From Expiratory Flow Limitation to Hyperinflation: the central point in COPD

Symptoms, signs, causes, measurement, and treatment

26ο Πανελλήνιο
ΠΝΕΥΜΟΝΟΛΟΓΙΚΟ ΣΥΝΕΔΡΙΟ
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ΕΛΛΗΝΙΚΗ ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
HELLENIC THORACIC SOCIETY

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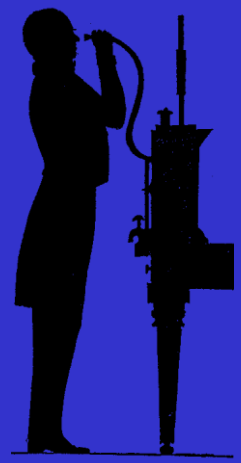
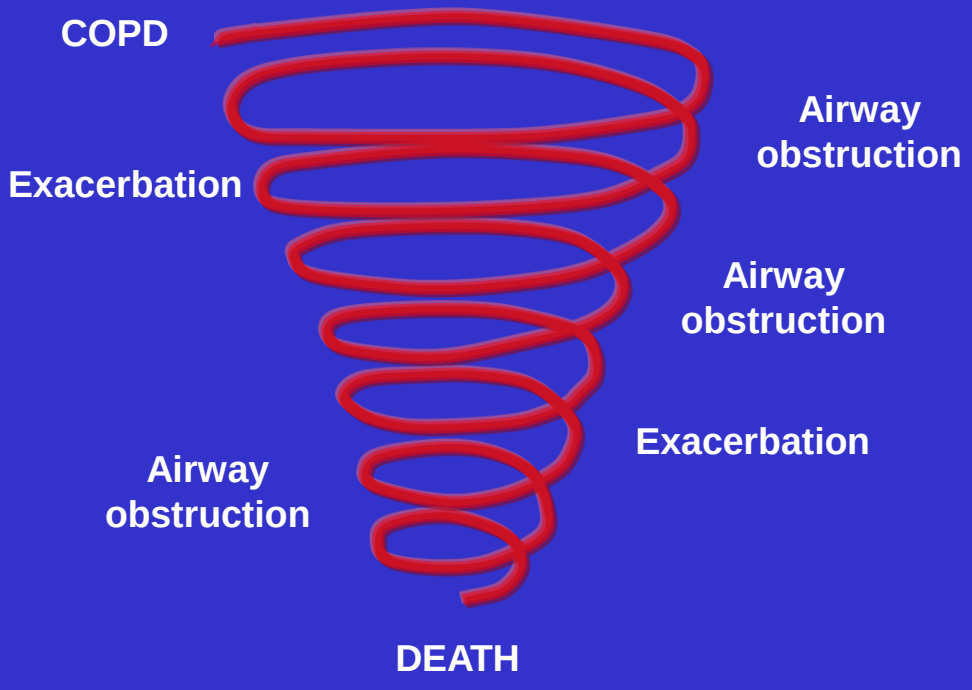
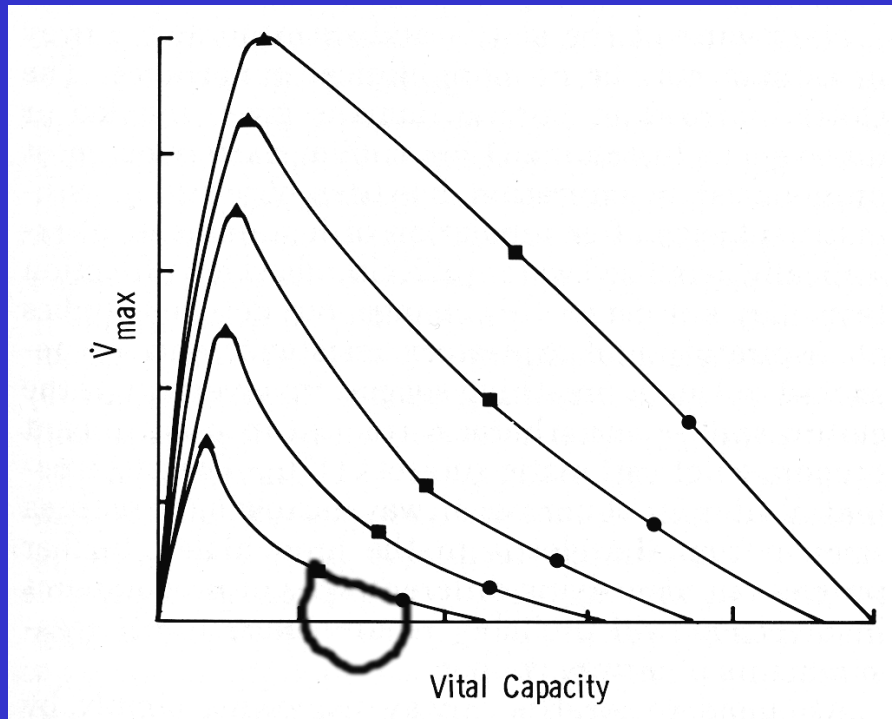


Chronic airflow limitation indicates the reduction in maximum expiratory flow that progressively occurs in COPD and in other pulmonary diseases

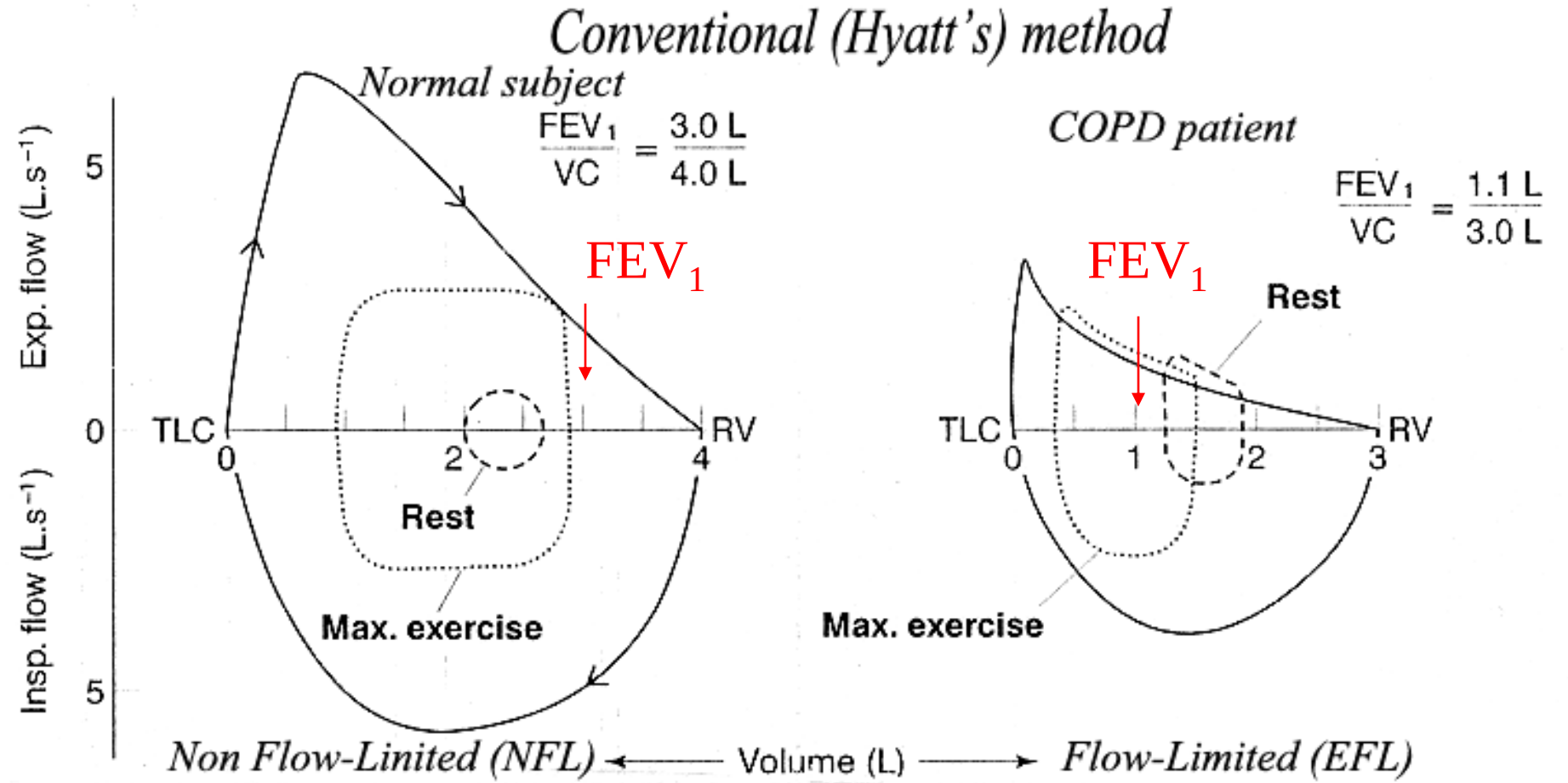
Expiratory flow limitation (EFL) indicates that maximal expiratory flow is achieved during tidal breathing and is characteristic of intra-thoracic airflow obstruction (dynamic airway compression)

Pride NB. In: Hughes & Pride (eds). Lung Function Tests. London WB Saunders, 1999





Conventional (Hyatt's) method of detecting Expiratory Flow Limitation



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Significance of expiratory flow limitation during tidal breathing

1. Promotes lung damage
2. Promotes dynamic hyperinflation

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An attractive and provocative hypothesis

proposed by J Milic-Emili

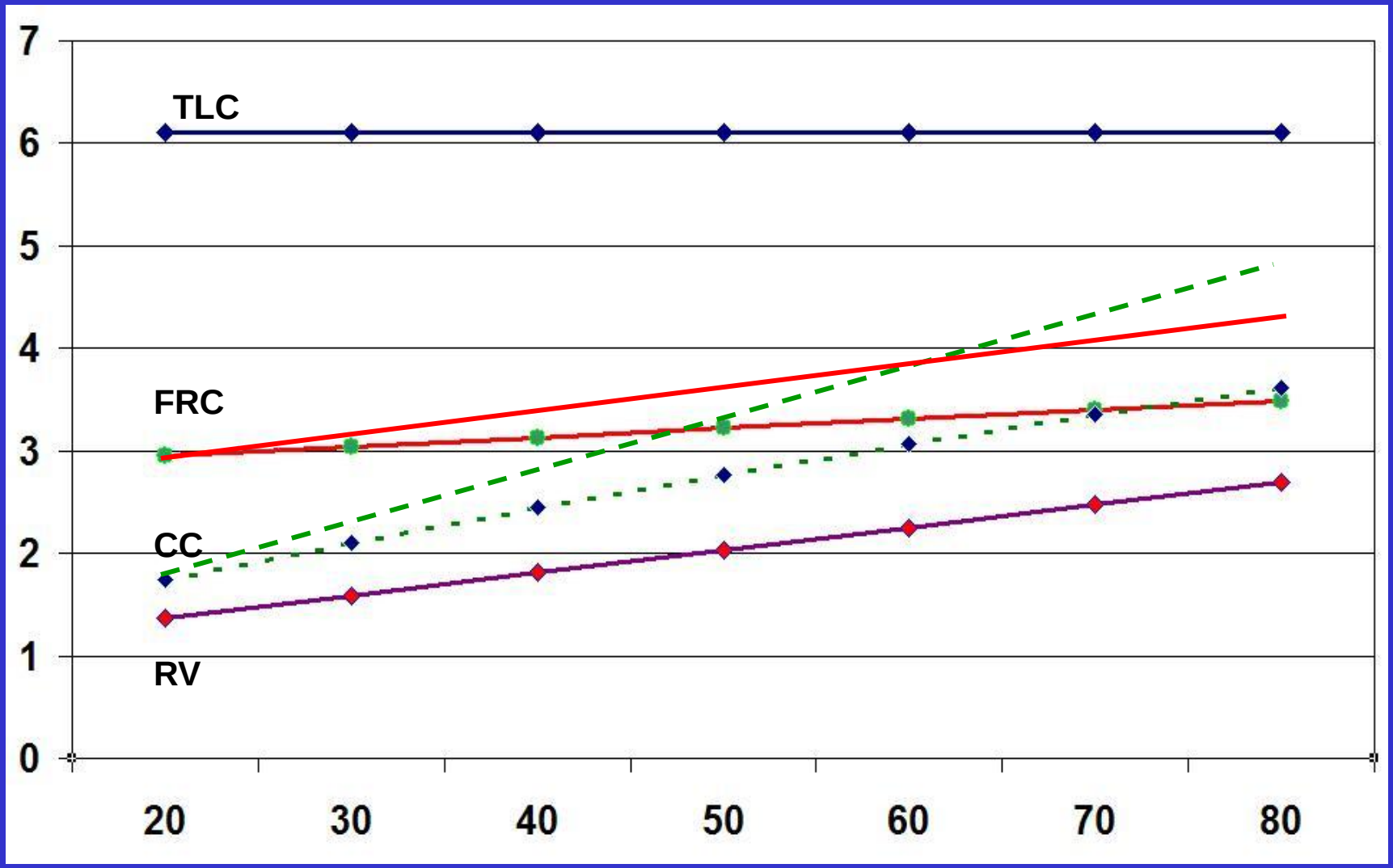
In smokers who are destined to develop COPD the transition from peripheral airway disease to overt COPD is characterized by three sequential stages in which EFL plays a central role:

Stage I, during which the closing volume (CV) eventually exceeds the functional residual capacity;

Stage II, during which EFL first develops; This implies sequential dynamic heterogeneous compression of the peripheral airways during expiration and re-expansion during inspiration

Stage III, during which dynamic hyperinflation (DH) progressively increases leading to dyspnoea and exercise limitation.

