibility criteria are often impossible to meet in preschool children.

In 2007 the ATS/ERS Working Group on Lung Function in Young Children [1] has recommended modified acceptability criteria for preschool spirometry, making this test more feasible in preschool children. First of all the child should have the time to familiarise with the equipment and the operator, especially if it is his/her first attempt at spirometry. Computerised incentives may be used, but are not mandatory. Since FEV_1 may not always be obtained, the use of FEV in 0.5 s ($FEV_{0.5}$) or 0.75 s ($FEV_{0.75}$) is recommended. For the start of test criterion, if a manoeuvre has a volume of back extrapolation (VBE) higher than 80 mL or 12.5% of forced vital capacity (FVC), the manoeuvre should be reinspected, but not necessarily rejected. For the end of test criterion, if flow stops at more than 10% of peak flow, FVC

should not be reported because of premature termination, but $FEV_{0.5}$ or $FEV_{0.75}$ may still be reported. Regarding repeatability, at least two acceptable curves should be obtained with the two FVC and $FEV_{0.5}$ or $FEV_{0.75}$ within 0.1 L or 10%, but if a single acceptable curve is obtained, this should not be excluded because of poor repeatability [1].

Using these modified criteria, the feasibility of spirometry is reported to be 55-85% in preschool children, especially in 4-5 year old children [2], but below age 4 still tends to be much lower. Several reference values for preschool spirometry are available [2] and the recent publication of global multiethnic reference equations from 3 to 95 years of age (Global Lung Function Initiative 2012) [5] has made it easier to use spirometry in preschoolers.

Regarding the clinical applications of spirometry in preschool children, a recent ATS workshop report has concluded that spirometry is able to discriminate healthy control subjects from preschool children with cystic fibrosis (CF) (although substantial overlap between CF and healthy subjects may occur) [2] and from preschool children with recurrent wheezing (although bronchodilator response, BDR, rather than baseline values, appears to be most sensitive) [2]. However, due to the complexity of spirometry in preschool children, a careful and rigorous approach to its use must be taken in this age group [2]. Also, there are still gaps in our knowledge that currently limit the application of spirometry to clinical care in preschool children [2].

Interrupter Technique

The interrupter technique was reported for the first time in 1927, but its underlying physiology was fully understood just over the 1970s-1980s period, when it was highly appreciated for its capability to evaluate lung function in awake, quietly breathing preschool children. The principle on which it is based is that during a sudden flow interruption at tidal breathing alveolar pressure and mouth pressure would rapidly equilibrate, thus allowing alveolar pressure to be estimated by measuring mouth pressure. Resistance (R_{int}) can then be calculated dividing the change in mouth pressure by the flow measured immediately before (as in the classical technique) or after (as in the "opening" technique) the interruption. Due to the viscoelastic properties of the respiratory system, after a rapid initial increase pressure will keep slowly increasing during the interruption. As such, although R_{int} should be considered a measure of the resistance of the whole respiratory system, it tends to approach pure airway resistance when pressure is measured at the beginning of the interruption (as in the classical technique) and the resistance of the whole respiratory system when pressure is measured at the end of the interruption (as in the "opening" technique). Therefore these two variants of the interrupter technique should not be used interchangeably [1].

The ATS/ERS recommendations [1] state that R_{int} should be measured with the child sitting with a neutral position of the head and the cheeks supported while wearing a nose clip and breathing quietly through a mouthpiece with an antibacterial filter. The valve should rapidly close (in <10 ms) at peak expiratory flow and each interruption should last $\leq$100 ms (to avoid active breathing during the interruption); 10 measurements should be recorded with the aim of getting at least 5 acceptable measurements, whose median value should then be reported [1].

The feasibility of R_{int} in preschool children is very high (81% to 98%) [2], both in the ambulatory setting and in field studies. The within-test coefficient of variation (CV, standard deviation divided by mean) is around 12% in healthy children, while the inter-measurement short-term coefficient of repeatability (CR, 2 times the standard deviation of the difference between the two measurements) was shown to range between 0.17 and 0.28 $kPa.L^{-1}.s$ [2] and to be similar to long-term CR in healthy children [2]. Several reference equations have been published for R_{int} [2] and the data from various centers have been recently unified obtaining a single international reference equation for the classical technique for 3-13 year old children [6]. BDR cut-off values in healthy children were also reported [7].

Regarding clinical applications, R_{int} has mainly been shown to be useful in preschool children with recurrent wheezing and, like for spirometry, BDR was found to better distinguish between health and disease than baseline values, with a sensitivity that varies from 24% to 76% and a specificity from 70% to 92% [2]. R_{int} was also used in pharmacological intervention studies [2]. Overall, the capability of R_{int} of easily detecting changes in the airway caliber makes it a potentially useful clinical tool for preschool children, although longitudinal studies on its clinical utility are still lacking [2, 3].

Forced Oscillation Technique

The forced oscillation technique (FOT) is also a non-invasive technique, which allows the evaluation of lung function during tidal breathing and is therefore very attractive as a lung function tool for preschool children. Low-frequency pressure oscillations generated by a loudspeaker are applied to the respiratory system through a mouthpiece and the resulting changes in flow and pressure can be measured at the mouth to calculate the impedance of the respiratory system (Z_{rs}) broken down into its two components, resistance (R_{rs}) and reactance (X_{rs}). FOT has thus the advantage of also providing information on X_{rs}, which can be thought of as the distensibility of the respiratory system [2]. Sinusoidal waves or impulses (IOS) have been used as forcing signals, both as single-frequency or multiple-frequency signals, with frequencies between 5 and 10 Hz being considered to reflect the mechanical properties of the total airways [1, 2].

Regarding measurement conditions in preschoolers, for FOT too the child should be seated with the head slightly extended, wearing a nose clip and breathing quietly through a mouthpiece and antibacterial filter, with the cheeks supported by the operator's hands [1]. The forcing signal should include frequencies in the 4-8 Hz range and each acquisition should cover several breathing cycles (at least 8 s). The mean of 3-5 measurements should be reported and the CV should be calculated for each frequency and used as an index of measurement reliability [1].

Like R_{int}, FOT has a very good feasibility in preschool children (between 79% and 95%) [2]. Several studies have also reported its repeatability, showing a short-term inter-measurement CR of 1.1 to 2.6 $hPa.L^{-1}.s$ for R_{rs} (corresponding to a relative change of 12-30%) and 1.2 to 2.0 $hPa.L^{-1}.s$ for X_{rs} [2], with similar values reported for the long-term CR [2]. Several reference equations have also been published for FOT [2, 8], and data on the BDR cut-offs are also available [1, 2, 8].

FOT has been used in many studies in children with asthma, with a sensitivity between 76-90% and a specificity between 55-65% in discriminating healthy children from children with a possible diagnosis of asthma, especially when BDR is used [2]. FOT has also been used in children with chronic lung disease of prematurity and in children with CF [2]. As for R_{int}, although FOT has proved to be able to easily detect changes in the airway caliber in preschool children, longitudinal studies on its clinical utility in this age group are still lacking [2, 3].

Multiple Breath Washout

Multiple breath washout (MBW) is another technique that only requires passive collaboration and tidal breathing and is thus suitable to be used in preschool children. MBW is typically based on the washout of nitrogen with 100% oxygen to assess ventilation inhomogeneity and measure functional residual capacity (FRC). Non-resident inert gases such as helium, argon, or sulfur hexafluoride (SF_6) have also been used, but some of them are currently not universally available [2]. The most commonly used MBW index is the lung clearance index (LCI), which represents the number of lung volumes (expressed as FRCs) required to complete the washout period [1]. The analysis of the concentration-normalized slope of phase III of the washout curve is a more complicated method [1].

A recent ERS/ATS statement has reported the general standard operating procedure for MBW [9]. However, several technical details regarding MBW in preschool children still need to be agreed on and a specific standardization project for MBW in preschoolers is currently ongoing. According to the

current recommendations for preschoolers [1], MBW should be performed while the child is seated, breathing at tidal volume through a mouthpiece or mask closely fitted to his/her face. Washout should continue until the end-tidal gas concentration has reached levels lower than 1/40 of the initial concentration over a period of more than 3 consecutive breaths. The average value of LCI between two washouts where FRCs differ by less than 10% should be reported as the final result [1].

The feasibility of measuring LCI is good in preschool children (nearly 80%, ranging from 50% in 2-3 year olds to 87% in 5-6 year olds) [2]. As far as the variability of the technique is concerned, in preschoolers the within-test CV of LCI has been reported to be as good as 5.2% and long-term LCI repeatability is less than ±10% month to month [2]. Although LCI initially seemed to be independent of age and growth in healthy subjects [1], its dependence on body size has been recently shown for children younger than 6 years and reference equations have been published [10].

LCI has been used successfully for clinical purposes, especially in children with CF [2]. A 2005 study reported that MBW was more sensitive than spirometry and plethysmography in detecting abnormal lung function in preschool children with CF [11] and a more recent study showed that LCI is able to predict pulmonary exacerbations in 5-19 year old subjects with CF [12]. However, longitudinal studies on the clinical utility of MBW in preschool children are still lacking [2] and a very recent CF Foundation workshop report concluded that the data to support the use of LCI or MBW parameters in the routine clinical management of patients with CF are currently insufficient [13].

Conclusions

Lung function is now accurately measurable in preschool children. These new techniques have proved to be powerful research tools. Further studies are needed to establish their long-term clinical utility in the management of lung disease in preschool children.

