COPD : Pathophysiology and inflammation beyond smoking

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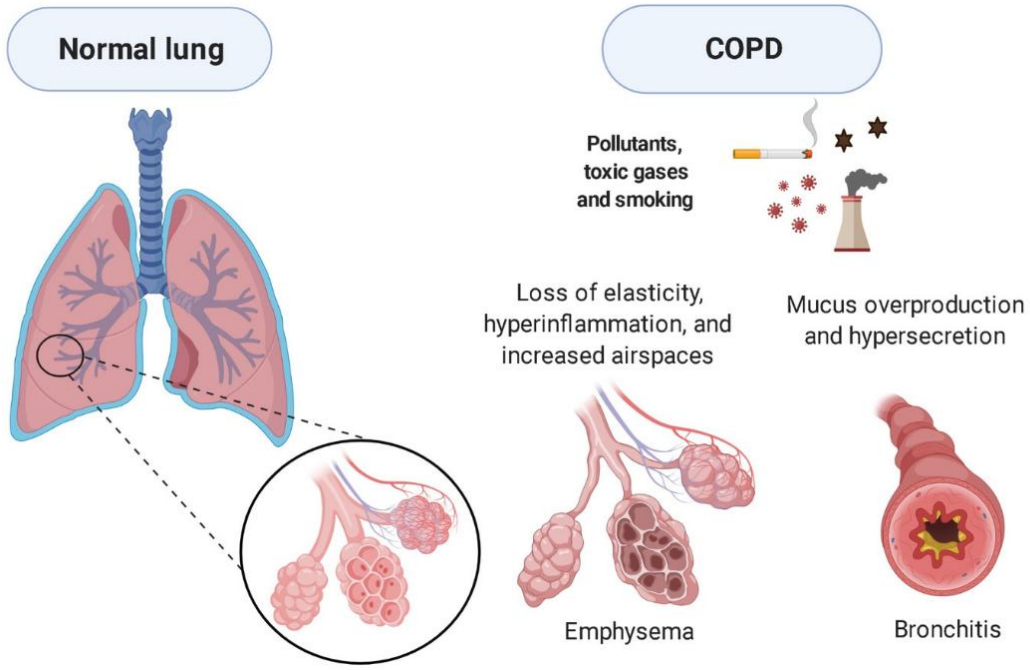
EUMC SEOUL EWHA WOMANS UNIVERSITY SEOUL HOSPITAL

COPD – two major phenotype

- Emphysema
  - Alveolar wall destruction
  - hyperinflammation, oxidative stress → elastic recoil
- Chronic bronchitis
  - Overproduction and hypersecretion of mucus by goblet cells → airflow limitation