Male, 170 cm high



Tidal Airway Closure

Tidal airway closure (ACT), which is present when the closing capacity (CC) exceeds the end-expiratory lung volume (EELV), leads to impaired gas exchange and risk of peripheral airway injury in the lung.

An attractive and provocative hypothesis

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In smokers who are destined to develop COPD the transition from peripheral airway disease to overt COPD is characterized by three sequential stages in which EFL plays a central role:

Stage I, during which the closing volume (CV) eventually exceeds the functional residual capacity;

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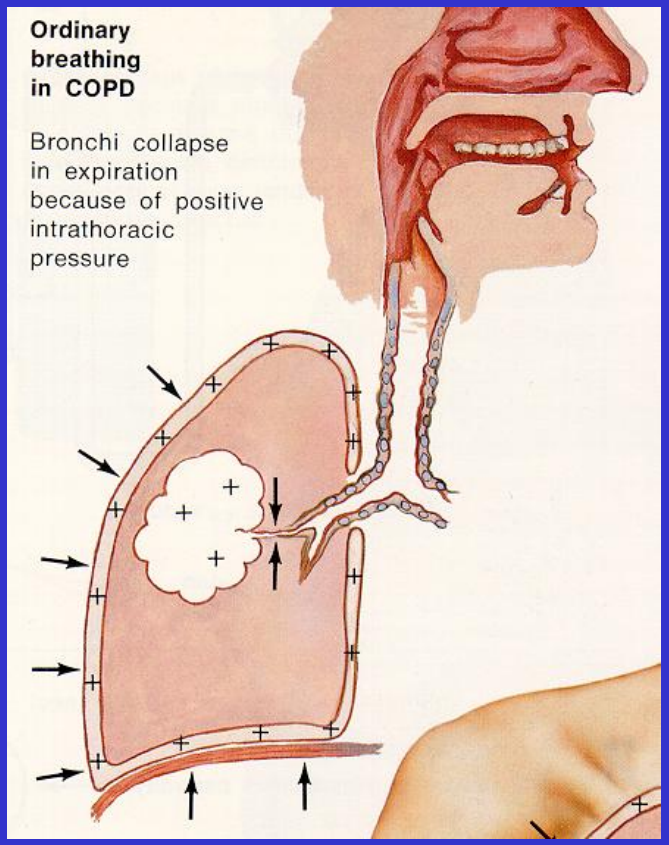
Stage III, during which dynamic hyperinflation (DH) progressively increases leading to dyspnoea and exercise limitation.

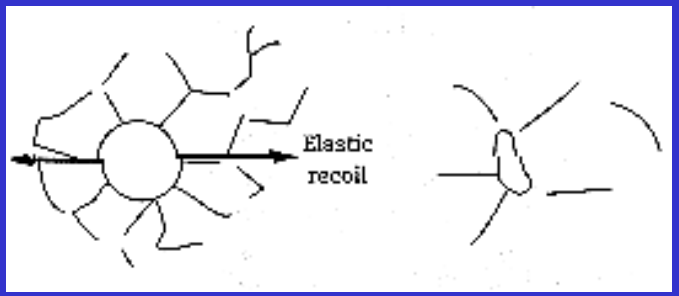
The presence of airway closure (*Stage I*), and EFL (*Stage II*) in the tidal volume range may promote peripheral airway injury and accelerate the abnormalities of lung function. This enhances inflammation due to smoke *per se*, leading to severe functional and structural abnormalities within the lung. This vicious cycle cannot be reversed, possibly apart from *Stage I*.

Milic-Emili J. Provocative hypothesis; Does mechanical injury of the peripheral airways play a role in the genesis of COPD in smokers? COPD 2004; 1: 1-8.

Milic-Emili J, Pecchiari M, D'Angelo E. Pathophysiology of chronic obstructive pulmonary disease. Current Respiratory Medicine Reviews, 2008; 4: 250-257.

Gennimata SA, Milic-Emili J, Palamidas AF, Karakontaki F, Kosmas EN, Koutsoukou A, Loukides S, Koulouris NG. Evolution of peripheral airways disease (PAD) to overt chronic obstructive pulmonary disease. COPD 2010; 7: 269-275.





Dynamic compression of the airways or flow-limitation during tidal expiration (EFL) is a factor that causes peripheral airway and parenchymal injury.

- necrosis and sloughing of bronchiolar epithelia
- rupture the alveolar-bronchiolar attachments,
- increased number of polymorphonuclear leukocytes (presence of parenchymal inflammation).

D'Angelo et al. Low volume ventilation induces peripheral airways injury and increased airway resistance in normal open chest rabbits. J Appl Physiol 2002; 92: 949-956.

D'Angelo et al. The fall in exhaled nitric oxide with ventilation at low lung volumes in rabbits. An index of small airway injury. Respir Physiol Neurobiol 2008; 160: 215-223

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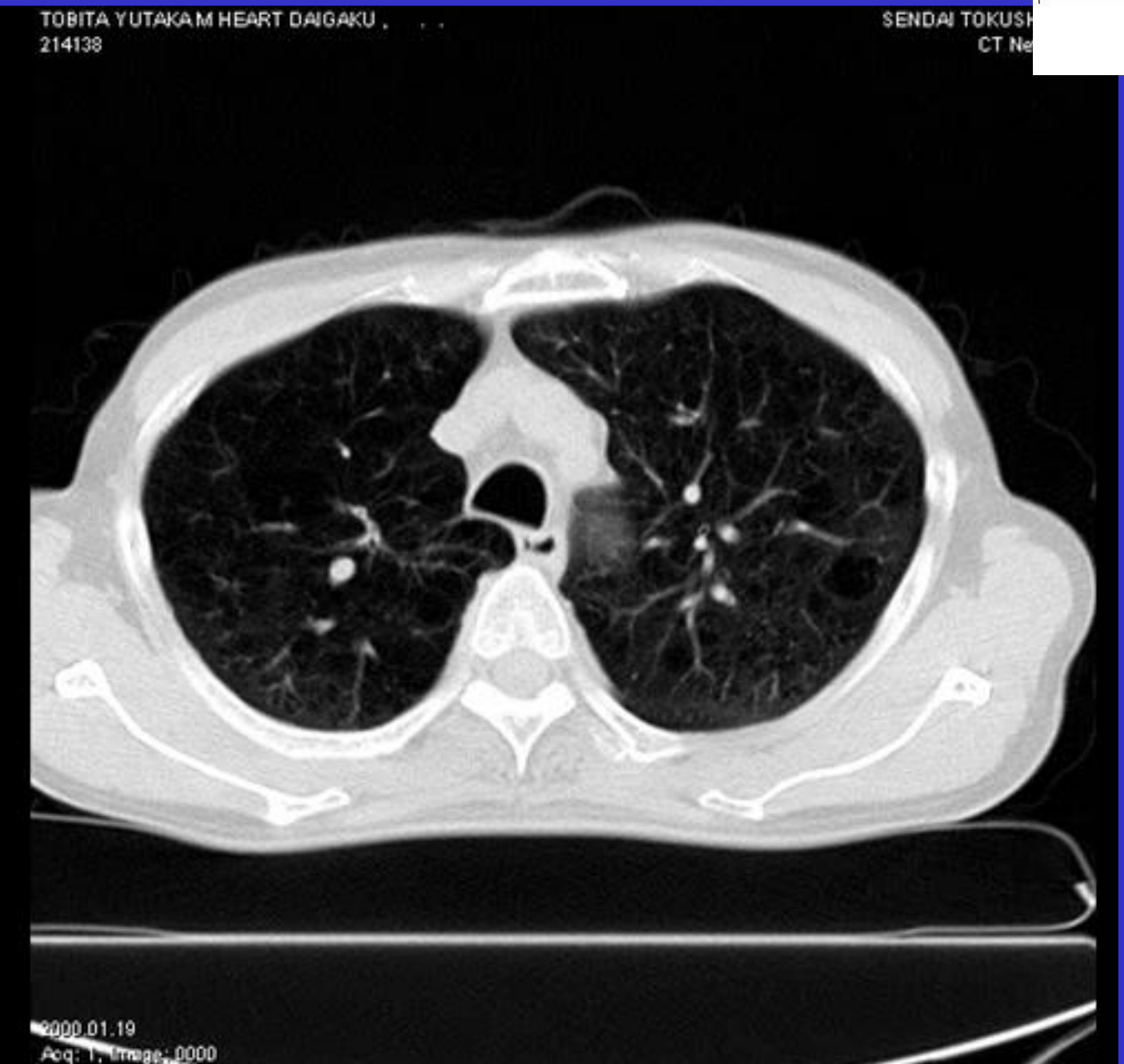
IMAGES IN CLINICAL MEDICINE

Dynamic Airway Narrowing



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Significance of expiratory flow limitation during tidal breathing

1. Promotes lung damage
2. Promotes dynamic hyperinflation

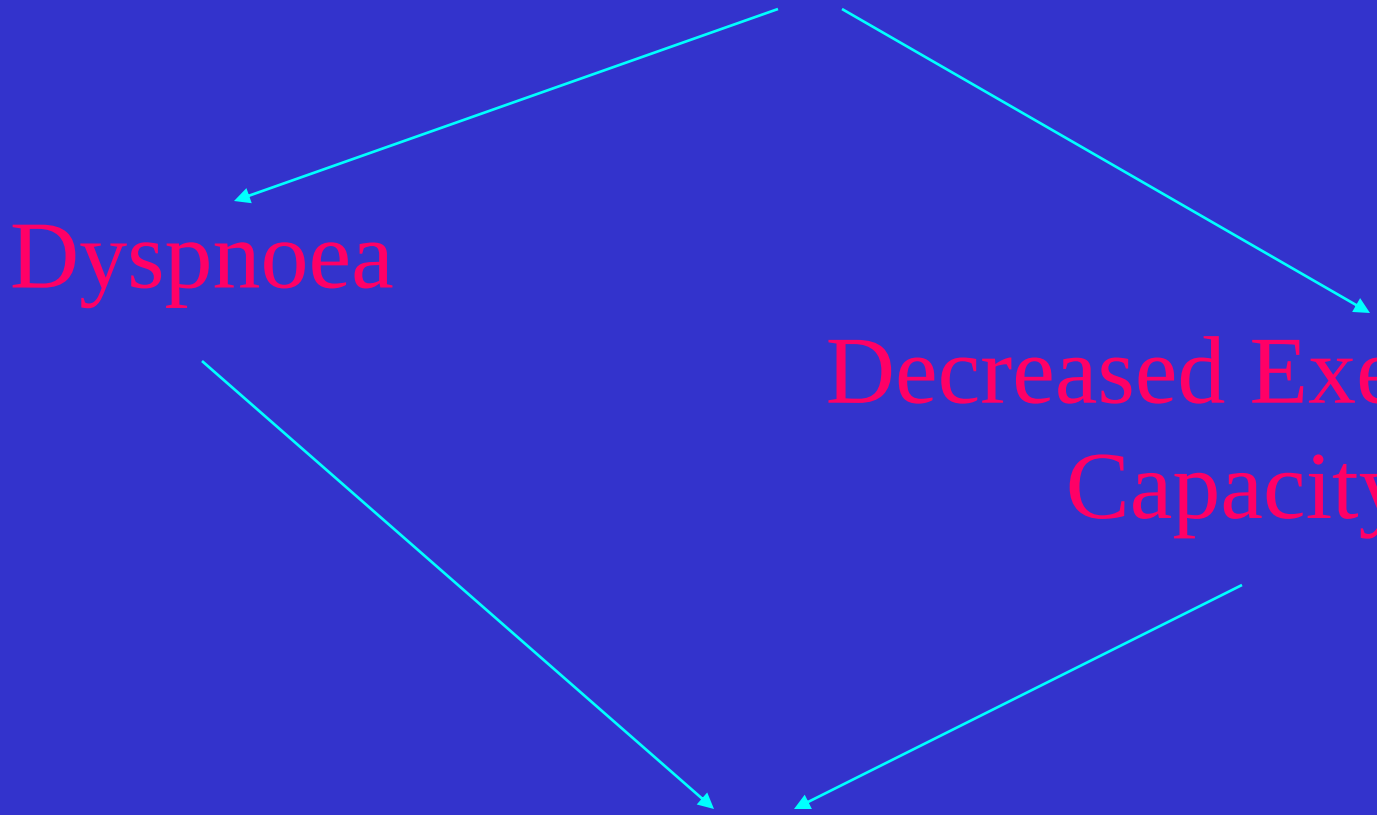
Hyperinflation

Old concept but with new implications for lung pathophysiology

Hyperinflation in COPD is not a new idea. In 1837, the Irish physician William Stokes, whose name is given to Stokes–Adams attack and Cheyne–Stokes respiration, published a textbook entitled “A Treatise on the Diagnosis and Treatment of Diseases of the Chest”