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EVALUATION

1. The most useful index for spirometry in a 3 year old child is:
   a. FEV1
   b. FEV0.75
   c. FVC
   d. FEF25-75

2. The feasibility of the interrupter technique (Rint) and the forced oscillation technique (FOT) in 3 to 5 year old children is:
   a. 40%
   b. 60%
   c. 80%
   d. 100%

3. The interrupter resistance (R_{int}) reflects the resistance of:
   a. peripheral airways
   b. total airways
   c. chest wall
   d. respiratory system

4. Resistance measured at 8 Hz (Rrs8) with the forced oscillation technique (FOT) reflects the resistance of:
   a. peripheral airways
   b. total airways
   c. chest wall
   d. respiratory system

5. Which ONE among the following statements on lung function tests in preschool children is TRUE?
   a. they only require “passive collaboration” with no sedation
   b. performing spirometry is not possible below age 6
   c. reference values are not available for most techniques
   d. information on repeatability is not available for Rint and FOT

Lung Function Tests in Preschool Children

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26
SAT

14:00-17:30 / ROOM E104-106 / Physiology

PG18 Postgraduate course Advanced respiratory and cardiovascular testing Clinical

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Preschool Children (2-5 yr)

The Real Challenge

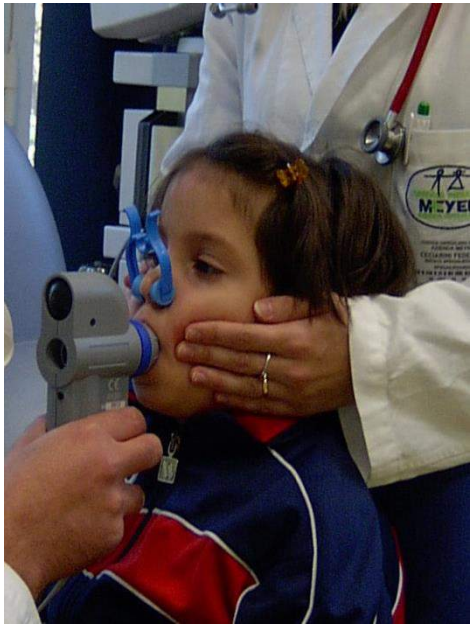
- Too old to sedate
- Too young to cooperate
  - short attention span
  - can either blow “hard” OR “long”, but frequently cannot blow “hard AND long”
- Physiologically different from older children and adults

Beydon N, et al. *AJRCCM* 2007;175:1304-45

Preschool Children (2-5 yr)

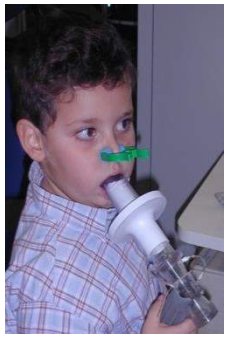
Need for PFTs

- Considerable growth and development of the respiratory system
- Frequent respiratory symptoms
- Children with CLD or CF
- Longitudinal assessment of lung function from birth throughout childhood
- In children with asthma >5 years of age it is useful to perform office based spirometry at least annually, and more frequent assessments may be indicated



Beydon N, et al. *AJRCCM* 2007;175:1304-45
Moeller A, et al. *ERJ* 2015;45:906-25

Pulmonary Function Tests for Preschool Children



Spirometry

R_{int}

FOT

sRaw

MBW

American Thoracic Society Documents

An Official American Thoracic Society/European Respiratory Society Statement: Pulmonary Function Testing in Preschool Children

Nicole Beydon, Stephanie D. Davis, Enrico Lombardi, Julian L. Allen, Hubertus G. M. Arets, Paul Aurora, Hans Bisgaard, G. Michael Davis, Francine M. Ducharme, Howard Eigen, Monika Gappa, Claude Gaultier, Per M. Gustafsson, Graham L. Hall, Zoltán Hantos, Michael J. R. Healy, Marcus H. Jones, Bent Klug, Karin C. Lødrup Carlsen, Sheila A. McKenzie, François Marchal, Oscar H. Mayer, Peter J. F. M. Merkus, Mohy G. Morris, Ellie Oostveen, J. Jane Pillow, Paul C. Seddon, Michael Silverman, Peter D. Sly, Janet Stocks, Robert S. Tepper, Daphna Vilozni, and Nicola M. Wilson, on behalf of the American Thoracic Society/ European Respiratory Society Working Group on Infant and Young Children Pulmonary Function Testing

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) AND THE EUROPEAN RESPIRATORY SOCIETY (ERS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, SEPTEMBER 2006, AND THE ERS EXECUTIVE COMMITTEE, DECEMBER 2006

Am J Respir Crit Care Med Vol 175. pp 1304–1345, 2007

AMERICAN THORACIC SOCIETY DOCUMENTS

An Official American Thoracic Society Workshop Report: Optimal Lung Function Tests for Monitoring Cystic Fibrosis, Bronchopulmonary Dysplasia, and Recurrent Wheezing in Children Less Than 6 Years of Age

Margaret Rosenfeld, Julian Allen, Bert H. G. M. Arets, Paul Aurora, Nicole Beydon, Claudia Calogero, Robert G. Castile, Stephanie D. Davis, Susanne Fuchs, Monika Gappa, Per M. Gustaffson, Graham L. Hall, Marcus H. Jones, Jane C. Kirkby, Richard Kraemer, Enrico Lombardi, Sooky Lum, Oscar H. Mayer, Peter Merkus, Kim G. Nielsen, Cara Oliver, Ellie Oostveen, Sarath Ranganathan, Clement L. Ren, Paul D. Robinson, Paul C. Seddon, Peter D. Sly, Marianna M. Sockrider, Samatha Sonnappa, Janet Stocks, Padmaja Subbarao, Robert S. Tepper, Daphna Vilozni; on behalf of the American Thoracic Society Assembly on Pediatrics Working Group on Infant and Preschool Lung Function Testing

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS OCTOBER 2012

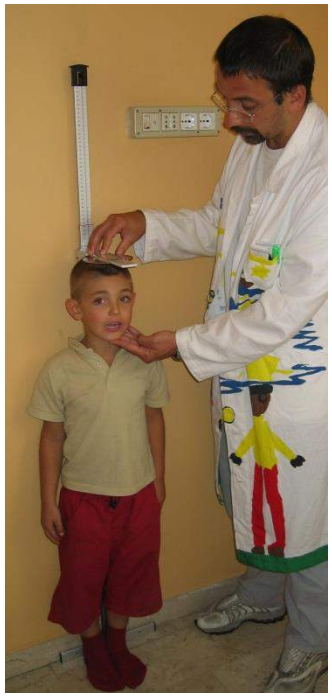
Ann Am Thorac Soc Vol 10, No 2, pp S1–S11, Apr 2013

PFT Issues in Preschoolers

- The feasibility of the test depends on the operator's capability of starting a good relationship with the child

Personnel

- **Child-friendly technician**
  - **welcome**
  - **understanding and patience**
  - **concentration**
  - **instructions**
  - **TIME !!**



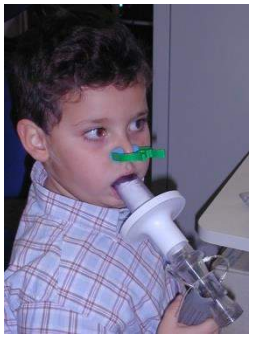
Beydon N, et al. *AJRCCM* 2007;175:1304-45

PFT Issues in Preschoolers

- Child-friendly environment
- Calibrated stadiometer and scale
- During tidal breathing, the level of distraction must be enough to take the child's attention away from his/her breathing, but not so exciting that he/she breathes irregularly

Beydon N, et al. *AJRCCM* 2007;175:1304-45

Pulmonary Function Tests for Preschool Children



Spirometry

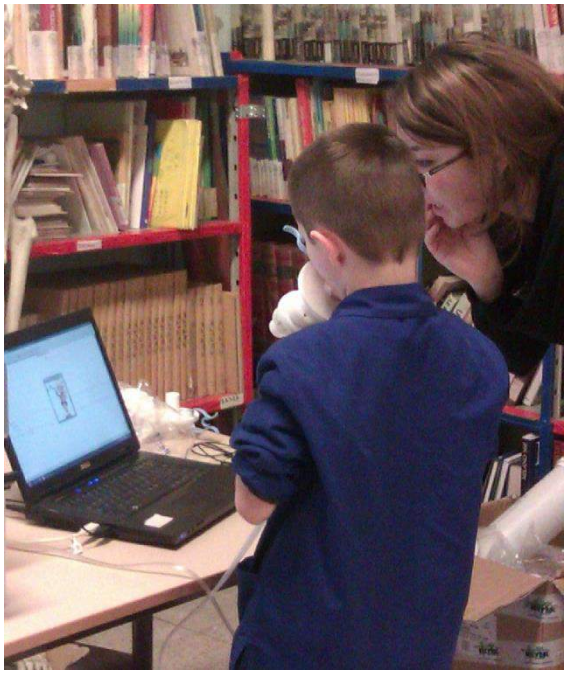
R_{int}

FOT

MBW

Preschool Spirometry

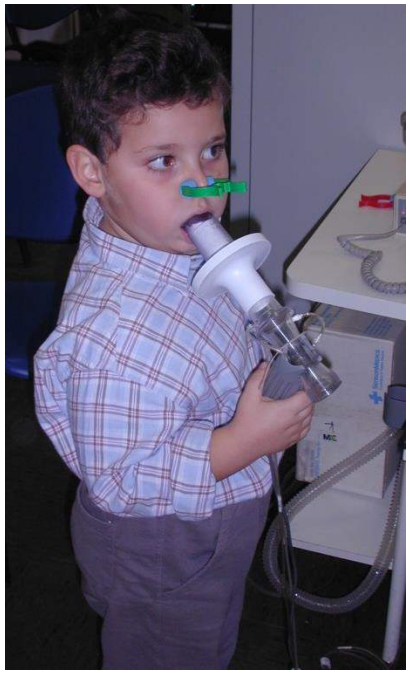
- Many of the criteria used for spirometry in older children and adults are simply unrealistic in preschoolers
- FEV1 can often not be measured
- Start of test and end of test criteria can often not be met
- Adult spirometry reproducibility criteria are often impossible to meet



Aurora P, et al. *AJRCCM* 2004;169:1152-9

Preschool Spirometry
Modified Acceptability Criteria

- Incentives may be useful, but not mandatory
- If FET <1 s, use of FEV in 0.5 s ($FEV_{0.5}$) or 0.75 s ($FEV_{0.75}$) is recommended
- Start of test: if a maneuver has a VBE higher than 80 mL or 12.5% of FVC, the maneuver should be reinspected, but not necessarily rejected
- End of test: if flow stops at more than 10% of PEF, FVC should not be reported, but $FEV_{0.5}$ or $FEV_{0.75}$ may still be reported
- Repeatability: at least 2 acceptable curves should be obtained with the two FVC and $FEV_{0.5}$ or $FEV_{0.75}$ within 0.1 L or 10%, but if a single acceptable curve is obtained, this should not be excluded



Beydon N, et al. *AJRCCM* 2007;175:1304-45

Preschool Spirometry
Feasibility & Reference Values

- Feasibility 55-90% in preschool children, especially in 4-5 year old children, but below age 4 still tends to be much lower

Rosenfeld M, et al. Ann ATS 2013;10:S1-S11
Bar-Yishay E, et al. Isr Med Assoc J 2009;11:198-200