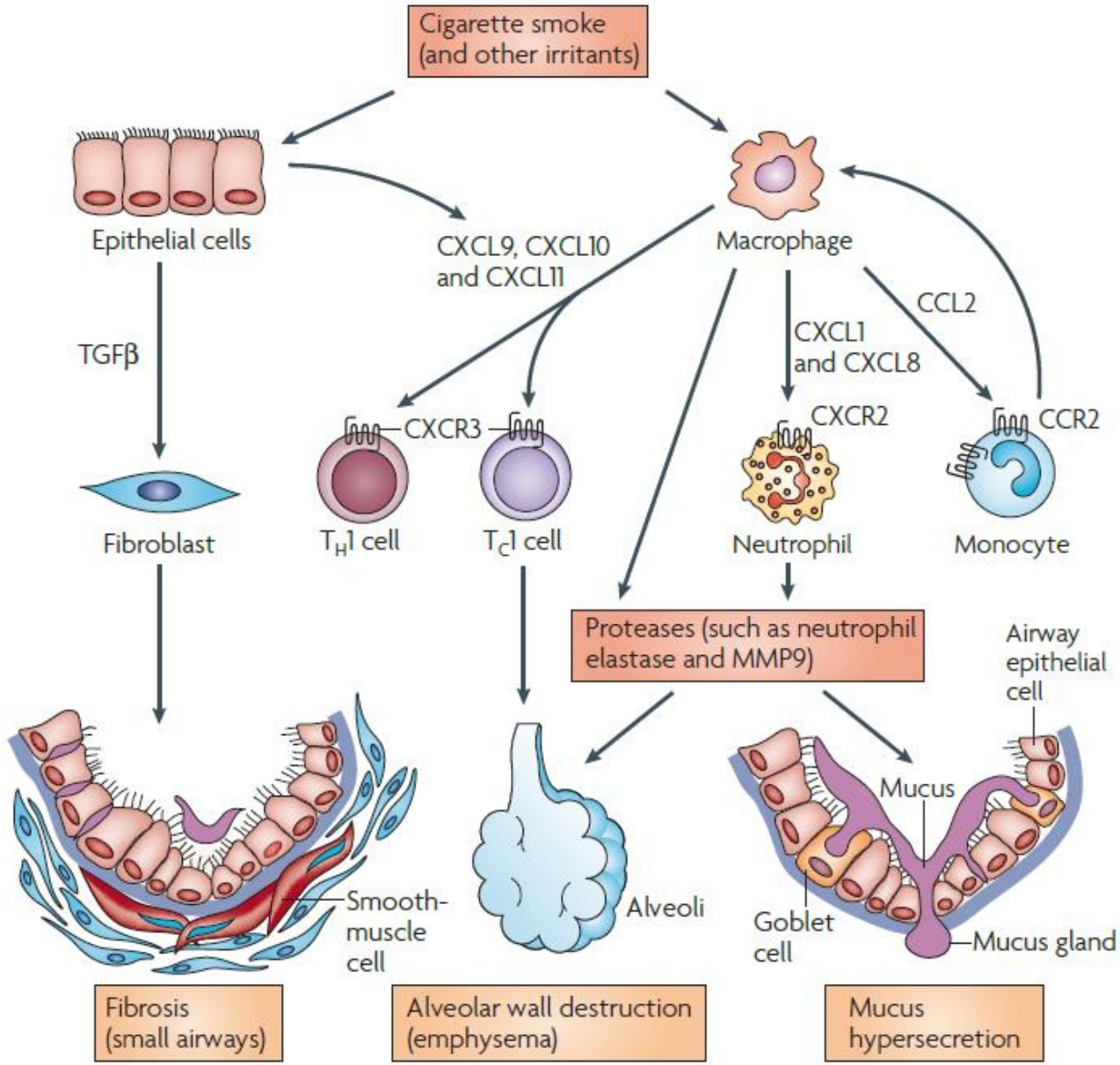
Xu et al, Front. Immunol (2024)

Chronic Inflammation

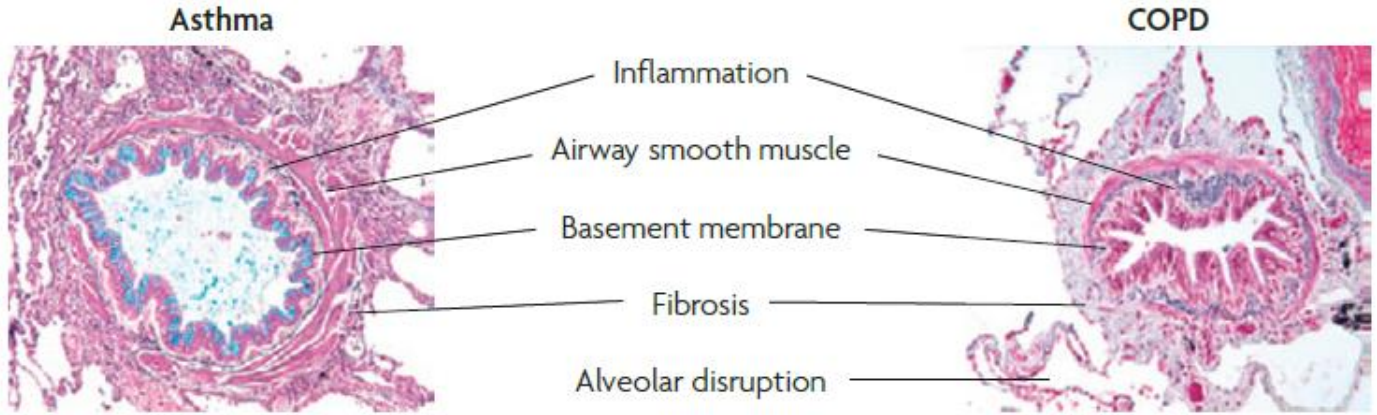
- Abnormal inflammatory response → damages airways (bronchitis-bronchiolitis) and alveoli (emphysema) →physiologic decline lung function acceration → leads to airflow limitation