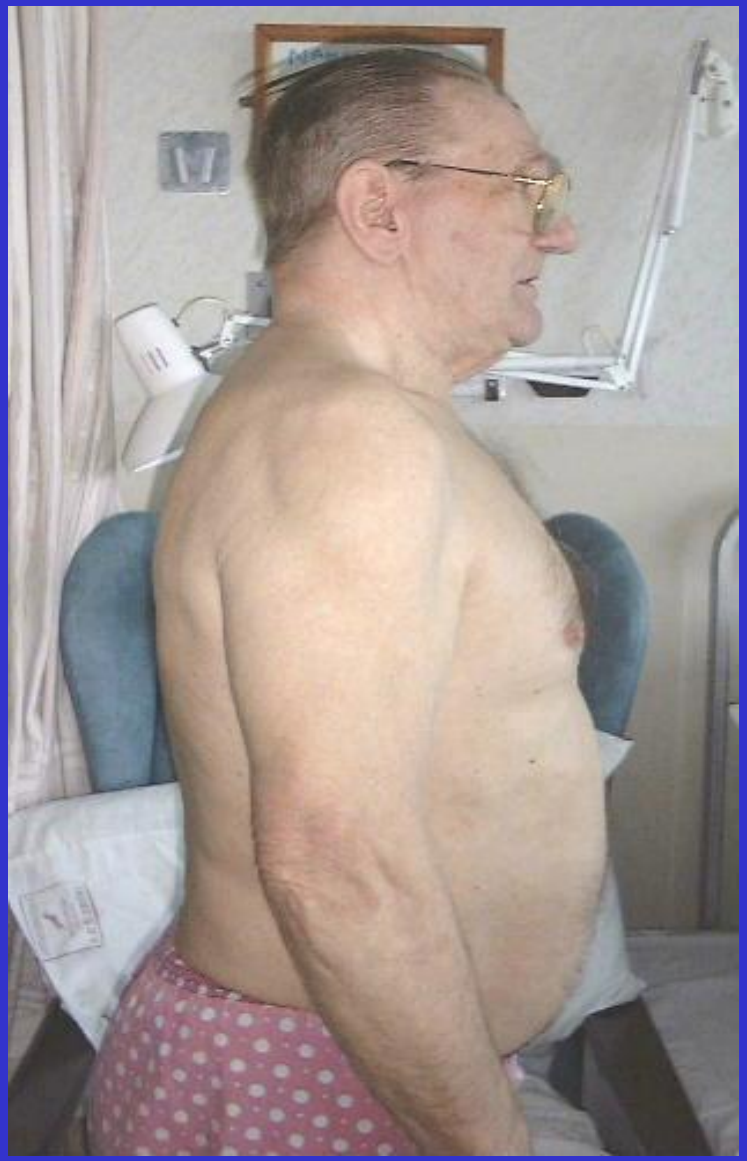
Stokes W. A treatise on the diagnosis and treatment of diseases of the chest. Part 1. Diseases of the lung and windpipe. London: The New Sydenham Society; 1837. pp. 168–169.

HYPERINFLATION



Main Symptoms of COPD Patients

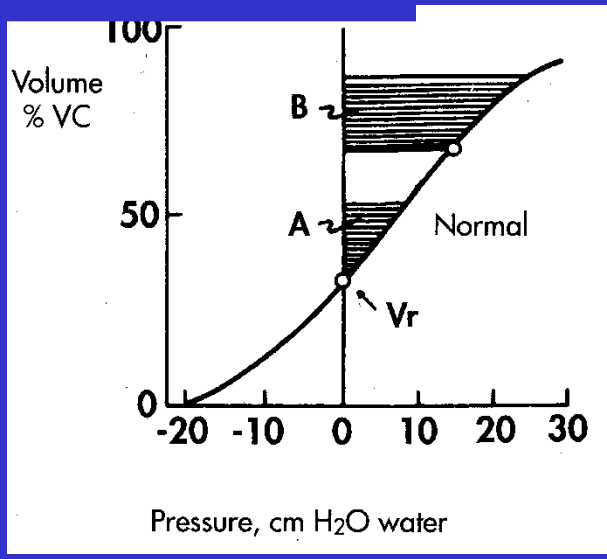
Hyperinflation

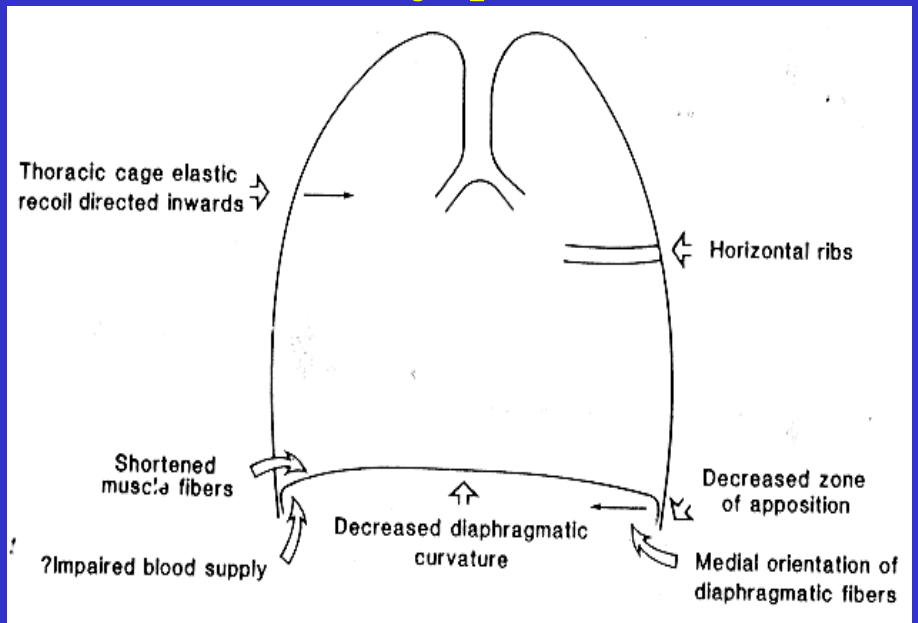


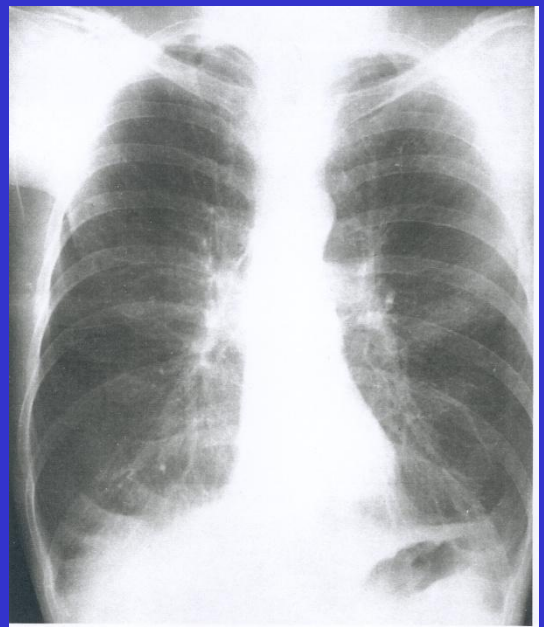
- *Increase in antero-posterior diameter (barrel-chest)*
- *Movements of the chest wall are symmetrically reduced, especially during expiration.*
- *Hyperresonant percussion note*
- *Reduced vesicular sounds*

Significance of expiratory flow limitation during tidal breathing

1. Promotes lung damage
2. Promotes dynamic hyperinflation
   - Impairs inspiratory muscle function
   - Increases work of breathing
   - Promotes PEEPi
   - Adversely affects haemodynamics
   - Contributes to dyspnoea



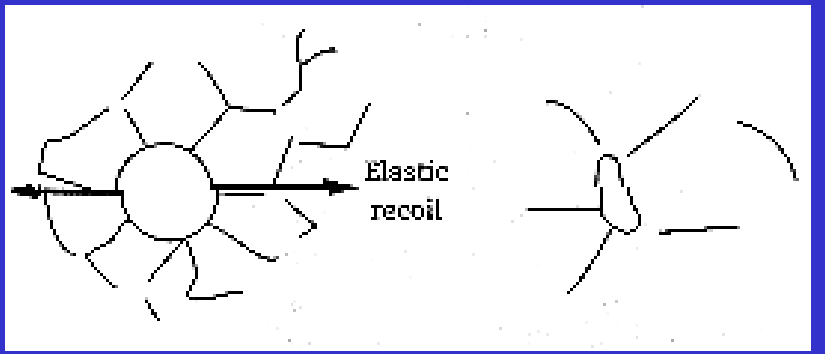


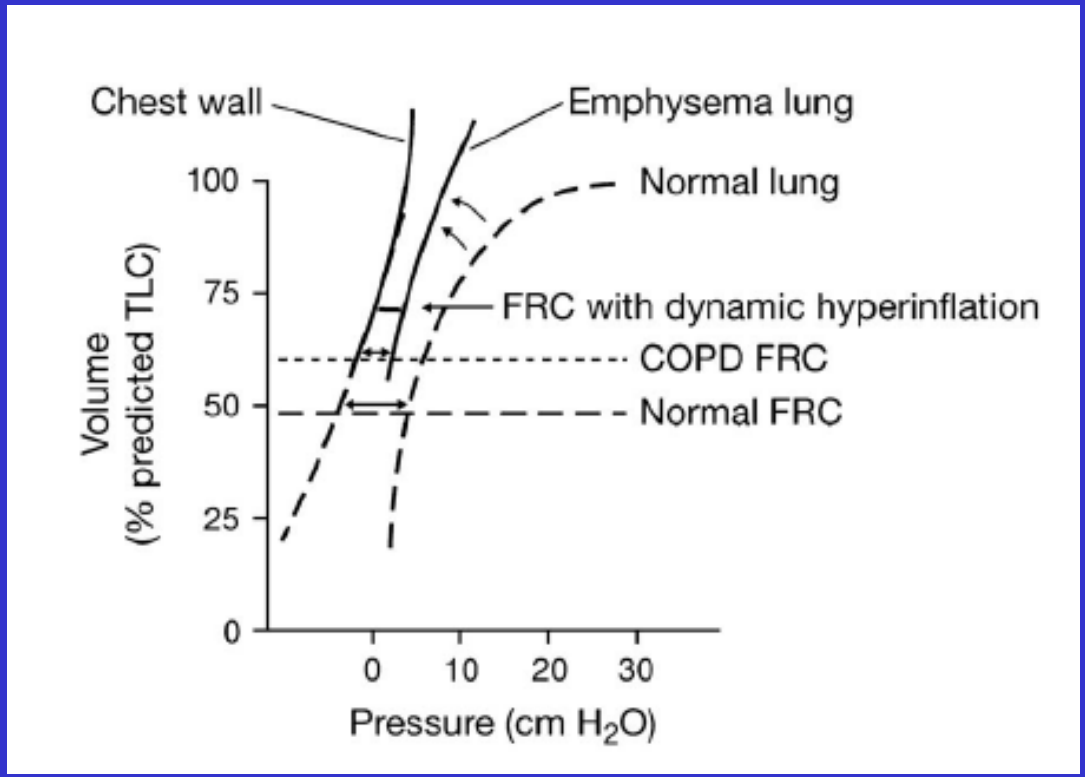


HYPERINFLATION

***Hyperinflation** of the lung is defined in various ways, but is commonly considered to be an elevation above normal of the resting FRC or EELV or Vr (relaxation volume). **Static Hyperinflation** results from destruction of elastic tissue associated with emphysema, which alters lung recoil (It is usually a modest contributor of total hyperinflation).*

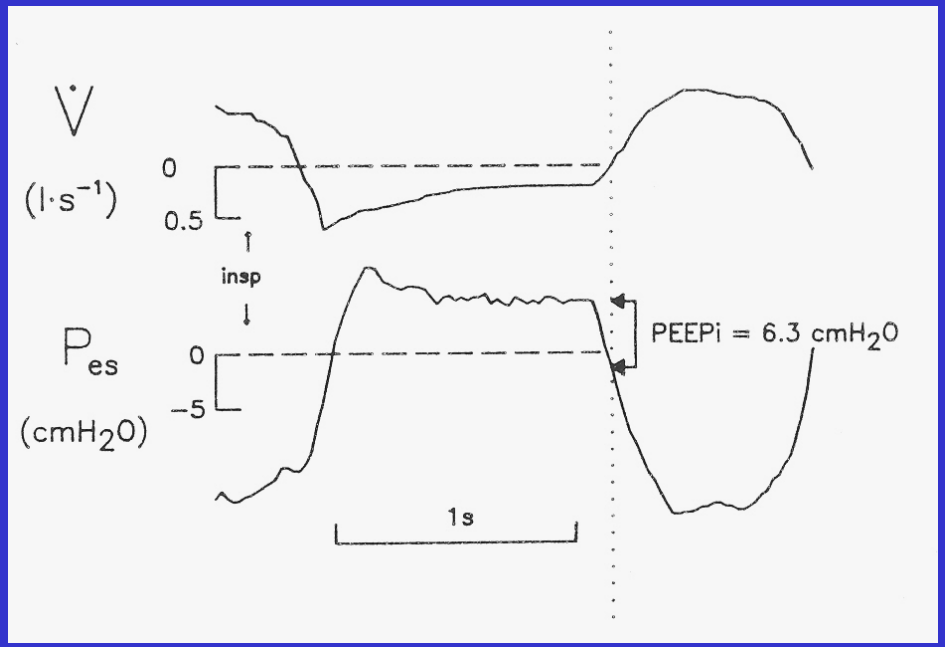
Ferguson GT. Proc Am Thorac Soc 2006; 3: 176-179