- Several reference values for preschool spirometry are available

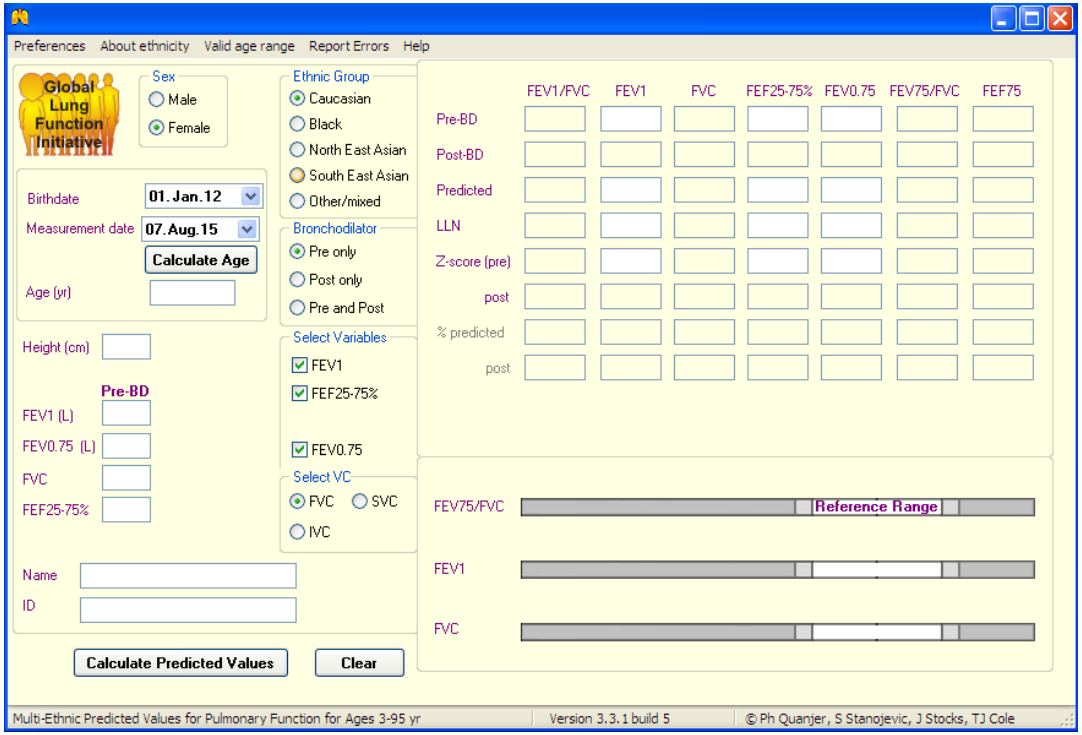
Eigen et al, Am J Respir Crit Care Med 2001;163:619-23
Vilozni et al, Am J Respir Crit Care Med 2001;164:2200-5
Nystad et al, Thorax 2002;57:1021-7
Zapletal et al, Pediatr Pulmonol 2003
Leung et al, Pediatr Pulmonol 2013;48:1119-26
Burity et al, J Pediatr (Rio J) 2013;89:374-80
Boutin et al, Eur Respir J 2015;45:107-15

ERS TASK FORCE

Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations

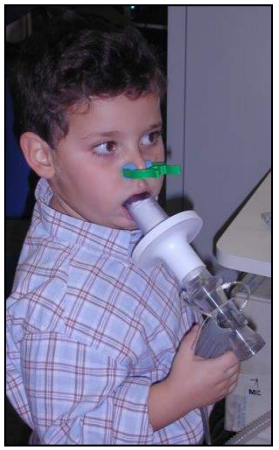
Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Xaver Baur, Graham L. Hall, Bruce H. Culver, Paul L. Enright, John L. Hankinson, Mary S.M. Ip, Jinping Zheng, Janet Stocks and the ERS Global Lung Function Initiative

www.lungfunction.org



Quanjer PH, et al. *ERJ* 2012;40:1324-43

Preschool Spirometry
Clinical Applications



- Spirometry can be performed to establish baseline lung function and document BDR

  Aurora P, et al. AJRCCM 2004;169:1152-9

- A post-BD increase between 9-15% in $FEV_{0.5}$, $FEV_{0.75}$ or FEV_1 is more commonly observed in preschool children with a clinical diagnosis of asthma

  Vilozni D, et al. Chest 2005;128:1146-55
  Dundas I, et al. Thorax 2005;60:13-6

- During methacholine challenge, spirometry was able to distinguish between healthy and asthmatic young children

  Joseph-Bowen J, et al. AJRCCM 2004;169:850-4

- Protocols for bronchoprovocation and exercise in preschoolers have been reported, but data are insufficient to allow their use in clinical practice

  Vilozni D, et al. Pediatr Pulmonol 2009;44:720-7

- Used in several clinical and epidemiologic studies on preschoolers

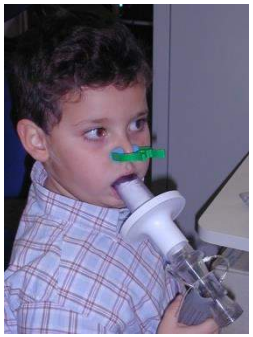
  Ramsey KA, et al. AJRCCM 2014;190:1111-6
  Morales E, et al. Thorax 2015;70:64-73

Preschool Spirometry
Conclusions

- Spirometry can be successfully applied to the preschool population in the clinical setting to identify disease states and track lung function over time
- As for all lung function testing, appropriate equipment and testing conditions, skilled and experienced personnel, and rigorous adherence to published guidelines are critical
- Until additional information is available, a circumspect approach to the interpretation of preschool spirometry data should be undertaken
- There remain gaps in our knowledge that currently limit the application of this technique to clinical care

Rosenfeld M, et al. *Ann ATS* 2013;10:S1-S11

Pulmonary Function Tests for Preschool Children

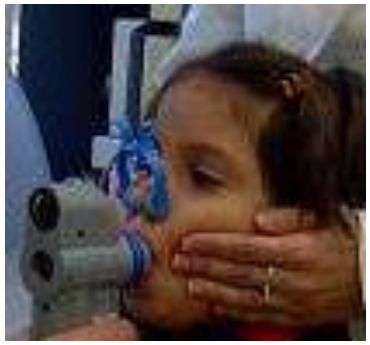


Spirometry

R_{int}

FOT

MBW



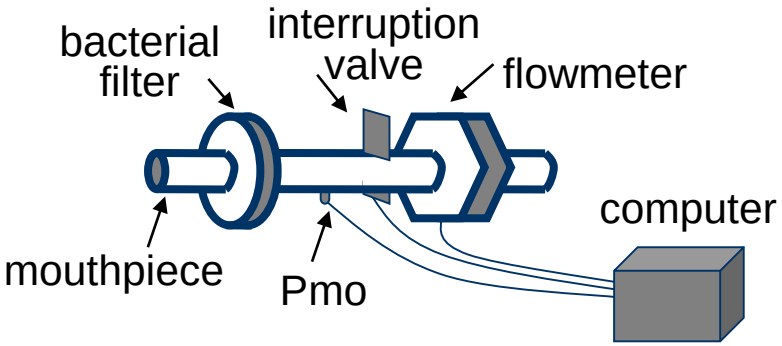
Interrupter Technique

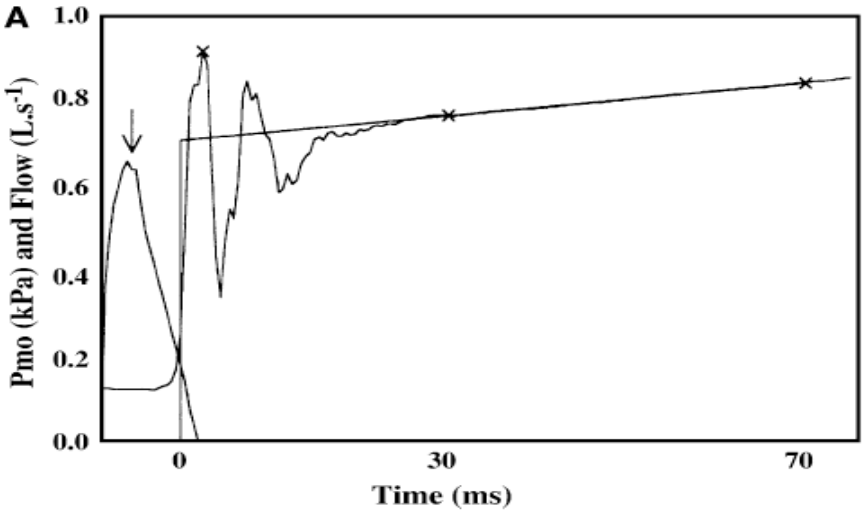
Assumptions

- Immediately after interruption, pressure at the airway opening and alveolar pressure will equilibrate

$$P_{mo} = P_{alv} \qquad R_{int} = \Delta P_{mo}/V'$$

- Airway occlusion is instantaneous
- Upper airway compliance is negligible





Beydon N, et al. *AJRCCM* 2007;175:1304-45
(reproduced with permission of the ATS & ERS)

Interrupter Technique in Preschoolers

Simple to perform

- Occlusions lasting for 100 ms
- Occlusions triggered by peak expiratory flow
- Record 10 occlusions with the aim of retaining a minimum of 5 acceptable manoeuvres
- Report the median of all technically-acceptable occlusions
- The best algorithm to calculate Pmo needs to be determined (meanwhile use linear back-extrapolation)

Beydon N, et al. *AJRCCM* 2007;175:1304-45

Interrupter Technique in Preschoolers
Feasibility & Repeatability

- Feasibility >80% in preschool children (88-98% in >3 yr)

Rosenfeld M, et al. Ann ATS 2013;10:S1-S11

- Intra- and intermeasurement variability

Authors	Diagnosis	n	Age Range (yr)	Intrameasurement Variability CV (%)	Time Interval	Intermeasurement Variability CR ($kPa \cdot L^{-1} \cdot s$)
Beydon and colleagues (25)	Healthy	91	2.9–7.9	12.1 (SD, 3.2%)		
Beydon and colleagues (27)	Asthma	74	3.2–7.8	11.7 (SD, 3.9%)		
Beydon and colleagues (26)	Cystic fibrosis	39	3.0–8.2	11.9 (SD, 3.6%)		
Delacourt and colleagues (159)	Stable asthma/cough	118	3–16	11.4 (SD, 6.4%)		
Merkus and colleagues (22)	Healthy, cough/wheeze	139	1–7	11.6 (SD, 5.6%)		
Bridge and colleagues (24)	Healthy, cough/wheeze	22	2–3		30 s	0.21
		40	3–4		30 s	0.17
		58	4–5		30 s	0.15
Beelen and colleagues (158)	Healthy (field conditions)	32	3.7–4.9		20–30 min	0.28
	History of wheeze (field conditions)	25	3.7–4.9		38 d	0.37
	Healthy (standardized conditions)	15	3.2–5.9		11 d	0.28
Chan and colleagues (57)	Healthy, cough, stable wheeze	85	2.0–9.9		15 min	0.17
	Healthy	72	2.2–9.8		3 wk	0.23
	Cough	57	2.0–9.4		3 wk	0.38
	Stable wheeze	95	2.0–9.5		3 wk	0.44
Lombardi and colleagues (21)	Stable wheeze/cough	69	2.6–6.5		1 min	0.24
	Stable wheeze/cough	26	3.1–5.8		2.5 mo	0.21

Definition of abbreviations: CR = coefficient of repeatability (2 SD of the mean difference between two sets of measurements); CV = coefficient of variation (SD/mean × 100).