- Type 1, Type 2 inflammation

Inflammatory and immune cells involved in chronic obstructive pulmonary disease (COPD)



Barnes et el. Natrue review. (2008)



Inflammation	+++	+++
Airway smooth muscle	+++	+
Basement membrane	++	–
Fibrosis	+ (subepithelial)	+++ (peribronchiolar)
Alveolar disruption	–	+++
Airway vessels	++	No change
Mast cells	++ (and activated)	Normal
Dendritic cells	++	ND
Eosinophils	++	Normal
Neutrophils	Normal	++
Lymphocytes	T_H2 type	T_H1 and T_C1 type
Epithelium	Often shed	Pseudostratified
Goblet cells	++	++

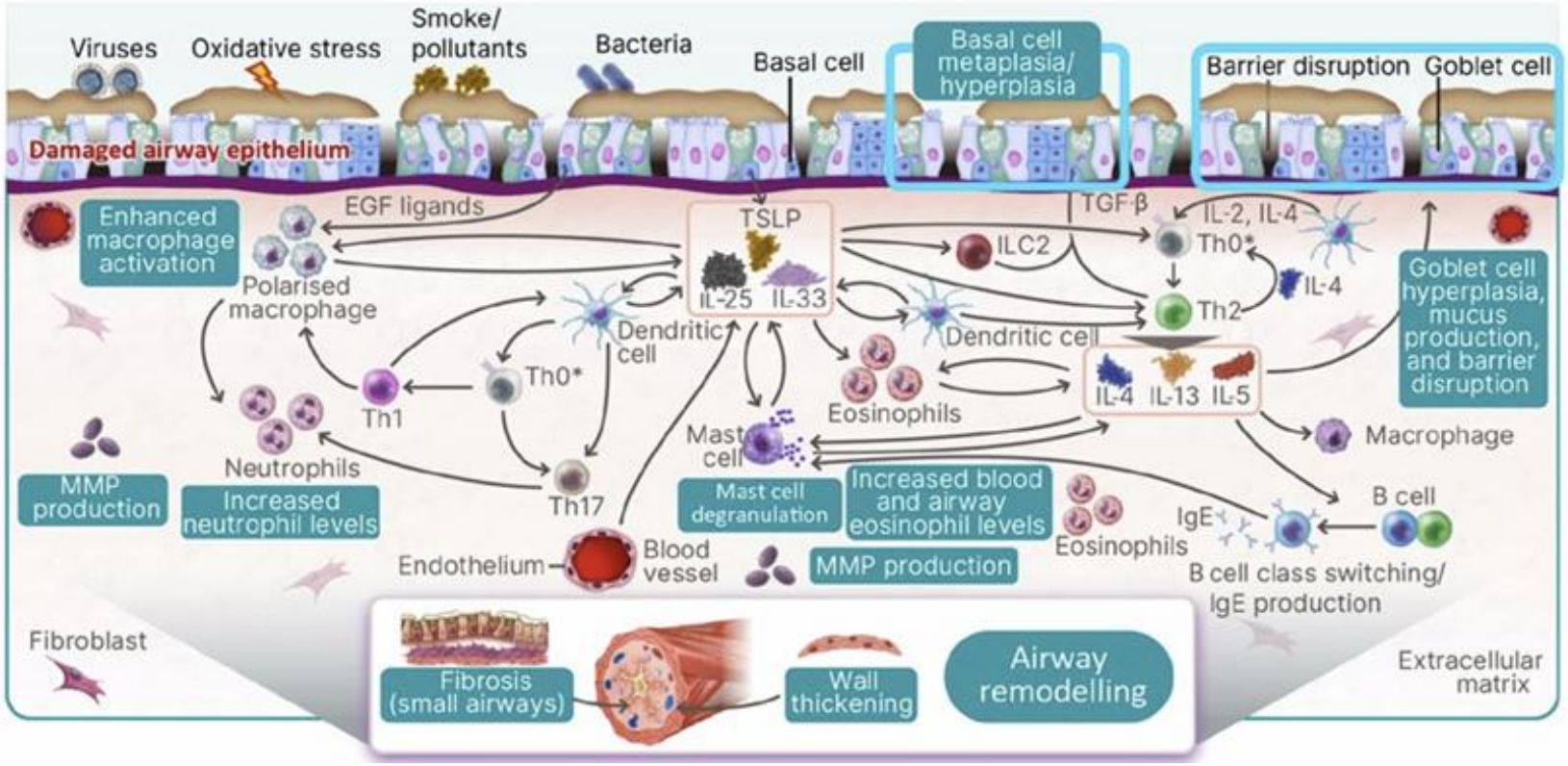
Barnes et el. Nature review. (2008)