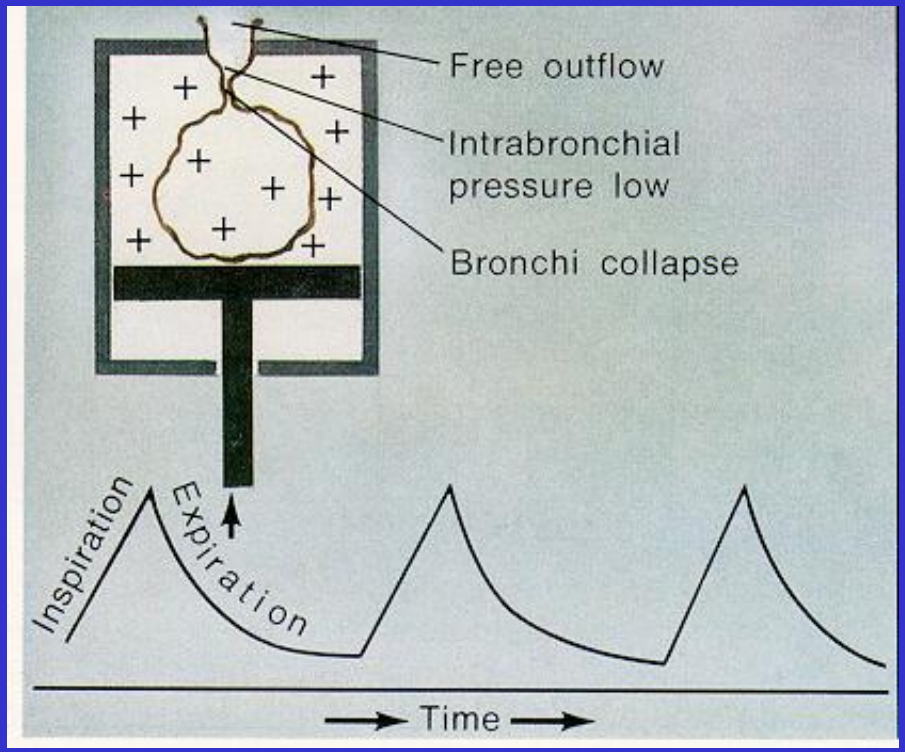




Dynamic hyperinflation occurs when patients commence inhalation before full exhalation has been achieved.

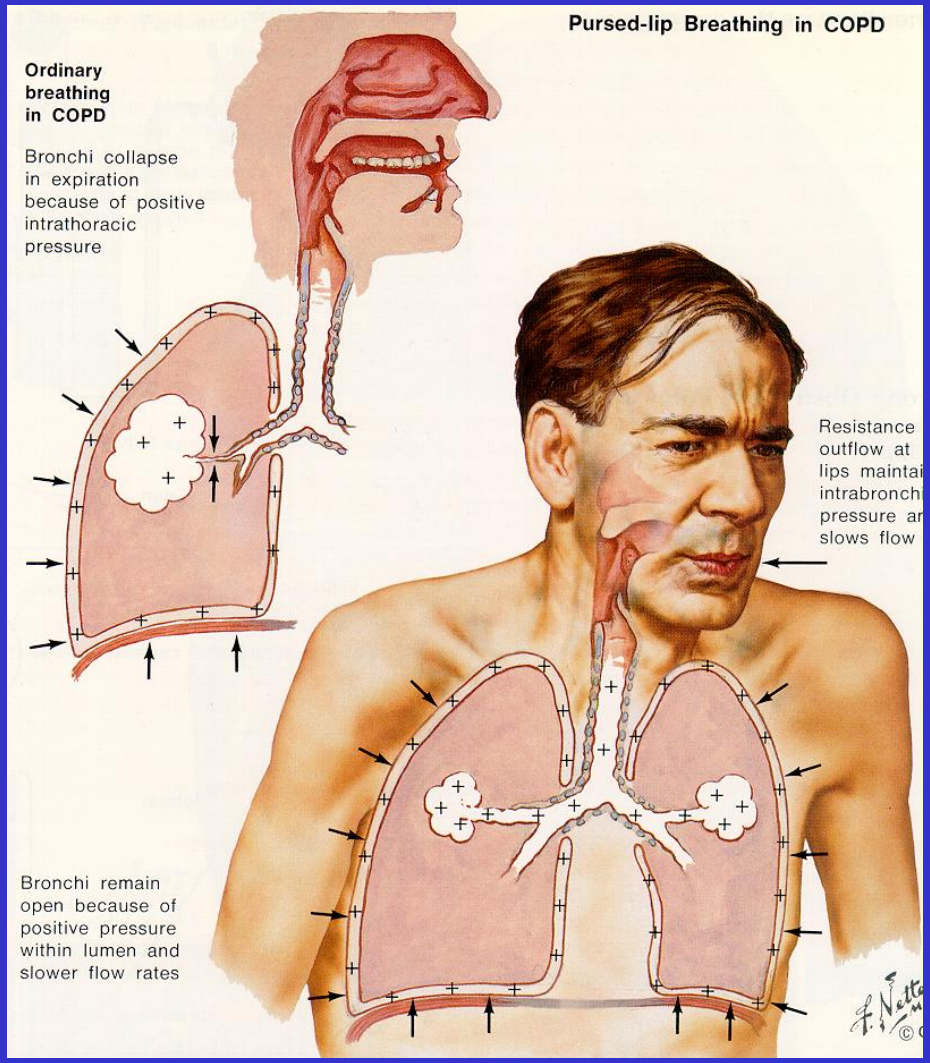
Haluszka et al. Am Rev Respir Dis 1990; 141: 1194-1197

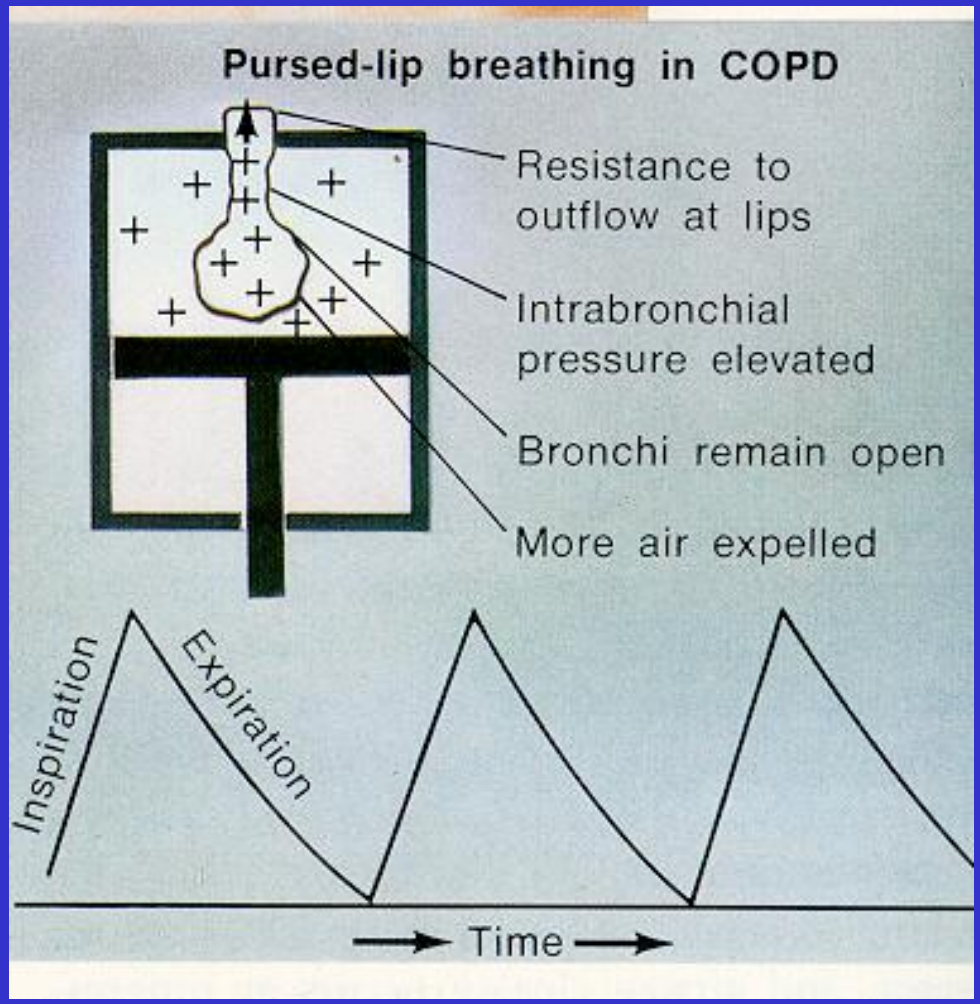




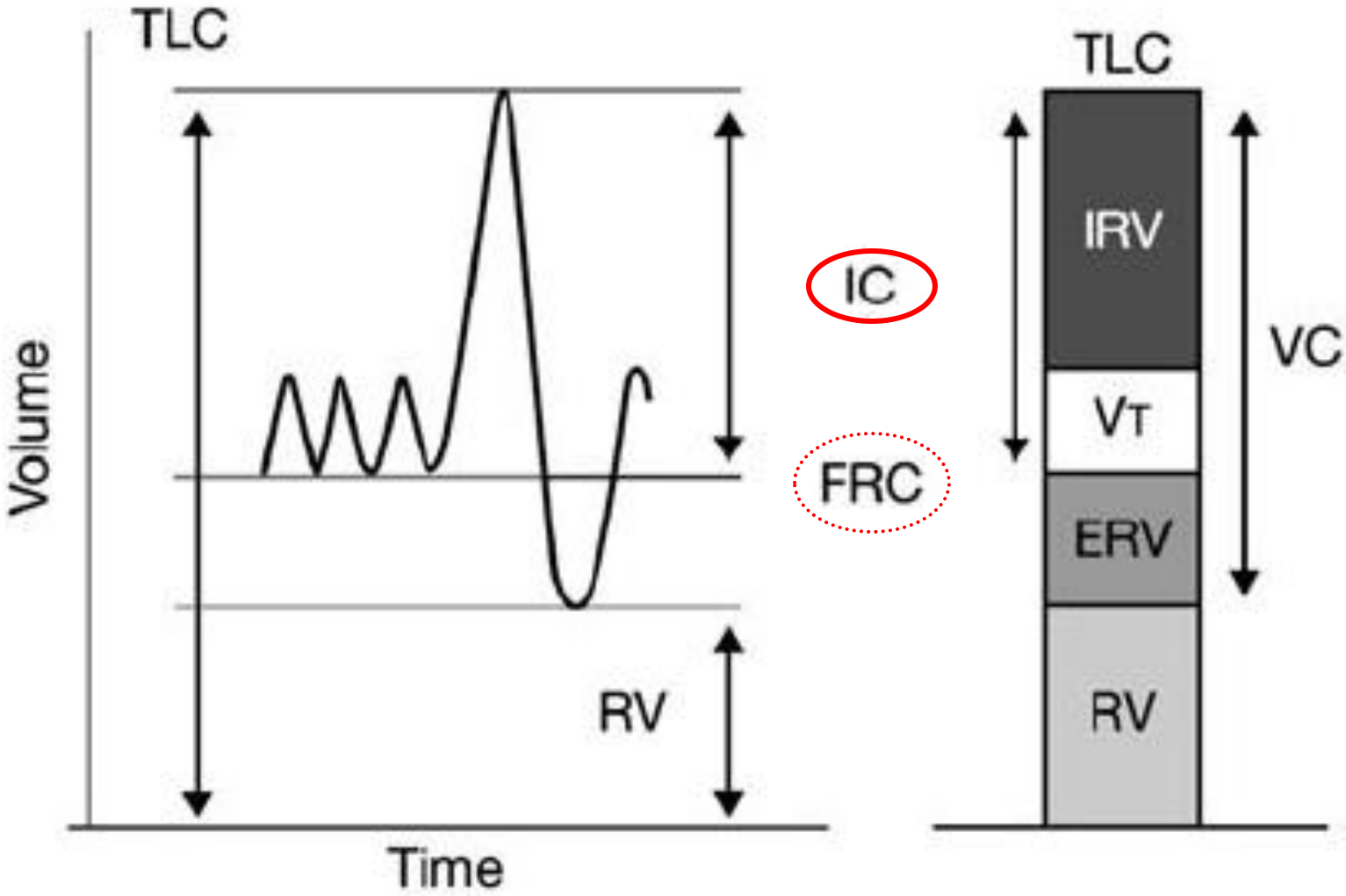
Dynamic Compression of the Airways≈Hyperinflation≈Peepi