Beydon N, et al. *AJRCCM* 2007;175:1304-45
(reproduced with permission of the ATS & ERS)

Interrupter Technique in Preschoolers

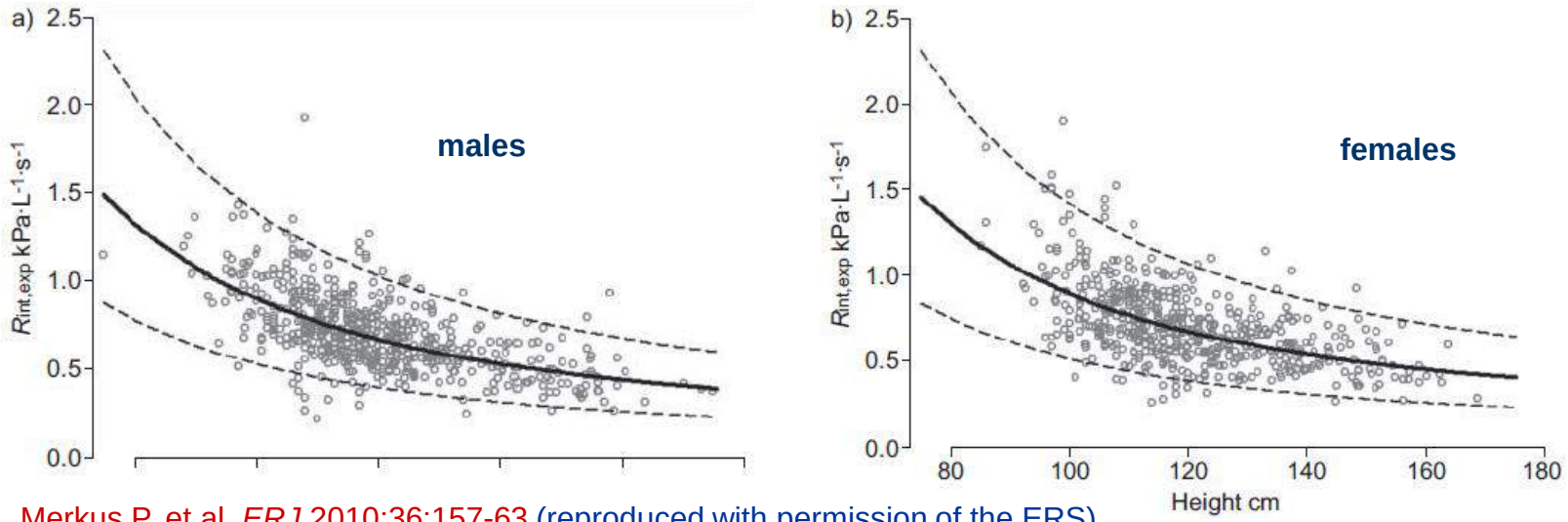
Reference Values

- Several reference values for preschool R_{int} are available

Klug B, et al. *Pediatr Pulmonol* 1998;25:322-31
Lombardi E, et al. *Thorax* 2001;56:691-5
Merkus P, et al. *ERJ* 2002;20:907-11
Beydon N, et al. *AJRCCM* 2002;165:1388-94
McKenzie S, et al. *Arch Dis Child* 2002;87:248-51
Rech VV, et al. *J Bras Pneumol* 2008;34:796-803
Li A, et al. *Chest* 2009;136:554-60
Gochicoa LG, et al. *Respirology* 2012;17:667-73

Reference ranges for interrupter resistance technique: the Asthma UK Initiative

P.J.F.M. Merkus*,#, J. Stocks¶, N. Beydon+, E. Lombardi§, M. Jones/, S.A. McKenzie**, J. Kivastik##, B.G.M. Arets¶¶ and S. Stanojevic¶,++



Merkus P, et al. *ERJ* 2010;36:157-63 (reproduced with permission of the ERS)

Interrupter Technique in Preschoolers

Clinical Applications

- 5-40% of young children with recurrent wheezing exhibit abnormal baseline values while clinically stable

Nielsen K, et al. *AJRCCM* 2001;164:554-9
Merkus P, et al. *AJRCCM* 2001;163;1350-5
Beydon N, et al. *AJRCCM* 2003;168:640-4

- R_{int} BDR Sensitivity & Specificity in detecting history of wheezing

	Healthy/Wz	Cut-off	Sensitivity %	Specificity %
McKenzie 2000	48/82	-18% baseline	76	80
Beydon 2003	84/74	-35% pred = -0.25 kPa.L^{-1}.s	24	92
Nielsen 2001	37/55	-2.5 SDw = -0.20 kPa.L^{-1}.s	58	70

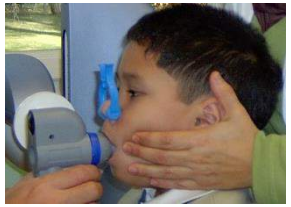
- R_{int} BDR Sensitivity & Specificity in detecting current signs or symptoms

	Sensitivity %	Specificity %	PPV %	NPV %
Δabs ≥0.26 kPa.L^{-1}.s	80.0	81.7	81.4	80.3
Δ%bas ≥32%	35.0	93.3	84.0	58.9
Δ%pred ≥33%	75.0	78.3	77.6	75.8
ΔZ-score ≥1.25	80.0	81.7	81.4	80.3

Mele L, et al. *Pediatr Pulmonol* 2010;45:633-8

Interrupter Technique in Preschoolers

Clinical Applications



- Spirometry and R_{int} measurements are not directly comparable in individual children and may reflect different aspects of lung function

  Arets H, et al. *Respir Med* 2003;97:366-74
  Davies PL, et al. *Pediatr Pulmonol* 2007;42:23-8

- Compared with spirometry R_{int} had poor sensitivity to detect baseline obstruction, but fairly good sensitivity and specificity to detect reversibility (70% & 69%)

  Beydon N, et al. *Pediatr Pulmonol* 2012;47:987-93

- R_{int} increased during methacholine challenge

  Phagoo SB, et al. *ERJ* 1996;9:1374-80
  Beydon N, et al. *Pediatr Pulmonol* 2001;31:238-46
  Kivastik S, et al. *Respir Med* 2007;101:2555-60

- Three studies found a significant change in R_{int} after pharmacological intervention

  Nielsen K, et al. *AJRCCM* 2000;162:1500-6
  Pao CS, et al. *AJRCCM* 2002;166:945-9
  Straub DA, et al. *Chest* 2005;127:509-14

- Two studies found no change in R_{int} after pharmacological intervention

  Kooi EM, et al. *Pulm Pharmacol Ther* 2008;21:798-804
  Schokker S, et al. *Pulm Pharmacol Ther* 2008;21:88-97

- Used in epidemiologic studies on preschool children

  Brussee JE, et al. *AJRCCM* 2004;169:209-13
  Caudri D, et al. *Thorax* 2010;65:801-7

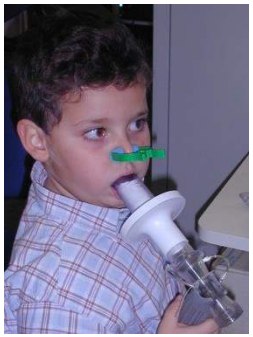
Interrupter Technique in Preschoolers

Conclusions

- Rint is able to detect changes in airway caliber
- However, before Rint can be incorporated into routine clinical practice, certain technical issues need to be addressed (effects of compliant face masks, best way to assess Pmo)
- In addition, the long-term change of Rint with treatment, or its predictive value in terms of prognosis, are unknown and need to be investigated
- Despite Rint having some potential as monitoring tool in preschool asthmatics, to date, there are no longitudinal studies confirming its usefulness

Rosenfeld M, et al. *Ann ATS* 2013;10:S1-S11
Moeller A, et al. *ERJ* 2015;45:906-25

Pulmonary Function Tests for Preschool Children



Spirometry

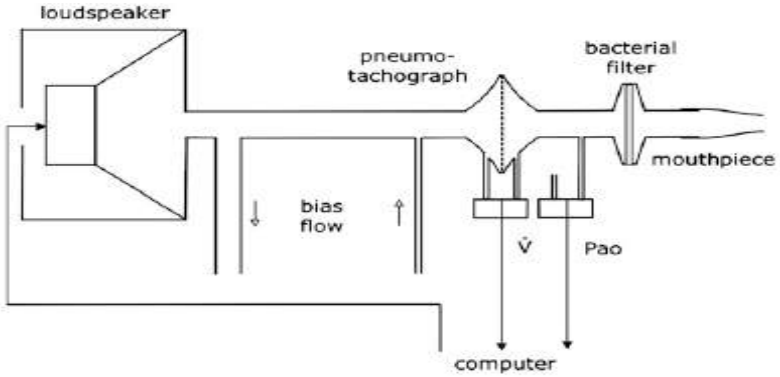
R_{int}

FOT

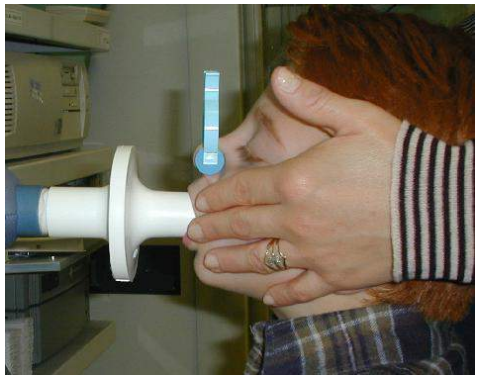
MBW

Forced Oscillation Technique (FOT)

- Pressure oscillations generated by a loudspeaker are applied to the mouth and the resulting changes in pressure and flow are analyzed to calculate respiratory impedance (Z_{rs})



- Z_{rs} expresses the impediment to flow in the respiratory system that includes both frictional losses (resistance R_{rs}) and elastic and inertial loads (reactance X_{rs}) $Z_{rs} = R_{rs} + X_{rs}$