Table 1 | **Comparison between patterns of inflammation in asthma and COPD**

	Asthma			COPD			Refs
	Mild	Severe	Exacerbation	Mild	Severe	Exacerbation	
Neutrophils	0	++	++++	++	+++	++++	7
Eosinophils	+	++	+++	0	0	+	110,111
Mast cells	++	+++	+++?	0	0	?	7,26,112
Macrophages	+	+	?	+++	++++	++++	113
T cells	T_H2 cells: ++ *i*NKT cells: ?	T_H1 cells: + T_H2 cells: + T_C1 cells: + T_C2 cells: +? T_H17 cells: ?	?	T_C1 cells: +	T_C1 cells: +++ T_H1 cells: +++ T_H17 cells: ?	?	18,66,114
B cells	IgE producing	IgE producing	?	+	+++	?	18,73
Dendritic cells	+	?	?	+?	+?	?	115
Chemokines	CCL11: +	CXCL8: +	CXCL8: ++	CXCL8: + CXCL1: + CCL2: +	CXCL8: ++	CXCL8: +++	116
Cytokines	IL-4: ++ IL-5: ++ IL-13: ++	TNF: ++	?	TNF: +	TNF: ++	TNF: +++	117,118
Lipid mediators	LTD_4: ++ PGD_2: +	LTB_4: ++ PGD_2: +	?	LTB_4: +	LTB_4: ++	LTB_4: +++	10,11
Oxidative stress	0	++	+++	++	+++	++++	119–122
Steroid response	++++	++	+	0	0	0	92

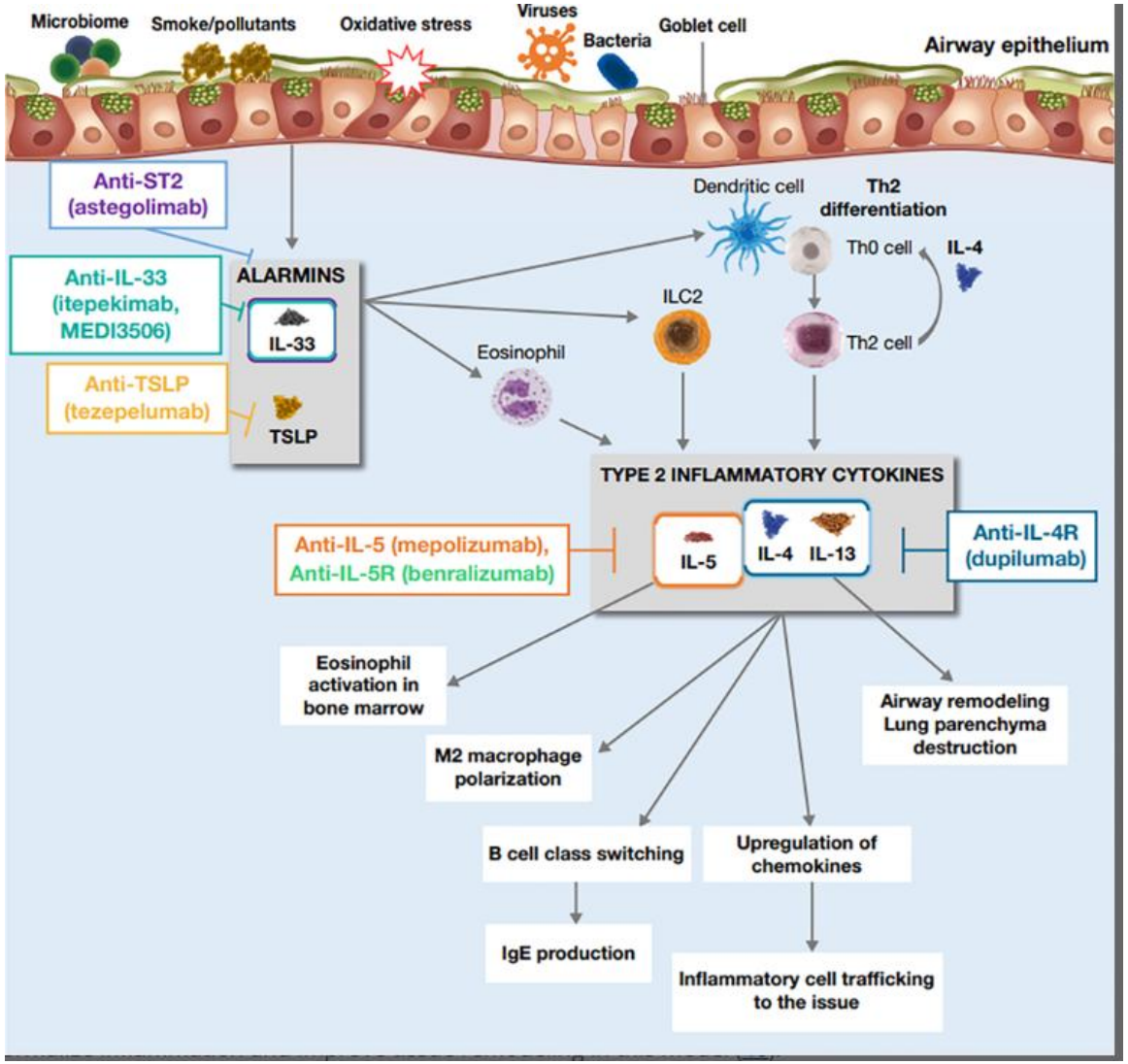
0, no response; + to ++++, magnitude scale; ?, uncertain. CCL, CC-chemokine ligand; COPD, chronic obstructive pulmonary disease; CXCL, CXC-chemokine ligand; *i*NKT, invariant natural killer T; LTB_4, leukotriene B_4; LTD_4, leukotriene D_4; PGD_2, prostaglandin D_2; T_C1, type 1 cytotoxic T; T_H, T helper; TNF, tumour-necrosis factor.