Pursed-lip breathing in COPD





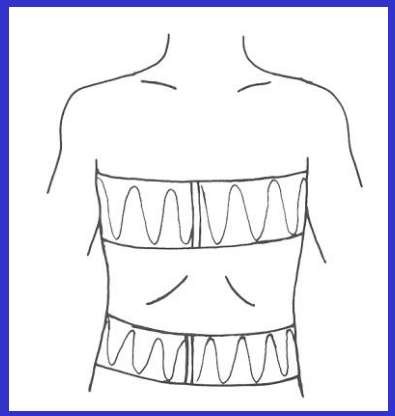
Measurement of Hyperinflation I



Ferguson GT. Proc Am Thorac Soc 2006; 3: 176-179

Measurement of Hyperinflation II

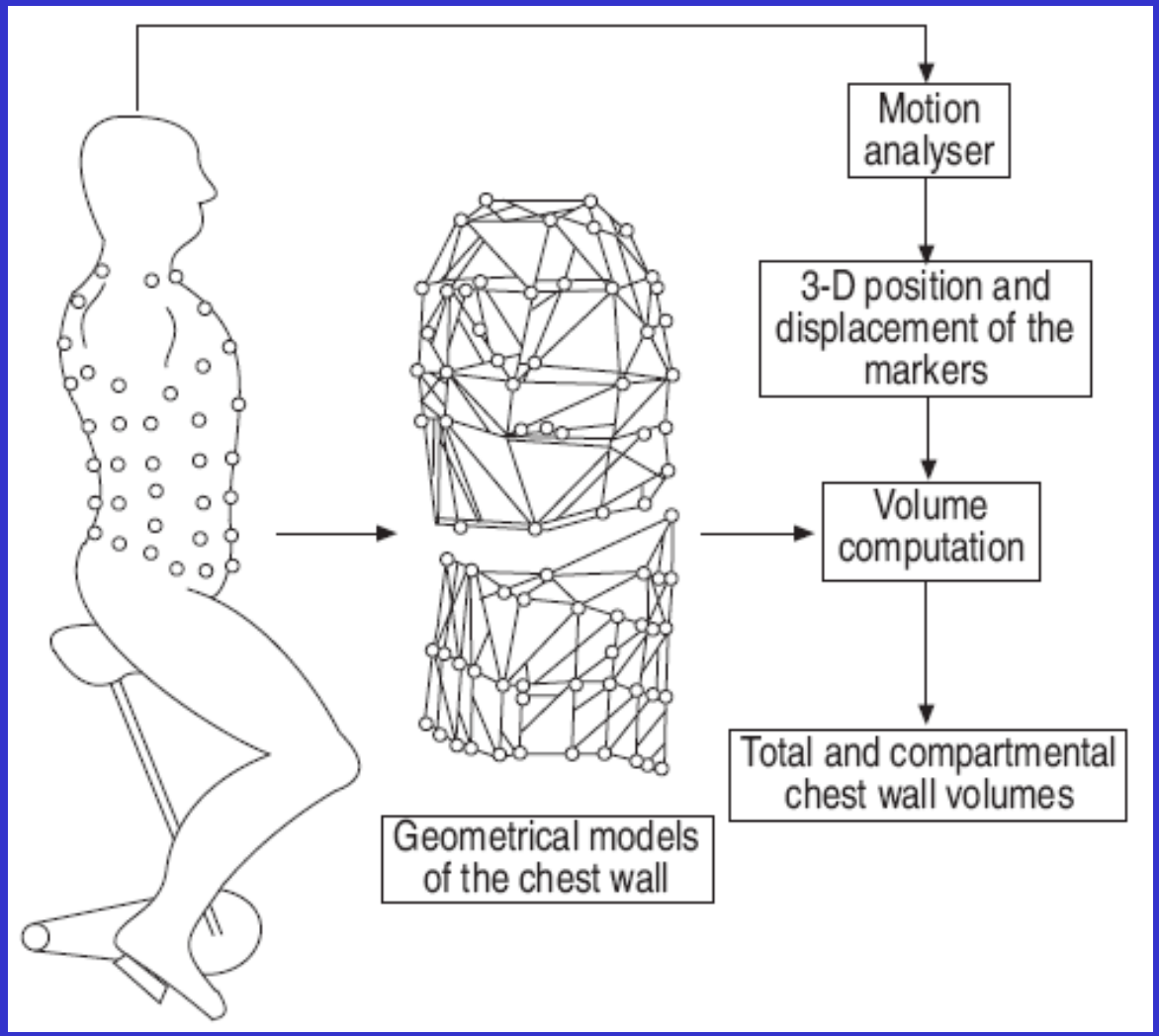
Magnetometers



Inductive Plethysmography (RIP)

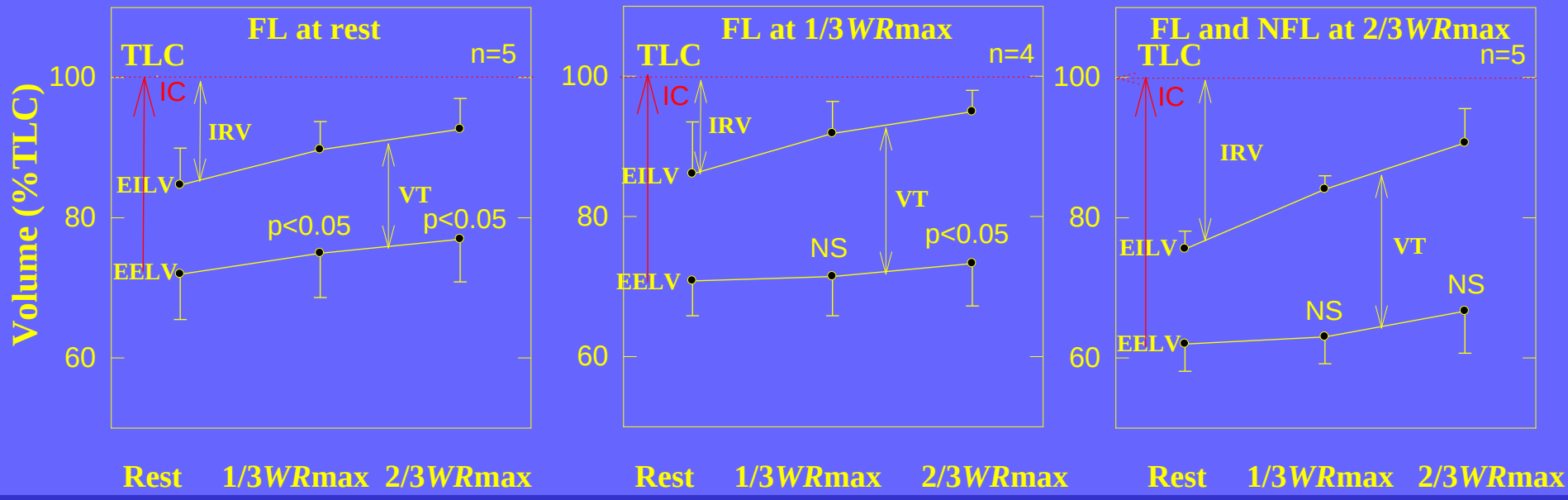
Optoelectronic Plethysmography (OEP)

Dellaca et al, Crit Care Med 2001; 29: 1807-1811

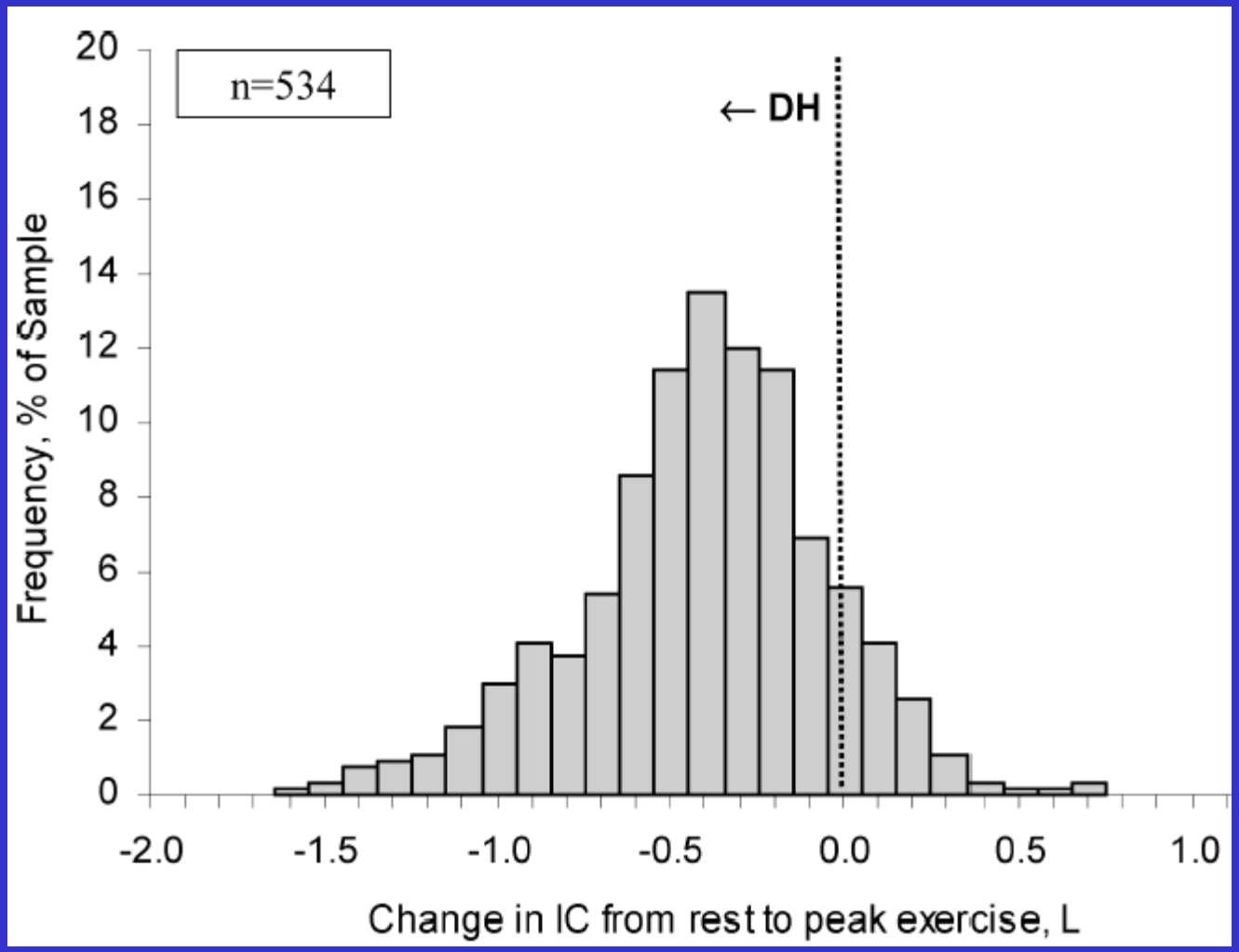


Exercise in COPD

Association of EFL with dynamic hyperinflation



Koulouris et al, JAP 1997; 82: 723-31



O'Donnell DE & Laveneziana P. COPD: Journal of Chronic Obstructive Pulmonary Disease 2006; 3: 219-232.