- Sinusoidal waves or impulses (IOS) have been used, both as single-frequency or multiple-frequency signals, with frequencies 5-10 Hz being considered to reflect the mechanical properties of the total airways

Beydon N, et al. *AJRCCM* 2007;175:1304-45
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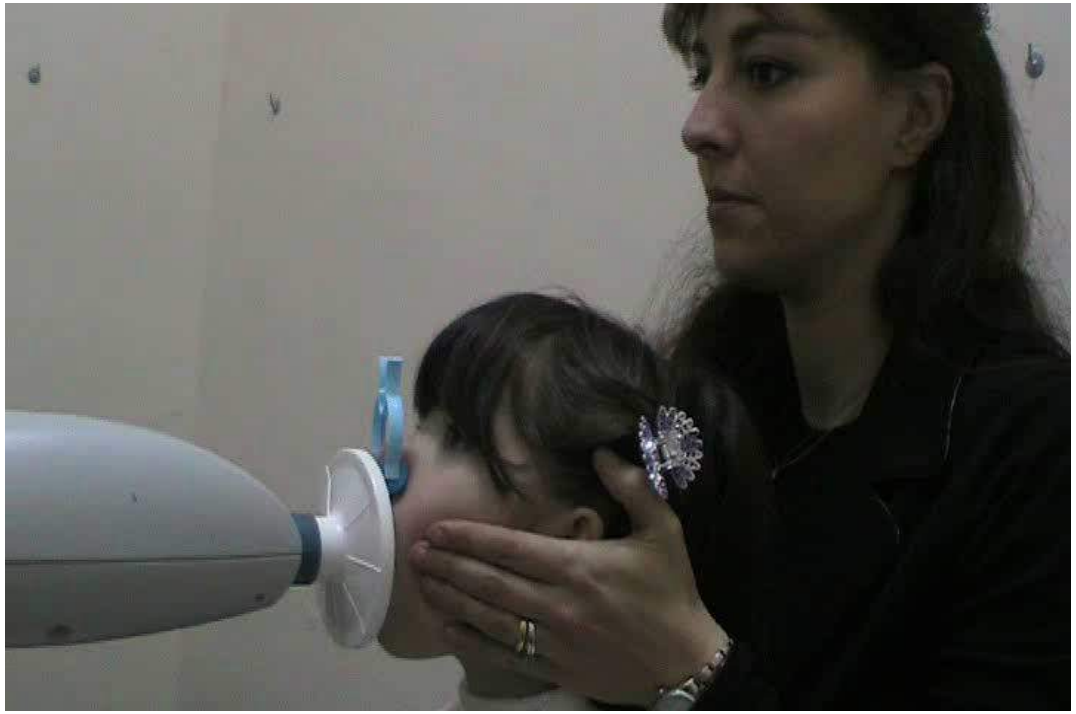
FOT in Young Children
Simple to perform

- The optimal excitation frequencies should include the range 4-8 Hz
- An acquisition period should cover several breathing cycles, typically lasting 8-16 s
- Three to 5 measurements
- Results should be reported as mean and coefficient of variation



Beydon N, et al. *AJRCCM* 2007;175:1304-45

FOT in Preschoolers
Feasibility & Repeatability

- Feasibility ≥80% in preschool children (79-95%, 69% in ≤4 yr-olds)

Rosenfeld M, et al. *Ann ATS* 2013;10:S1-S11
Bar-Yishay E, et al. *Isr Med Assoc J* 2009;11:198-200

- Short-term (15 min) repeatability

	Subjects	R_{rs} (CR)	X_{rs} (CR)
Klug 1998	120, healthy	2.6 hPa.L^{-1}.s or ~20%	2.0 hPa.L^{-1}.s
Malmberg 2002	19, healthy	1.1 hPa.L^{-1}.s or ~12%	1.3 hPa.L^{-1}.s
Hall 2007	58, healthy	~2.0 hPa.L^{-1}.s or ~30%	1.2-1.7 hPa.L^{-1}.s
Gangell 2007	25, CF	2.0-2.5 hPa.L^{-1}.s or ~20%	~1.4 hPa.L^{-1}.s
Udomittipong 2008	19, CLD	~2.5 hPa.L^{-1}.s or ~20%	2.0-2.5

- Medium-term (14 days) repeatability

	Subjects	R_{rs} (CR)	X_{rs} (CR)
Hall 2009	20, healthy or asymptomatic	~1.7 hPa.L^{-1}.s or ~20%	1.4-2.0 hPa.L^{-1}.s

FOT in Preschoolers

Reference Values & BDR

- Several reference values for preschool FOT are available

Hantos Z, et al. *Pediatr Pulmonol* 1985;1:91-8
Solymar L, et al. *Pediatr Pulmonol* 1985;1:134-40
Ducharme F, et al. *Chest* 1998;113:1322-8
Klug B, et al. *Pediatr Pulmonol* 1998;25:322-31
Hellynckx J, et al. *ERJ* 1998;12:438-43
Hall G, et al. *Thorax* 2007;62:521-6
Calogero C, et al. *Pediatr Pulmonol* 2010;45:1086-94.
Shackleton C, et al, *Arch Bronconeumol* 2013;49:326-9
Calogero C & Simpson S, et al. *Pediatr Pulmonol* 2013;48:707-15

- BDR cut-off in healthy subjects (post salbutamol 200 or 300 μg)

	Technique	R_{rs}	X_{rs}	AX
Hellinckx 1998	IOS	R_{rs5} -41% baseline	--	--
Nielsen 2001	IOS	R_{rs5} -28% baseline	X_{rs5} -42% baseline	--
Malmberg 2002	IOS	R_{rs5} -37% baseline	--	--
Thamrin 2007	pseudorandom	R_{rs8} -40% baseline	X_{rs8} 65% baseline	--
Calogero 2010	pseudorandom	R_{rs8} -34% baseline or -1.9 Z-score	X_{rs8} 61% baseline or 2.5 Z-score	--
Calogero & Simpson 2013	pseudorandom	R_{rs8} -32% baseline or -1.8 Z-score	X_{rs8} 65% baseline or 2.0 Z-score	-82% baseline or 2.0 Z-score

FOT in Preschoolers
Clinical Applications

- Significantly higher R_{rs} and lower X_{rs} in wheezers than healthy subjects at baseline
  Malmberg LP, et al. *Thorax* 2003;58:494-9
  Oostveen E, et al. *ERJ* 2010;35:865-72
  Vu LT, et al. *Pediatr Pulmonol* 2010;45:380-6

- Similar lung function in preschool wheezers and healthy subjects at baseline
  Thamrin C, et al. *Thorax* 2007;62:814-9
  Song TW, et al. *Pediatr Allergy Immunol* 2008;19:763-8
  Harrison J, et al. *Pediatr Pulmonol* 2010;45:1049-56

- FOT BDR Sensitivity & Specificity in detecting history of wheezing

		Sensitivity %	Specificity %	PPV %	NPV %
Nielsen 2001	ΔRrs5 cut-off -1 SDw	76	65	76	65
	ΔXrs5 cut-off 1.5 SDw	33	89	82	47
Malmberg 2003	ΔRrs5%pred cut-off -21.2%	90	55	46	93
	ΔXrs5%pred cut-off 55.3%	38	91	67	77

- Changes in R_{rs} after BD have been reported to be correlated with change in clinical signs in preschool children with an acute asthma exacerbation
  Chalut DS, et al. *J Pediatr* 2000;137:762-8

FOT in Preschoolers
Clinical Applications

- Suggested to be more sensitive than spirometry, because of no "deep inspiration" effect
  Marotta A, et al. *JACI* 2003;112:317-22
- In older children, the area under the reactance curve (AX) might detect alterations in airway mechanics not reflected by spirometry nor by other FOT indices
  Larsen GL, et al. *JACI* 2009;123:861-7
- Useful in detecting BHR during with several challenge tests
  Nielsen KG, et al. *AJRCCM* 2000;161:1805-9
  Malmberg LP, et al. *Pediatr Pulmonol* 2008;43:538-44
  Hall GL, et al. *Chest* 2009;136:184-9
- Sensitive to short or prolonged treatment with antiinflammatory therapy in preschool children with asthma
  Nielsen KG, et al. *AJRCCM* 2000;162:1500-6
  Kooi EM, et al. *Pulm Pharmacol Ther* 2008;21:798-804
  Moeller A, et al. *Pediatr Pulmonol* 2008;43:179-86
- FOT indices found to be impaired in preschoolers born preterm or with BPD
  Vrijlandt EJ, et al. *J Pediatr* 2007;150:256-61
  Udomittipong K, et al. *ERJ* 2008;31:1292-9
- Used in preschool children with CF with variable results
  Nielsen KG, et al. *AJRCCM* 2004;169:1209-16
  Ren CL, et al. *Pediatr Pulmonol* 2012;47:574-81
- Used in epidemiologic studies on preschool children
  Dom S, et al. *ERJ* 2014;44:371-81

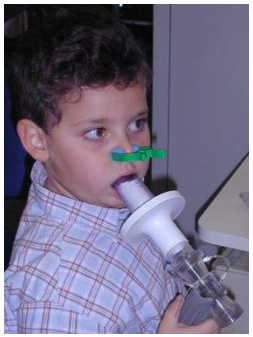
FOT in Preschoolers

Conclusions

- Little is known about which FOT outcome may offer the most clinically relevant information and the potential role of X_{rs}
- Further studies on the comparability of FOT setups and intercenter comparisons are needed
- Longitudinal studies are also required to document changes with growth and development in healthy children as well as to address the ability of FOT to contribute to clinical management
- Despite FOT having some potential as monitoring tool in preschool asthmatics, to date, there are no longitudinal studies confirming its usefulness

Rosenfeld M, et al. *Ann ATS* 2013;10:S1-S11
Moeller A, et al. *ERJ* 2015;45:906-25