Heterogeneity of Airway inflammation



Christenson et el, EMJ, 2023

Type 2 inflammation in COPD



Rabe et el, ATS, 2023

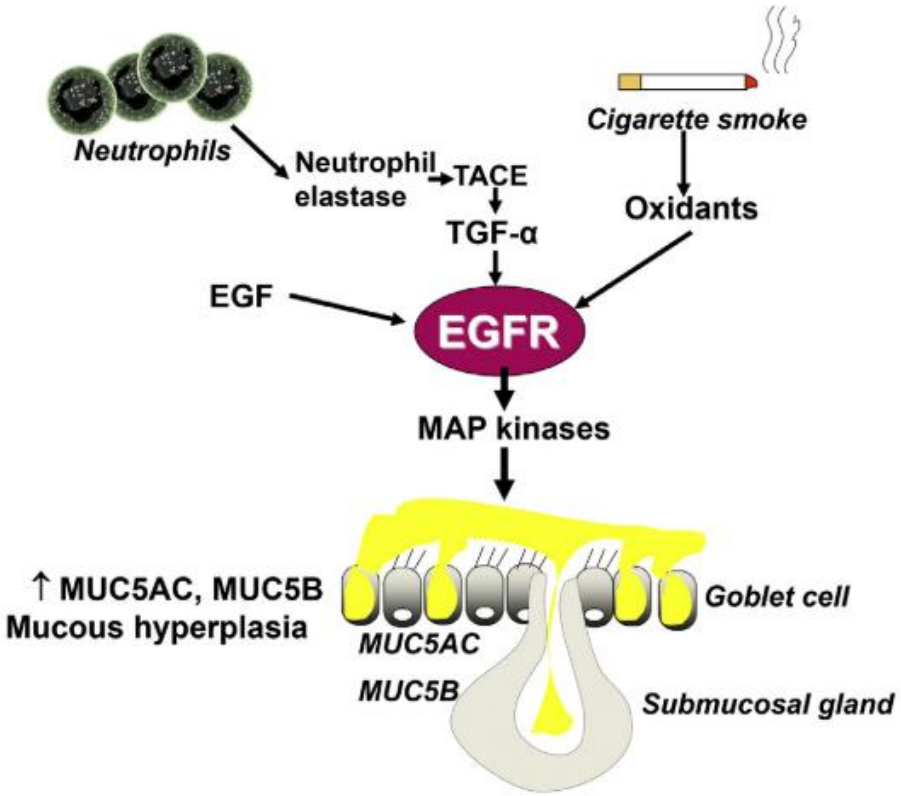
TABLE 1 Prototypical type 2 cytokines

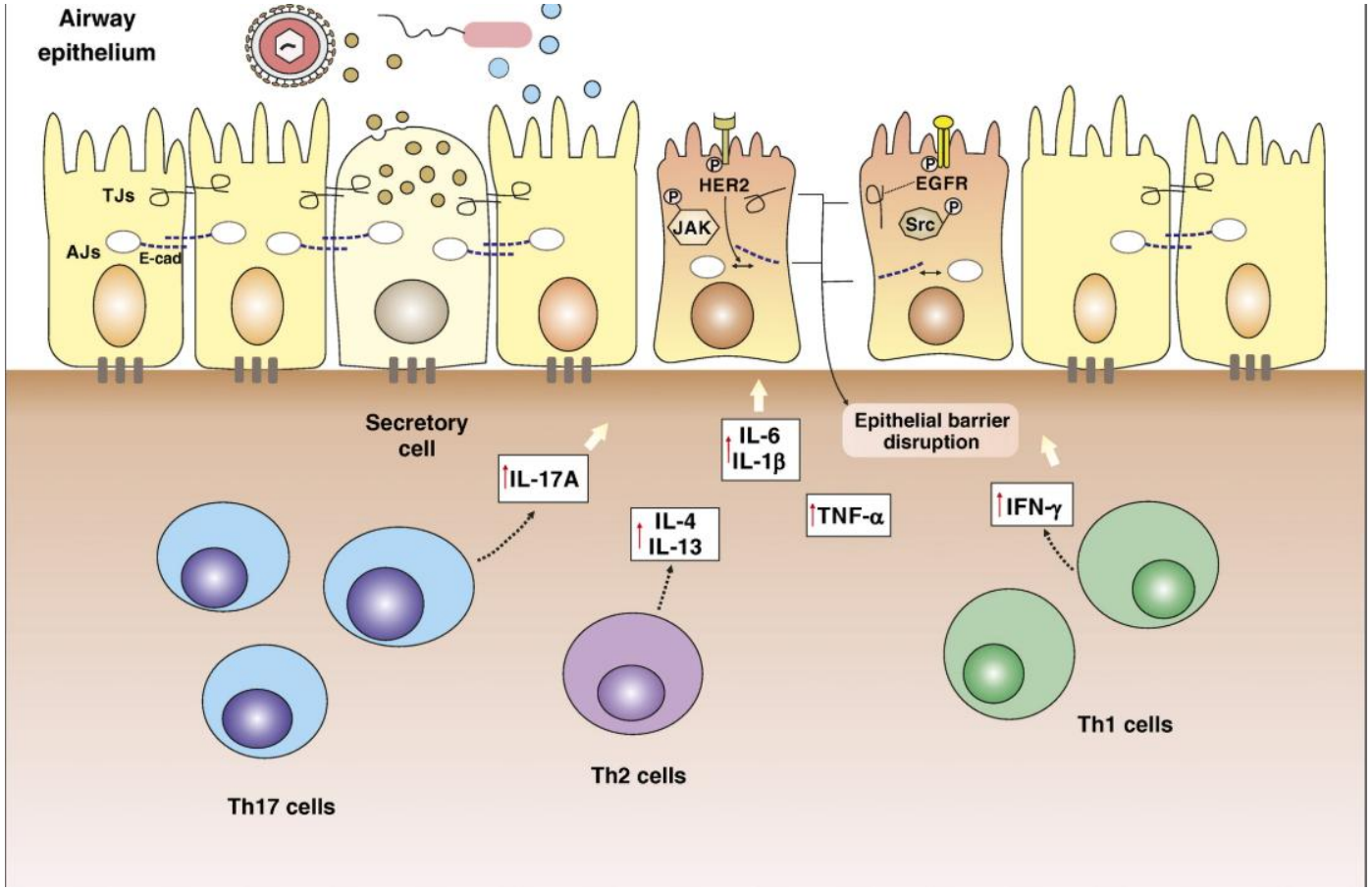
Type 2 cytokine	Source	Function in the lung
IL-4	Th2 cells, ILC2s, mast cells, basophils, NK T cells, eosinophils	Promotes the differentiation of naïve T cells into Th2 cells and the production of IgE antibodies by B cells and contributes to inflammatory cell recruitment including Th2 cells, B cells and mast cells
IL-5	Th2 cells, ILC2s, mast cells, basophils, eosinophils, activated B cells	Crucial for the growth and differentiation of eosinophils
IL-13	Th2 cells, ILC2s, eosinophils, mast cells, basophils, NK T cells, epithelial cells	Induces IgE synthesis from B cells and contributes to mucus production, inflammatory cell recruitment and small airway remodelling
IL-9	Th2 cells, ILC2s, mast cells, Tregs, Th9 cells	Contributes to mast cell growth and function, and to the recruitment and maturation of ILC2s
IL-10	Th2 cells, Tregs, macrophages and monocytes, dendritic cells, B cells, NK cells, mast cells, epithelial cells	Generally considered an anti-inflammatory cytokine owing to its activity in maintaining immune homeostasis; can also promote Th2 responses under stress