Exercise in COPD

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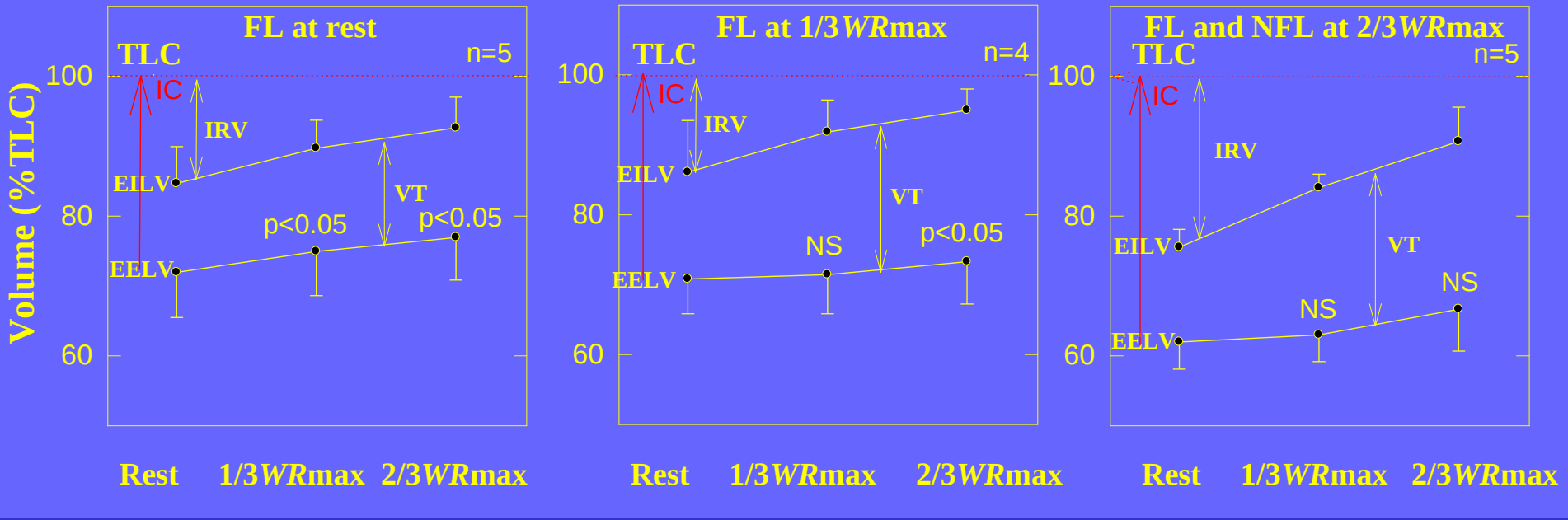
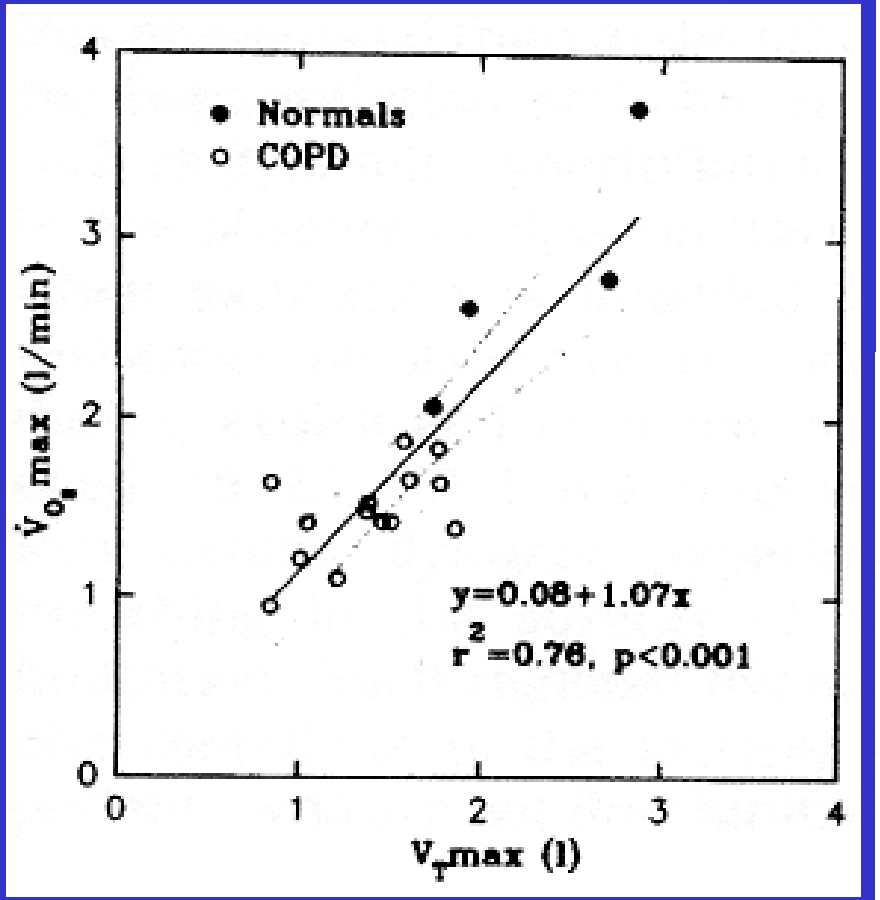
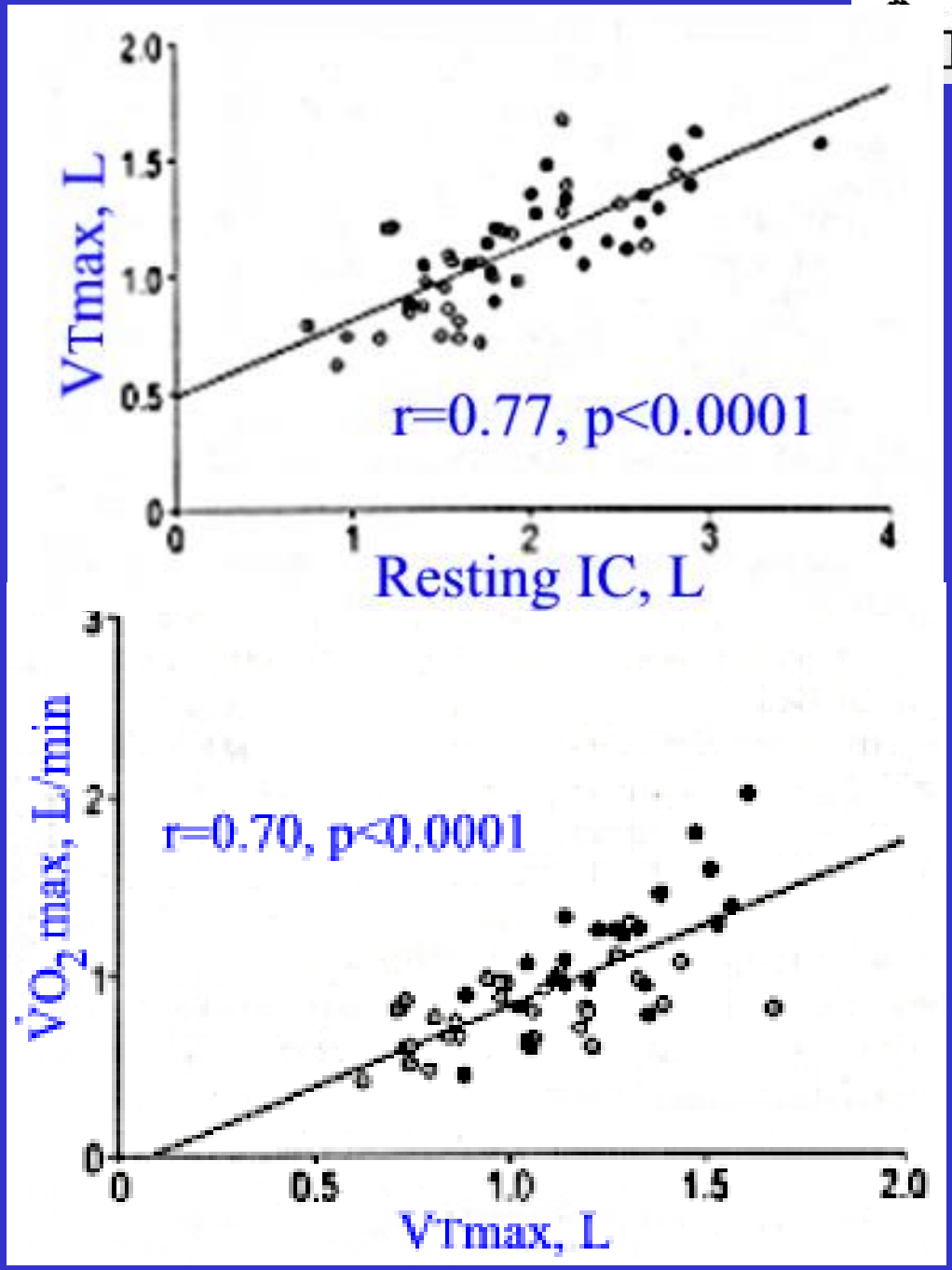


Koulouris et al, JAP 1997; 82: 723-31

Exercise in COPD

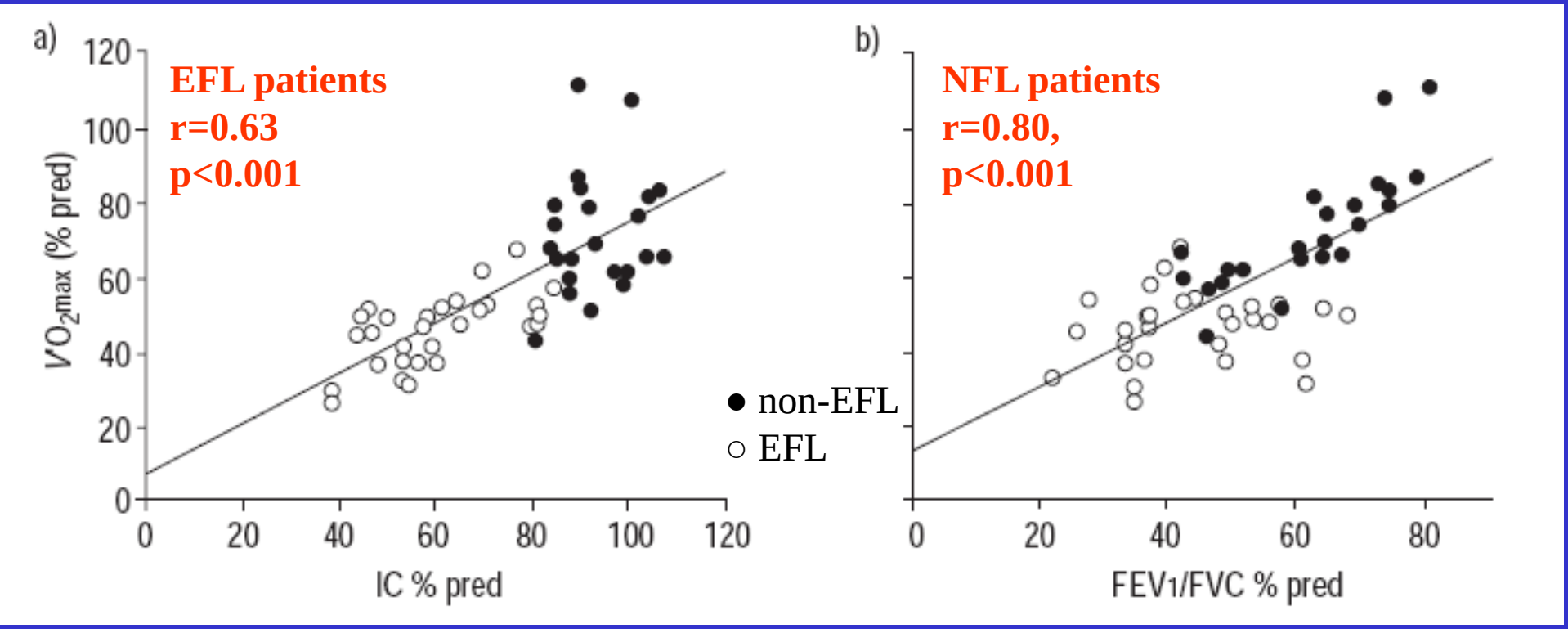


Koulouris et al, JAP 1997; 82: 723-31



Diaz et al, Eur Respir J 2001; 17: 120-27

Exercise in COPD



Diaz et al, Eur Respir J 2000; 16: 269-75

Significance of measuring IC at rest for COPD patients

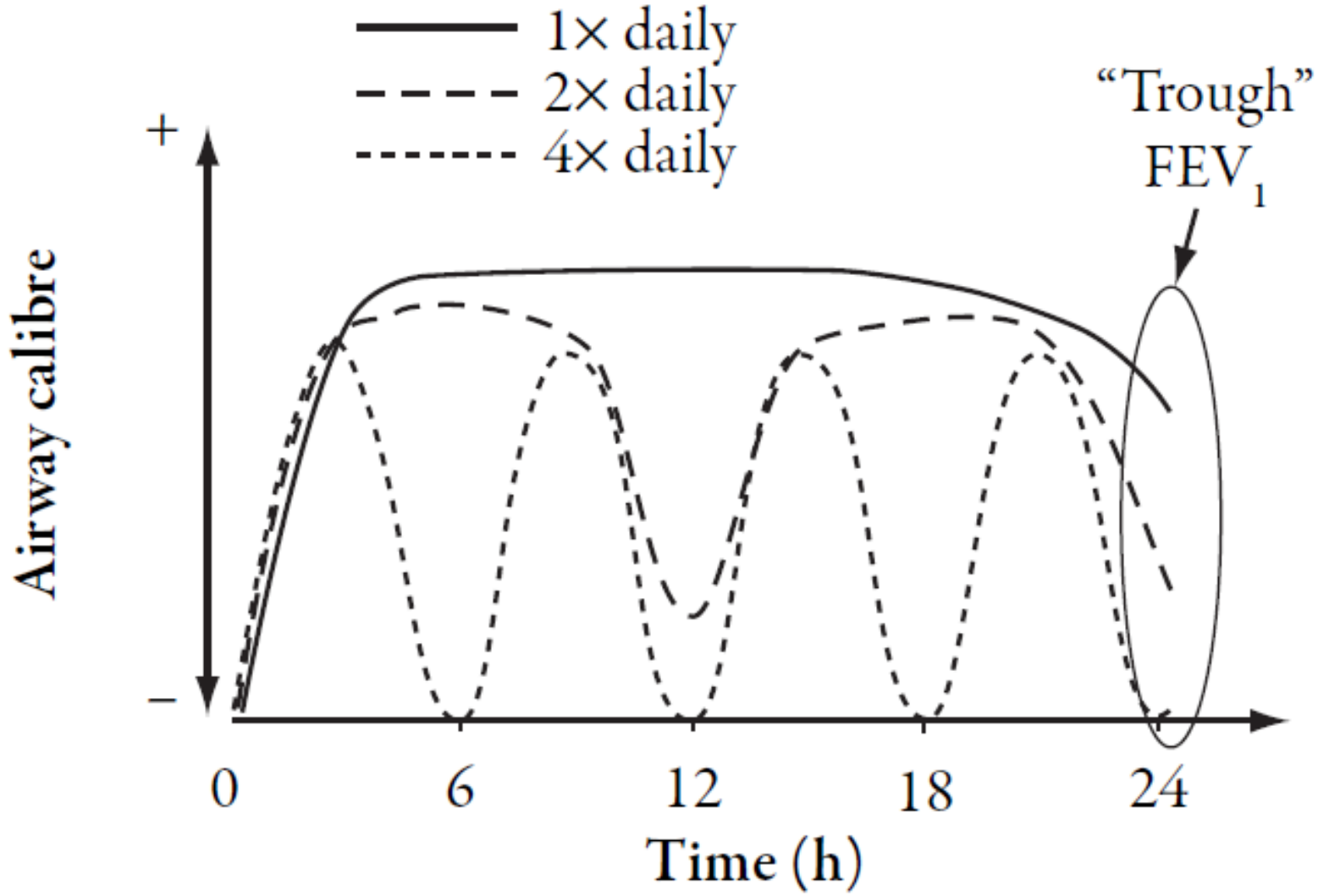
Hyperinflation appears to be the main determinant of exercise capacity and the magnitude of resting IC (a well recognized marker of Hyperinflation), the best clinical predictor.