Pulmonary Function Tests for Preschool Children



Spirometry

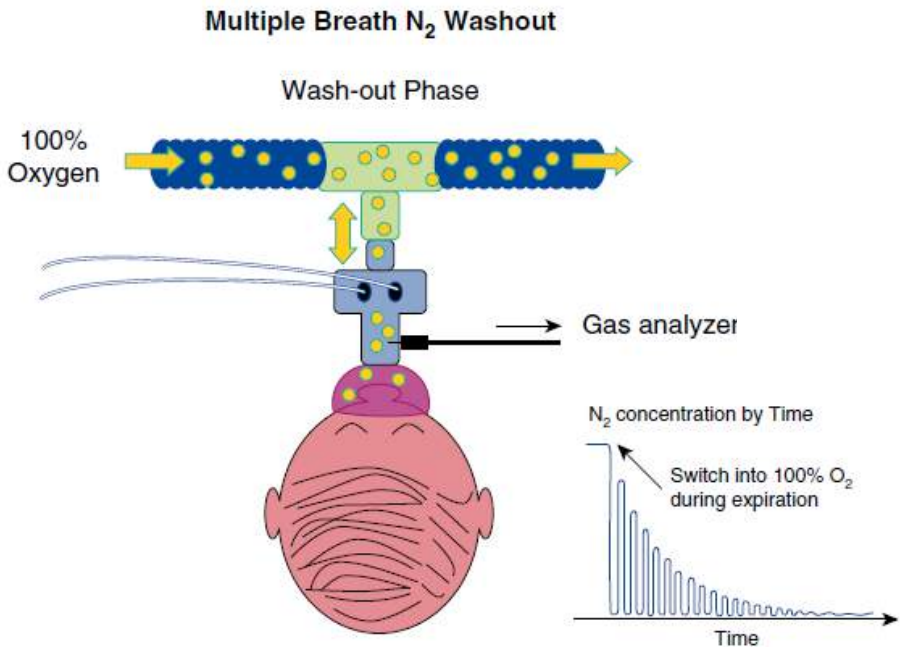
R_{int}

FOT

MBW

Multiple Breath Washout (MBW)

- Washout of N_2 with 100% O_2 to assess ventilation distribution in the lungs and to measure functional residual capacity (FRC)
- Other marker gases with low solubility in blood and tissues can also be used (He, SF_6, Ar)



- The lung clearance index (LCI) (cumulative expired volume required to clear an inert gas from the lungs, divided by FRC) is the most used index
- Normalised phase III slope (S_{nIII}) analysis is also possible

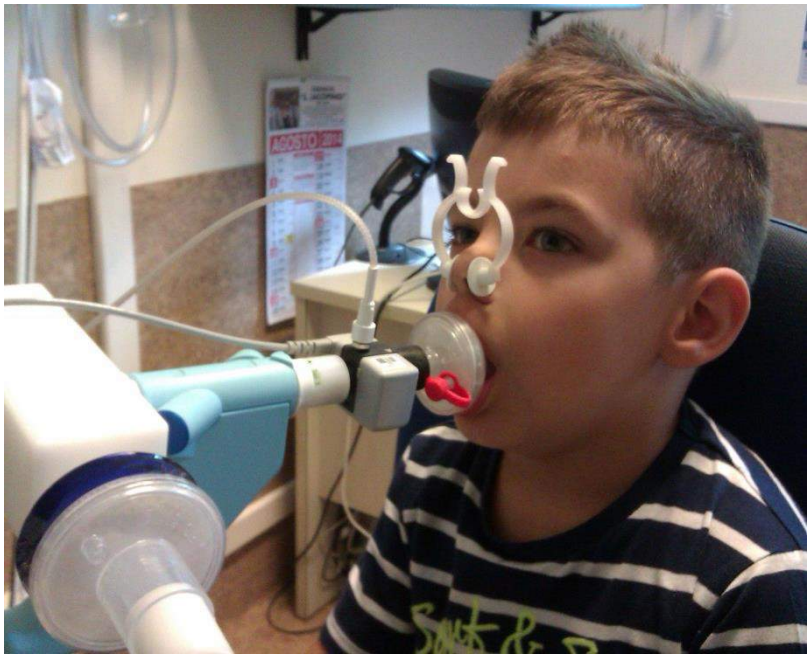
Subbarao P, et al. Ann ATS 2015;12:932-9
(reproduced with permission of the ATS)

MBW in Preschoolers

Simple to perform

- ERS/ATS “Consensus statement for inert gas washout measurements using multiple- and single- breath tests” Robinson P, et al. *ERJ* 2013;41:507-22
- A specific standardization project for MBW in infants and preschoolers is currently ongoing

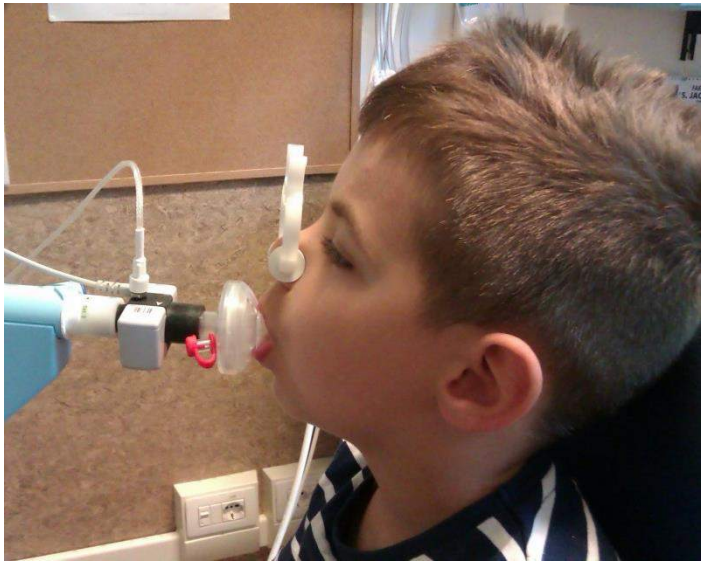
- Child seated, breathing at tidal volume through a mouthpiece or mask closely fitted to his/her face
- Washout should continue until end-tidal gas concentration is <1/40 of the initial concentration over >3 consecutive breaths
- The average value of LCI between two washouts where FRCs differ by less than 10% should be reported



Beydon N, et al. *AJRCCM* 2007;175:1304-45

MBW in Preschoolers
Feasibility, Repeatability & BDR

- The feasibility of measuring LCI is reported to range from 50% in 2-3 year olds to 87% in 5-6 year olds
  Aurora P, et al. *AJRCCM* 2005;171:249-56
- In 4-16 year olds, at least one LCI was feasible in 90% of children, while 2 or more measurements were feasible in 41% of children
  Singer F, et al. *Pediatr Pulmonol* 2013;48:739-46
- In preschoolers the within-test CV of LCI has been reported to be as good as 5.2% and long-term LCI repeatability is less than ±10% month to month
  Aurora P, et al. *AJRCCM* 2005;171:249-56
  Sonnappa S, et al. *ERJ* 2013;42:116-24
- BDR cut-offs are reported
  Sonnappa S, et al. *ERJ* 2013;42:116-24

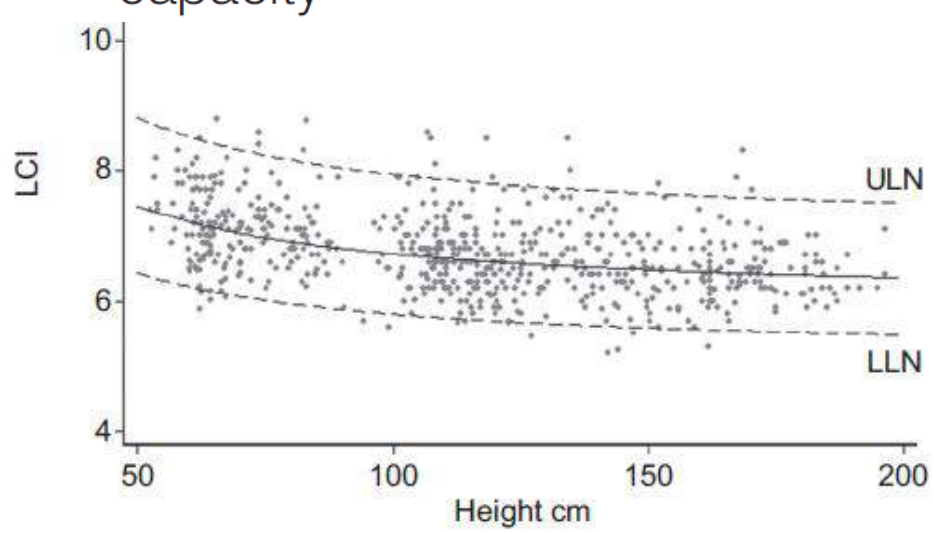


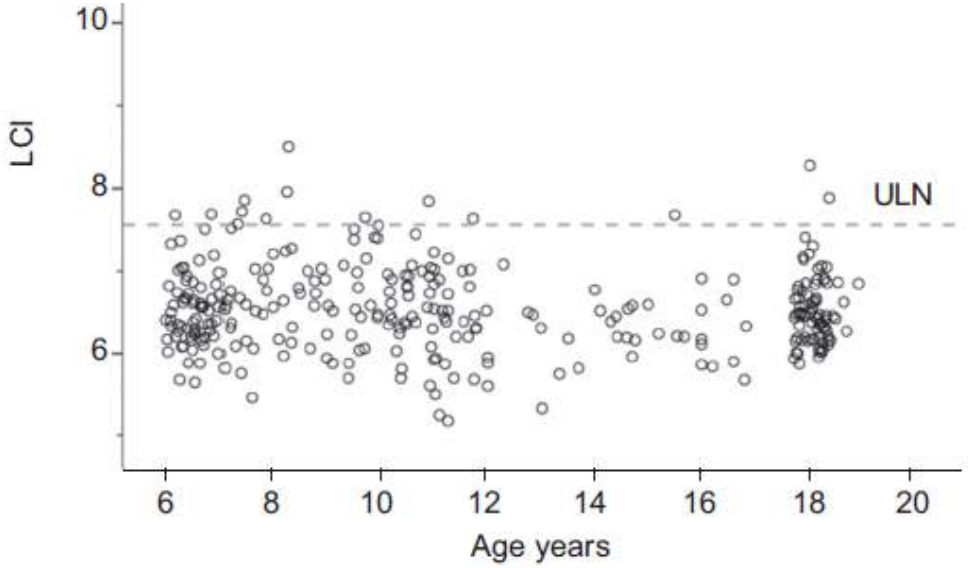
MBW in Preschoolers

Reference Values

Age and height dependence of lung clearance index and functional residual capacity

Lum S, et al. *ERJ* 2013;41:1371-7
(reproduced with permission of the ERS)