Treatment of Hyperinflation I

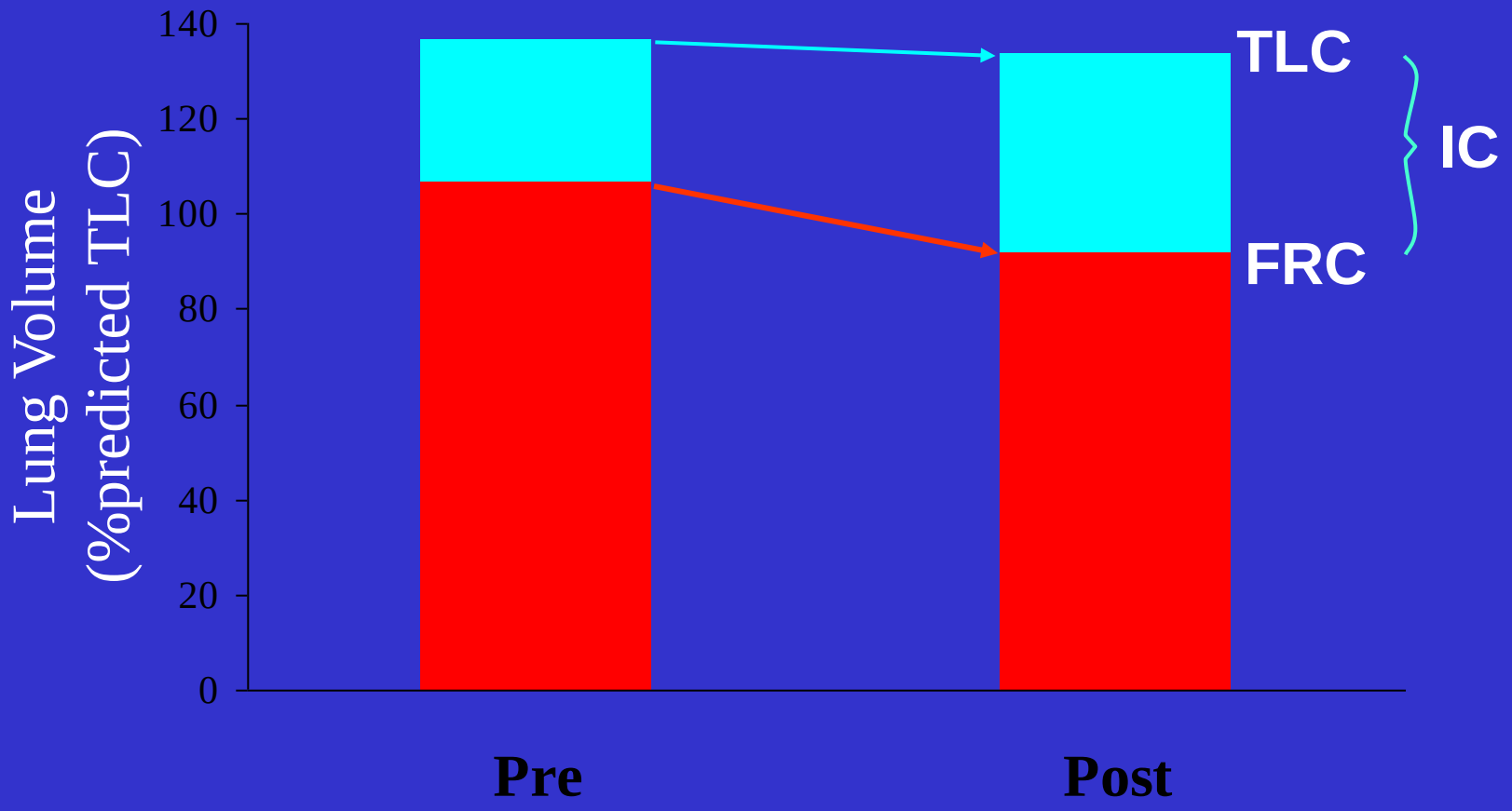
Dynamic hyperinflation is a temporary and reversible increase in EELV, therefore it is amenable to therapeutic interventions.

Up to date, bronchodilators are the main pharmacological means for improving dynamic hyperinflation.

“Pharmacological stenting”



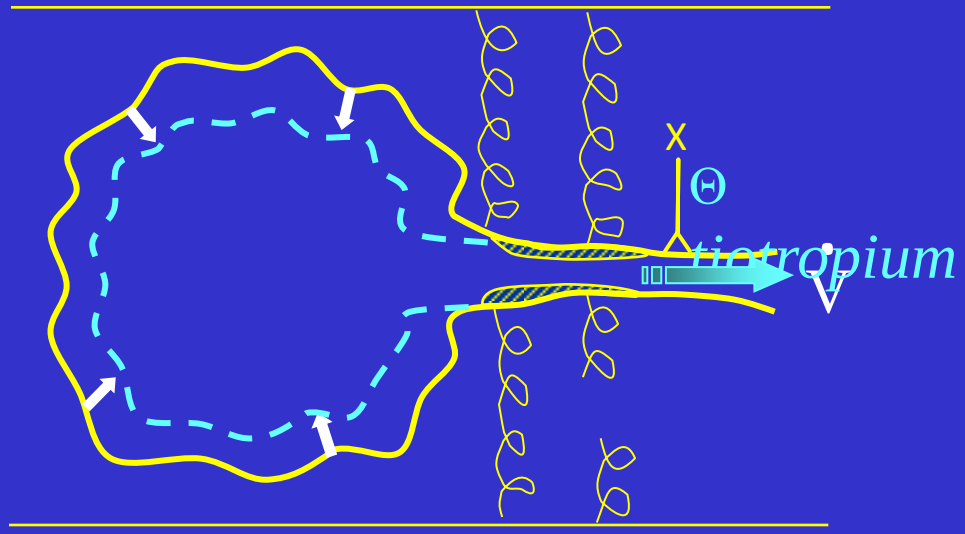
Pharmacological Volume Reduction by DEFLATORS

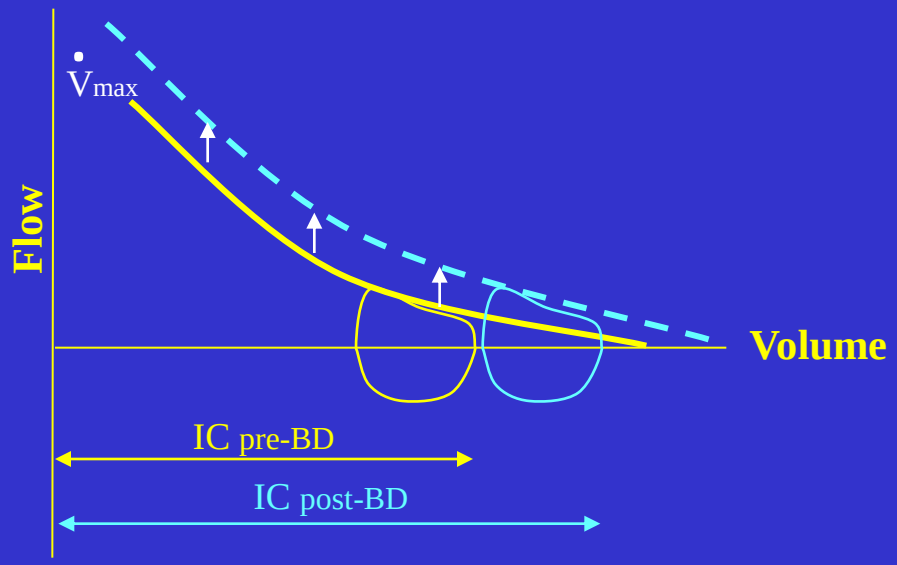


Adv Ther (2010) 27(3):150-159.
DOI 10.1007/s12325-010-0017-6

REVIEW

COPD: Response to Bronchodilators





Other treatments of Hyperinflation

Table 2 Effects of other interventions on hyperinflation, exercise endurance, and dyspnea in patients with chronic obstructive pulmonary disease

Intervention	Study	Year	N	Baseline FEV_1 (%)	Change in Static IC* (mL)	Increase in Dynamic IC† (mL)	Increase in Exercise Endurance	Change in Dyspnea	*P* Value
Oxygen	Somfay et al[27]	2001	10	31	−31	330‡	618 sec‡	↓	<0.05 vs. room air
Exercise training	Porszasz et al[28]	2005	24	36	NM	133	696 sec	NM	<0.05 vs. before training
LVR surgery	Fishman et al[29]	2003	608	27	NM	NM	Improved >10 W§	NM	<0.02 vs. no surgery
	Appleton et al[30]	2003	29	28	NM	NM	126 m (survivor group)	↓	<0.01 vs. baseline (dyspnea only)
	Miller et al[31]	2005	93	15–40	NM	NM	45 m	NM	<0.05 vs. baseline
Heliox breathing	Palange et al[18]	2004	12	37‖	−80 (NS)	200	288 sec	↓	<0.001 vs. air
	Pecchiari et al[32]	2004	22	41–61	+20	NM	NM	NM	NS
Bronchoscopic LVR	Hopkinson et al[33]	2005	19	28	NM	170	131 sec	↓	0.03 vs. no surgery for endurance only

FEV_1 = forced expiratory volume in 1 second; heliox = helium-oxygen; IC = inspiratory capacity; LVR = lung volume reduction; NM = not measured; NS = not significant; ↓ = decrease.

*IC measured during body plethysmography as total lung capacity minus functional residual capacity.

†IC measured at isotime during constant load submaximal exercise.

‡Measured with 50% inspired oxygen concentration.

§On incremental exercise testing.

‖Calculated on the basis of predicted value.

Cooper Ch B. AMJ 2006; 119: S21-S31

Many studies have shown that PR reduces dyspnea on exertion, increases exercise capacity and improves health-related quality of life (QOL) in COPD patients. Symptomatic individuals with COPD who have lesser degrees of airflow limitation who participate in pulmonary rehabilitation programs derive similar improvements in symptoms, exercise tolerance, and quality of life as do those with more severe disease. However, little is known on the effect of a PR program in EFL and NFL patients, who substantially differ in terms of COPD severity and hence exercise capacity and dyspnea (Eltayara et al., 1996; Goldstein et al., 2012; Lacasse et al., 2007; Nici et al.,

. Therefore, the aim of this study was to investigate the effectiveness of a PR program on EFL status and DH in stable COPD patients both at rest and during exercise.

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Effect of pulmonary rehabilitation on tidal expiratory flow limitation at rest and during exercise in COPD patients

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Table 1
Anthropometric and lung function data of NFL and EFL patients.

	All patients	NFL patients	EFL patients
n	42	26	16
Gender	M:36, F:6	M:24, F:2	M:12, F:4
Age, yrs	65 ± 8	66 ± 8	62 ± 8
Ht, cm	167 ± 7	168 ± 7	166 ± 6
BMI, kg/m^2	28 ± 5	29 ± 5	28 ± 4
FVC, %pred	89 ± 23	93 ± 23	82 ± 21
FEV_1, %pred	50 ± 25	56 ± 27	35 ± 10
FEV_1/FVC, %	43 ± 15	49 ± 15	34 ± 7

Values are means ± SD; n: number of subjects; M: male; F: female; BMI: body mass index, Ht: height; FVC: forced vital capacity; FEV_1: forced expiratory volume in the 1 s.

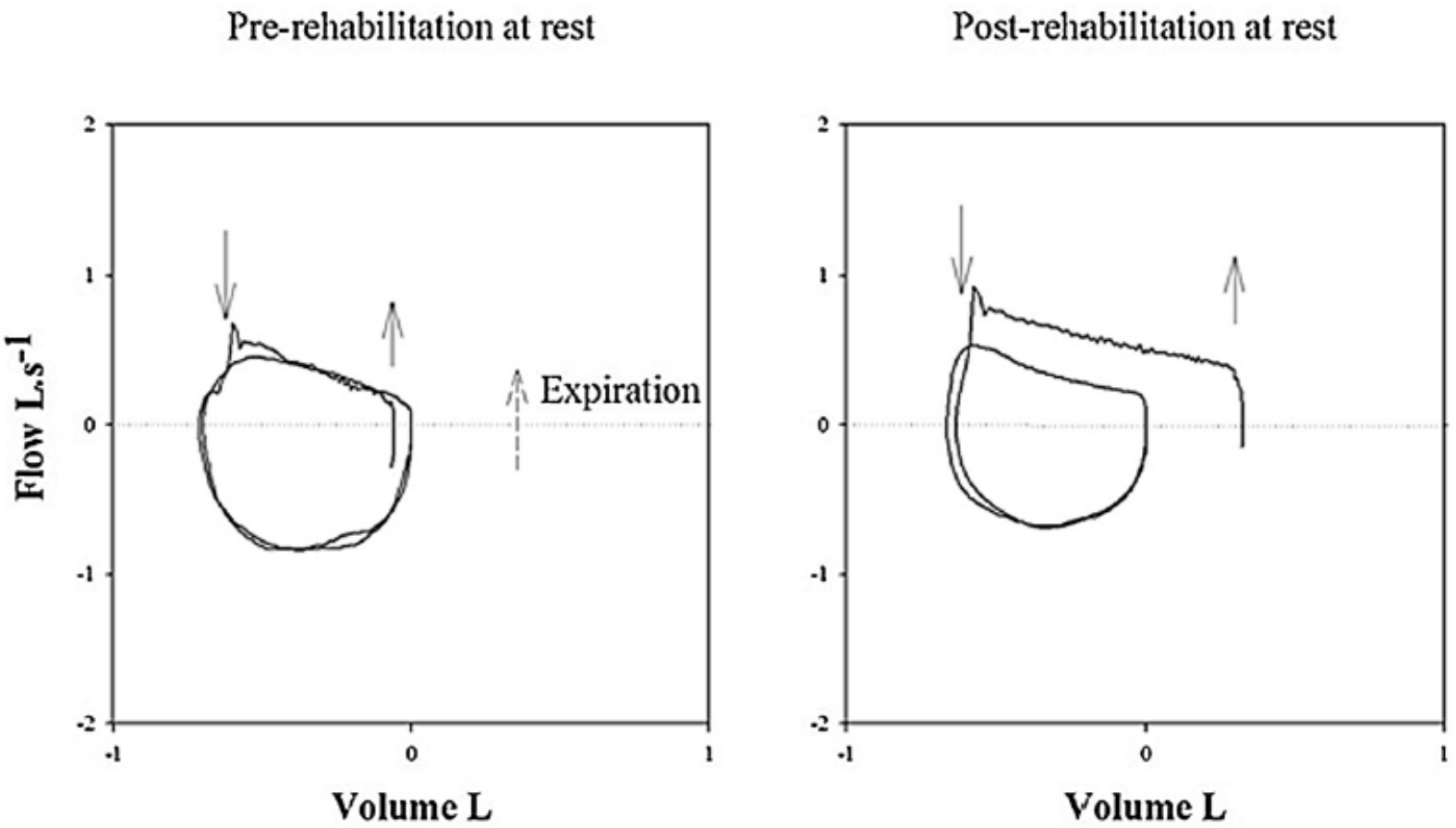


Fig. 1. A typical COPD patient, who was EFL at rest before the commencement of the PR program (left). The same COPD patient became NFL immediately after the completion of the PR program (right). Solid arrows indicate application (↓) and removal (↑) of negative pressure.

Table 2
Lung function data and patient-centered outcomes data between EFL and NFL patients pre- and post-PR.

Parameters	Patients	Pre PR	Post PR	paired *t*-test	% Change
FRC, %pred	All (n = 42)	122 ± 31	118 ± 29	NS	
	EFL (n = 16)	136 ± 36	117 ± 20	P = 0.02	
	NFL (n = 26)	113 ± 23	118 ± 34	NS	
	t-test	p = 0.013	NS		
IC, %pred	All (n = 42)	88 ± 28	91 ± 23	NS	
	EFL (n = 16)	73 ± 16	83 ± 19	P = 0.008	
	NFL (n = 26)	97 ± 30	96 ± 24	NS	
	t-test	p = 0.008	NS		
mMRC	All (n = 42)	2.3 ± 1	1.7 ± 1	P < 0.001	26%
	EFL (n = 16)	2.6 ± 1	2.1 ± 1	P = 0.014	17%
	NFL (n = 26)	2.0 ± 1	1.5 ± 1	P < 0.001	25%
6MWT, m	All (n = 42)	292 ± 66	339 ± 54	P < 0.001	15%
	EFL (n = 16)	270 ± 68	327 ± 43	P < 0.001	21%
	NFL (n = 26)	306 ± 62	346 ± 60	P < 0.001	13%
WR max, watts	All (n = 42)	78 ± 26	87 ± 28	P < 0.001	10%
	EFL (n = 16)	69 ± 19	81 ± 22	P < 0.001	17%
	NFL (n = 26)	84 ± 29	91 ± 31	P = 0.03	8%
SGRQ	All (n = 42)	47 ± 14	34 ± 14	P < 0.001	28%
	EFL (n = 16)	56 ± 7	34 ± 7	P < 0.001	39%
	NFL (n = 26)	44 ± 16	33 ± 16	P < 0.001	25%
Borg scale – Dyspnea (90% WR max)	All (n = 42)	5.7 ± 3	3.7 ± 3.6	p < 0.001	35%
	EFL (n = 16)	6.1 ± 2	4.0 ± 2	p < 0.001	33%
	NFL (n = 26)	4.8 ± 3	2.8 ± 2	p < 0.001	42%
Borg scale – leg Fatigue (90% WR max)	All (n = 42)	4.9 ± 3	3.2 ± 2	p < 0.001	35%
	EFL (n = 16)	5.8 ± 2	2.9 ± 2	p < 0.001	50%
	NFL (n = 26)	4.3 ± 2	2.8 ± 2	p < 0.001	35%

Values are means ± SD; NS: not statistically significant; n: number of subjects; FRC: functional residual capacity; IC: inspiratory capacity; mMRC: modified medical research council; 6MWT: 6-min walk test; WR max: maximum work rate; SGRQ: Saint George's respiratory questionnaire.

Table 5
Changes in breathing pattern pre- and post-rehabilitation according to EFL or NFL status at rest and various stages of exercise.

		T_E-pre s	T_E-post s	P value	T_I-pre s	T_I-post s	P value	T_{TOT}-pre s	T_{TOT}-post s	P value	f-pre RR (br/min)	f-post RR (br/min)	P value
Rest	EFL → NFL (n = 6)	2.20 ± 0.4	2.71 ± 0.4	P = 0.03	1.29 ± 0.4	1.46 ± 0.3	P = 0.025	3.55 ± 0.6	4.24 ± 0.5	P = 0.021	17 ± 3	15 ± 2	P = 0.035
	NFL → NFL (n = 36)	2.27 ± 0.7	2.53 ± 0.8	P < 0.001	1.39 ± 0.3	1.51 ± 0.4	P = 0.043	3.66 ± 0.8	4.04 ± 1.0	P < 0.001	19 ± 5	17 ± 6	P = 0.007
30% WR max	EFL → NFL (n = 9)	1.28 ± 0.4	1.56 ± 0.4	P = 0.047	1.03 ± 0.4	1.29 ± 0.4	P = 0.002	2.32 ± 0.6	2.85 ± 0.5	P = 0.006	24 ± 4	22 ± 4	P = 0.03
	NFL → NFL (n = 33)	1.32 ± 0.5	1.54 ± 0.5	P < 0.001	1.19 ± 0.4	1.30 ± 0.5	P = 0.007	2.52 ± 0.8	2.92 ± 0.8	P < 0.001	25 ± 6	22 ± 6	P < 0.001
60% WR max	EFL → NFL (n = 12)	1.05 ± 0.5	1.21 ± 0.5	P = 0.02	0.94 ± 0.3	1.10 ± 0.3	P = 0.006	1.99 ± 0.7	2.29 ± 0.6	P < 0.001	29 ± 5	25 ± 5	P < 0.001
	NFL → NFL (n = 30)	1.11 ± 0.4	1.32 ± 0.4	P < 0.001	1.10 ± 0.3	1.25 ± 0.3	P < 0.001	2.24 ± 0.6	2.59 ± 0.6	P < 0.001	28 ± 7	25 ± 6	P < 0.001
90% WR max	EFL → NFL (n = 16)	0.85 ± 0.5	1.02 ± 0.4	P = 0.013	0.82 ± 0.2	1.01 ± 0.3	P < 0.001	1.66 ± 0.6	2.03 ± 0.6	P < 0.001	32 ± 4	28 ± 5	P = 0.002
	NFL → NFL (n = 26)	0.90 ± 0.4	1.16 ± 0.4	P < 0.001	1.04 ± 0.3	1.17 ± 0.3	P = 0.019	1.96 ± 0.6	2.31 ± 0.6	P < 0.001	30 ± 7	27 ± 6	P < 0.001

Values are means ± SD; n: number of subjects; NS: not statistically significant difference; EFL: expiratory flow limitation; NFL: non expiratory flow limitation; T_E: expiratory time; T_I: inspiratory time; T_{TOT}: total time; f: frequency; RR: respiratory rate; br/min: breath per minute; WR max: maximal work rate.

Conclusions

Before PR, 16 patients presented with EFL at rest and/or during exercise. After PR, EFL was abolished in 15 out of those 16 EFL patients who exhibited a significant increase in IC values. These were mainly accomplished through a modification of the breathing pattern. In the 26 NFL patients no increase was noted in their IC or a modification of their breathing pattern. However, both NFL and EFL COPD patients improved exercise capacity and patients centered outcomes undergoing the same PR program.

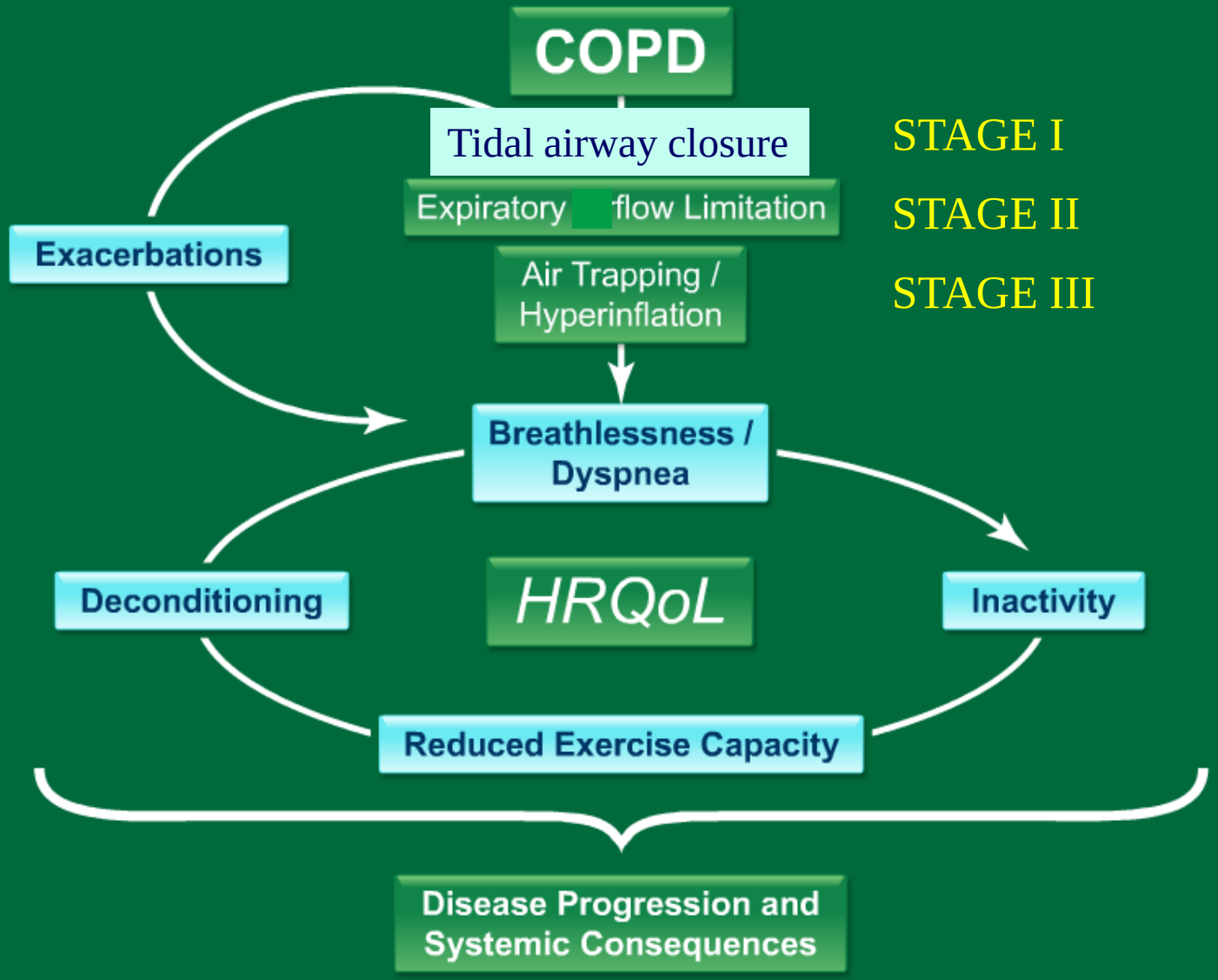
Conclusions

- Reducing hyperinflation in patients with COPD is a key mechanism for improving their dyspnoea, exercise tolerance and activity
- It is now possible to achieve sustained lung volume reduction not only by pharmacological means but with programs of Pulmonary Rehabilitation, which abolish almost completely the cause of hyperinflation in COPD patients, i.e., expiratory flow limitation by changing the pattern of breathing
- What remains to be clarified is whether the application of long term pharmacological lung volume reduction and other interventions will alter the natural history and mortality of this disease

Thanks for your attention!

Mykonos, Greece

Clinical Course of COPD



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