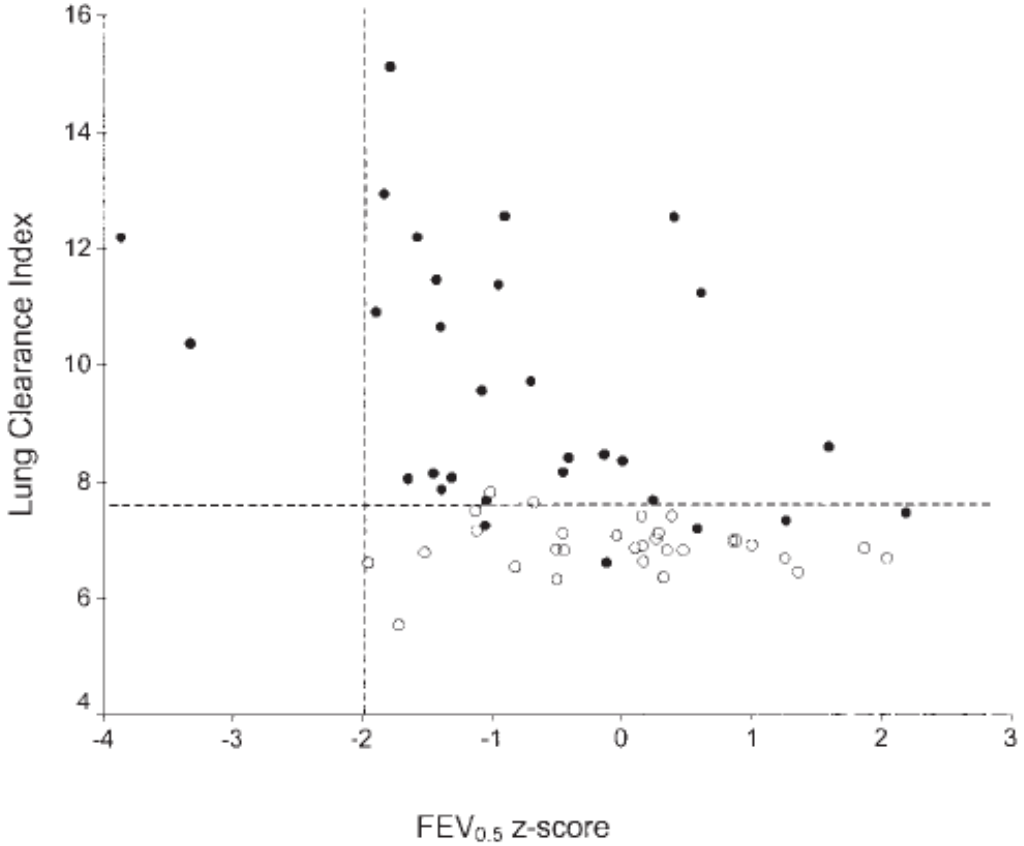
- **497 healthy subjects aged 2 wk to 19 yr**
- **3 centres (UK, Sweden, Canada)**
- **Mass spectrometer SF_6MBW**

FIGURE 2. Lung clearance index (LCI) plotted against age in subjects >6 years of age. When the analysis was limited to children >6 years, LCI was independent of both age and height, such that a constant upper limit of normal (ULN) of 7.56 could be used for cross-sectional assessments between 6 and 19 years of age.

MBW in Preschoolers

Clinical Applications

Multiple-Breath Washout as a Marker of Lung Disease in Preschool Children with Cystic Fibrosis



- 40 children with CF aged 2-5 yr
- 37 matched controls
- SF_6MBW + sRaw + spirometry

Aurora P, et al. *AJRCCM* 2005;171:249-56
(reproduced with permission of the ATS)

MBW in Preschoolers
Clinical Applications

- Increased LCI values are a consistently found in CF infants

  Lum S, et al. *Thorax* 2007;62:341-7

- In children with CF abnormal LCI values at 4 years are stronger predictors than spirometry of subsequent abnormal FEV_1 at school age

  Aurora P, et al. *AJRCCM* 2011;183:752-8

- One single-center study has shown the usefulness of LCI in detecting the long-term effects of hypertonic (7%) saline in 25 infants and preschoolers with CF

  Subbarao P, et al. *AJRCCM* 2013;188:456-60

- Increased LCI and convection-dependent (S_{cond}) inhomogeneity values have been reported in multiple-trigger wheeze compared with episodic (viral) wheeze and healthy control subjects

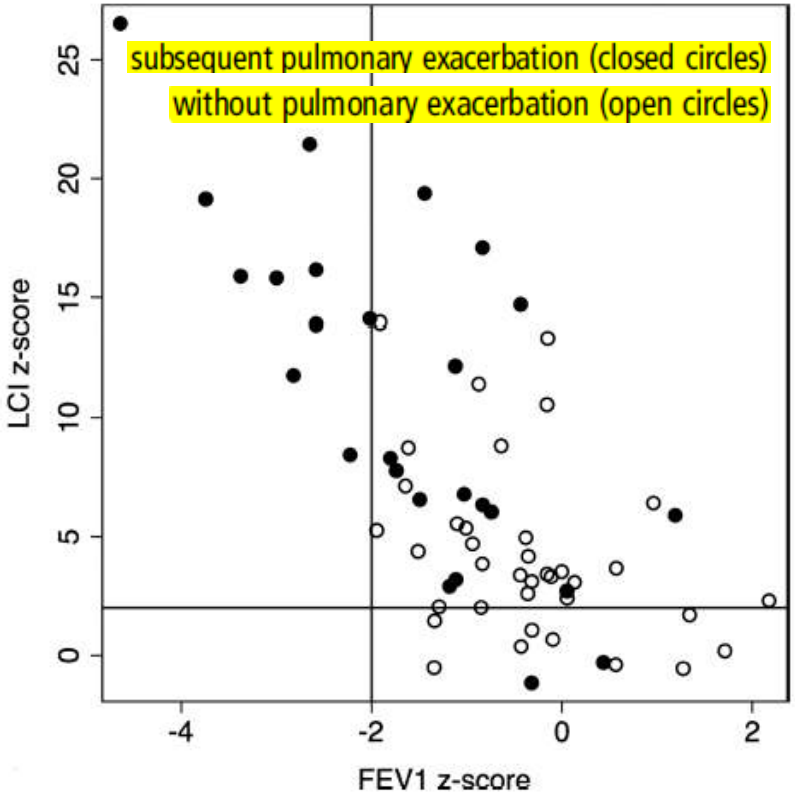
  Sonnappa S, et al. *JACI* 2010;126:519-26
  Sonnappa S, et al. *ERJ* 2011;38:1431-6

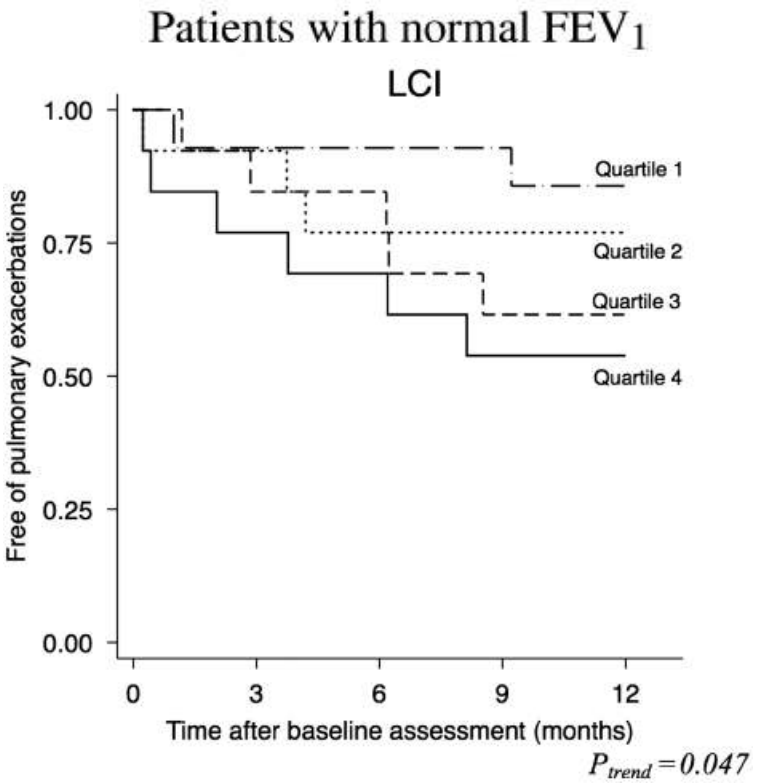
Lung clearance index predicts pulmonary exacerbations in young patients with cystic fibrosis

- 63 with CF (5.3-18.8 yr)
- 57 controls (4.4-17.9 yr)
- N_2MBW

What is the bottom line?

- In young patients with CF, baseline LCI predicts the time to the first pulmonary exacerbation in the 12 months after baseline assessment. The LCI also correlates with CFQ-R_{resp}, a validated patient-reported outcome.

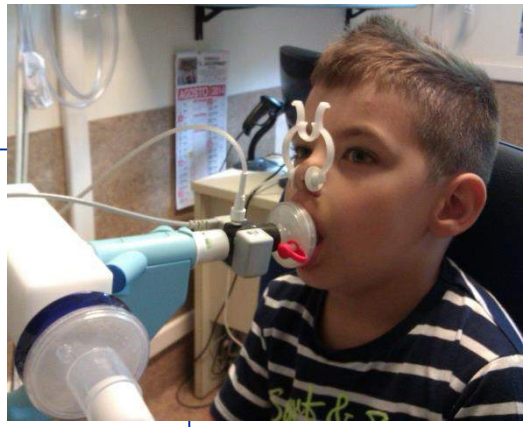




Vermeulen F, et al. *Thorax* 2014;69:39-45
(reproduced with permission from BMJ Publishing Group Ltd.)

MBW in Preschoolers

Conclusions



- The clinical utility of MBW is promising, but a number of challenges remain before the technique can be established in routine clinical care
- Nitrogen-based MBW is a feasible option, but modern data addressing the discrepancies of past studies, are needed
- Longitudinal trends need to be more clearly defined to establish clinically meaningful thresholds
- There are insufficient data to support the use of LCI or MBW parameters in the routine clinical management of patients with CF or asthma

Rosenfeld M, et al. Ann ATS 2013;10:S1-S11
Moeller A, et al. ERJ 2015;45:906-25
Subbarao P, et al. Ann ATS 2015

An Official American Thoracic Society Workshop Report: Optimal Lung Function Tests for Monitoring Cystic Fibrosis, Bronchopulmonary Dysplasia, and Recurrent Wheezing in Children Less Than 6 Years of Age

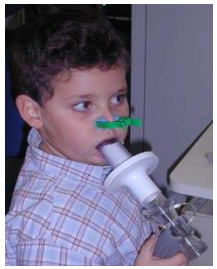
	Preschool Spiro	Preschool sRaw	Preschool Rint	Preschool FOT	MBW
Commercial equipment	Yes	Yes	Yes	Yes	Yes
Standard operating procedure	Yes	No	Yes	Yes	Yes
Safe	Yes	Yes	Yes	Yes	Yes
Feasible	Yes	Yes	Yes	Yes	Yes
Adequate population-based reference data	Yes‡	No	Yes‡	Yes‡	Yes‡
Within-test intrasubject variability measured	Yes	Yes	Yes	Yes	Yes
Discriminates disease population from healthy control subjects					
CF	Yes§	Yes	No	Conflicting	Yes
BPD	Unknown	Unknown	Unknown	Unknown	Probably not
Recurrent wheeze	Yes¶	Unknown	Yes¶	Unknown	Probably
Evidence for clinical utility	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed

Rosenfefeld M, et al. Ann ATS 2013;10:S1-S11
(reproduced with permission of the ATS)

Lung Function Tests in Preschool Children

Summary

- Preschool PFTs are
  - feasible
  - able to detect disease
  - useful in clinical and epidemiological studies
- More studies are needed to establish their long term clinical utility



Spirometry

R_{int}

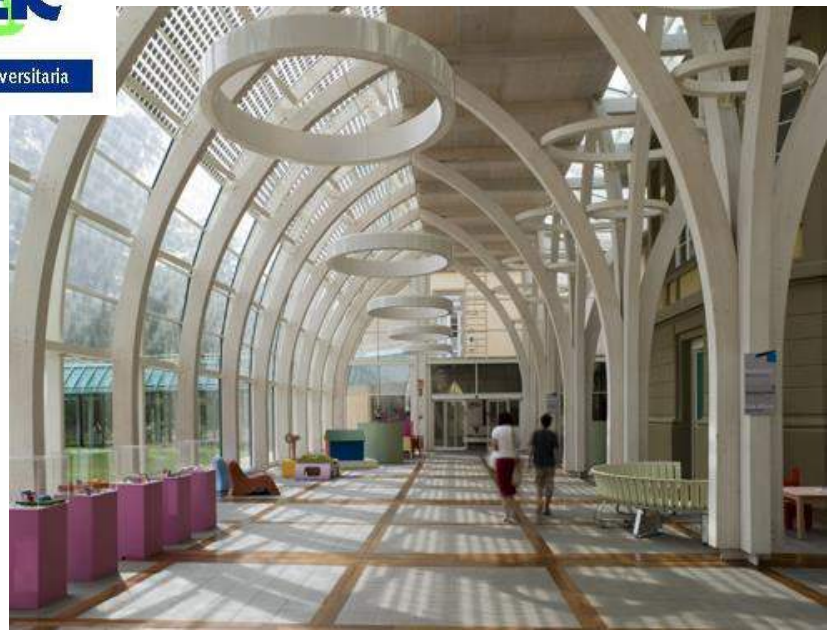
FOT

sRaw

MBW

MEYER

Azienda Ospedaliero-Universitaria



Additional course resources

Readings and guidelines

Respiratory mechanics: changes in disease

1. Dominelli PB, Sheel AW. Experimental approaches to the study of the mechanics of breathing during exercise. Respir Physiol Neurobiol 180:147-161, 2012.
2. O'Donnell DE, Ofir D, Laveneziana P. Patterns of cardiopulmonary response to exercise in lung diseases. In: Ward SA, Palange P, eds. Clinical Exercise Testing. European Respiratory Monograph, vol 12, no 40, Ch 3, pp 69-92, 2007.
3. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. Interpretative strategies for lung function tests. Eur Respir J 26:948-968, 2005

Measuring dyspnoea in health and disease

4. Lansing RW, Gracely RH, Banzett RB. The multiple dimensions of dyspnea: review and hypotheses. Respir Physiol Neurobiol 30: 167:53-60, 2009.
5. Laviolette L, Laveneziana P. ERS Research Seminar Faculty. Dyspnoea: a multidimensional and multidisciplinary approach. Eur Respir J 43:1750-1762, 2014.
6. Ries AL. Minimally clinically important difference for the UCSD Shortness of Breath Questionnaire, Borg Scale, and Visual Analog Scale. COPD 2:105-110, 2005.

Exercise testing to evaluate muscle strength/endurance and pulmonary rehabilitation

7. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, Pitta F, Sewell L, Raskin J, Bourbeau J, Crouch R, Franssen FM, Casaburi R, Vercoulen JH, Vogiatzis I, Gosselink R, Clini EM, Effing TW, Maltais F, van der Palen J, Troosters T, Janssen DJ, Collins E, Garcia-Aymerich J, Brooks D, Fahy BF, Puhan MA, Hoogendoorn M, Garrod R, Schols AM, Carlin B, Benzo R, Meek P, Morgan M, Rutten-van Mölken MP, Ries AL, Make B, Goldstein RS, Dowson CA, Brozek JL, Donner CF, Wouters EF; ATS/ERS Task Force on Pulmonary Rehabilitation. Am J Respir Crit Care Med 188:e13-e64, 2013
8. Gosselink, R, Troosters, T, Langer D, Decramer M. Laboratory tests. In: Ward SA, Palange P, eds. Clinical Exercise Testing. European Respiratory Monograph, vol 12, no 40, Ch 6, pp 129-147, 2007.

Lung function tests in preschool children

9. American Thoracic Society/European Respiratory Society statement: Pulmonary function testing in preschool children. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, Bisgaard H, Davis GM, Ducharme FM, Eigen H, Gappa M, Gaultier C, Gustafsson PM, Hall GL, Hantos Z, Healy MJ, Jones MH, Klug B, Lødrup Carlsen KC, McKenzie SA, Marchal F, Mayer OH, Merkus PJ, Morris MG, Oostveen E, Pillow JJ, Seddon PC, Silverman M, Sly PD, Stocks J, Tepper RS, Vilozni D, Wilson NM; American Thoracic Society/European Respiratory Society Working Group on Infant and Young Children Pulmonary Function Testing. Am J Respir Crit Care Med 175:1304-1345, 2007
10. Moeller A, Carlsen KH, Sly PD, Baraldi E, Piacentini G, Pavord I, Lex C, Saglani S. ERS Task Force Monitoring Asthma in Children. Monitoring asthma in childhood: lung function, bronchial responsiveness and inflammation. Eur Respir Rev 24(136):204-215, 2015.

Faculty disclosures

Prof. Denis O'Donnell has served on speaker's bureaus, consultation panels and advisory boards for AZ, BI, GSK and Novartis. He has received also research funding support from AZ, BI, GSK, Novartis.

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Answers to evaluation questions

*Please find all correct answers in **bold** below*

Respiratory mechanics: changes in disease - Dr. Pierantonio Laveneziana

1. Dynamic lung hyperinflation is defined as:
   a. A. an increase in expiratory reserve volume
   b. a temporary and variable increase in end-inspiratory lung volume (EILV) beyond its baseline value
   c. a temporary and variable increase in end-expiratory lung volume (EELV) beyond its baseline value
   d. a plateau in tidal volume (VT) response

2. The neuroventilatory dissociation (NVD) influences dyspnoea mostly in:
   a. healthy subjects
   b. patients with respiratory disorders
   c. both
   d. neither

3. Exertional dyspnoea in COPD strictly correlates with:
   a. decrease in FEV1
   b. increase in dynamic lung hyperinflation and constraints in VT expansion
   c. both
   d. neither

4. Perception of exertional dyspnoea in COPD is principally associated with:
   a. increased work/effort
   b. unsatisfied inspiration
   c. both
   d. neither

5. The intensity of dyspnoea in patients with weak respiratory muscles is:
   a. greater than in healthy
   b. lower than in healthy
   c. as much as in healthy

Measurement of Dyspnoea in Health and Disease - Dr Denis O'Donnell

1. The following statements are true except:
   Compared with healthy individuals, activity-related dyspnoea in patients with lung diseases is:
   a. Qualitatively different
   b. Similar during walking and cycling when the increase in work rate is matched
   c. Associated with lower inspiratory neural drive to the diaphragm
   d. Often the dominant exercise-limiting symptom

2. The following statements on dyspnoea measurement are true except:
   a. The Borg scale is superior to visual analogue scales (VAS) for the purpose of measuring dyspnoea intensity during a standardized stimulus
   b. The Medical Research Council (MRC) dyspnoea scale is sensitive for the evaluation of bronchodilator efficacy
   c. The minimal clinically important difference for the Transition Dyspnoea Index (TDI) is 1 unit
   d. Constant work rate endurance tests are superior to incremental tests for the evaluation of improved exercise tolerance during dyspnoea-relieving interventions

3. The following statements on dyspnoea are true except:
   a. The 2012 ATS statement recommends that dyspnoea be assessed across sensory intensity, quality, affective and impact domains
   b. Affective responses to respiratory discomfort are associated with decreased activation of the bulbo-pontine structures of the brain on functional Magnetic Resonance Imaging
   c. Qualitative descriptors of dyspnoea alluding to the sense of increased "work or effort" are common to health and disease
   d. Increased perceived expiratory difficulty is an uncommon qualitative descriptor choice of patients with chronic airway obstruction during exercise

Exercise testing for the evaluation of muscle strength/endurance and pulmonary rehabilitation - Prof. Dr Rik.Gosselink

1. Limb muscle weakness is present in
   a. Only patients with COPD GOLD stage 3 and 4
   b. All COPD GOLD stages
   c. Mainly in COPD GOLD stage 4
   d. COPD patients on supplemental oxygen

2. Assessment of limb muscle strength is applicable (more answers might be correct)
   a. Only in hospitals with research facilities
   b. In exercise physiology laboratories
   c. In outpatient clinics
   d. In primary care settings

3. The diagnosis of limb muscle weakness has clinical implication for (more answers might be correct):
   a. The content of the rehabilitation program
   b. Prognosis
   c. Identification of the severity of airflow obstruction
   d. The start of non invasive ventilation

Lung function tests in preschool children - Dr Enrico Lombardi

1. The most useful index for spirometry in a 3 year old child is:
   a. FEV1
   b. FEV0.75
   c. FVC
   d. FEF25-75

2. The feasibility of the interrupter technique (Rint) and the forced oscillation technique (FOT) in 3 to 5 year old children is:
   a. 40%
   b. 60%
   c. 80%
   d. 100%

3. The interrupter resistance (R_{int}) reflects the resistance of:
   a. peripheral airways
   b. total airways
   c. chest wall
   d. respiratory system

4. Resistance measured at 8 Hz (Rrs8) with the forced oscillation technique (FOT) reflects the resistance of:
   a. peripheral airways
   b. total airways
   c. chest wall
   d. respiratory system

5. Which ONE among the following statements on lung function tests in preschool children is TRUE?
   a. they only require "passive collaboration" with no sedation
   b. performing spirometry is not possible below age 6
   c. reference values are not available for most techniques
   d. information on repeatability is not available for Rint and FOT