IL: interleukin; Th2: type 2 helper T; ILC2: group 2 innate lymphoid cell; NK: natural killer; Tregs: regulatory T cell.

IL-4 and IL-13 : permeability of the mucosal surface of airways by downregulating key proteins that regulate intercellular tight junctions → leaky airway mucosa

Airway epithelium





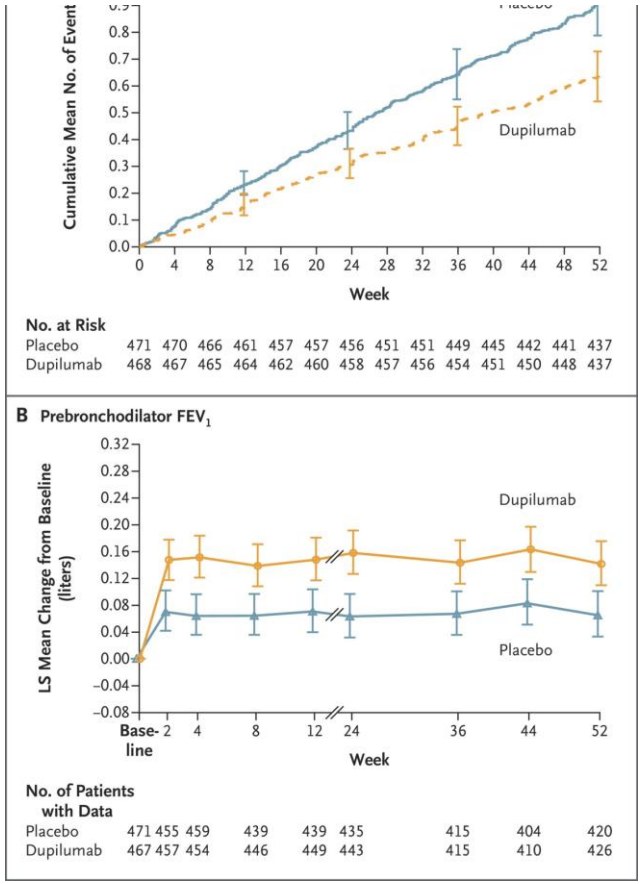
Barnes et al, JALLERGYCLINIMMUNOL (2016)

Aghapour et al, AJRCMB (2018)

ORIGINAL ARTICLE

Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

Authors: Surya P. Bhatt, M.D., M.S.P.H., Klaus F. Rabe, M.D., Ph.D., Nicola A. Hanania, M.D., Claus F. Vogelmeier, M.D., Jeremy Cole, M.D., Mona Bafadhel, M.D., Ph.D., Stephanie A. Christenson, M.D., +15 , for the BOREAS Investigators* Author Info & Affiliations



Moderate or Severe COPD Exacerbations and Change in Prebronchodilator FEV1 over Time.

Type 2 inf … their association with response … EAS): an analysis of a random … hase 3 trial

Stephanie A Christensc … , Claus F Vogelmeier, Alberto Papi, Dave Singh,
Elizabeth Laws, Paula L … cey B Robinson, Raolat M Abdulai

	Placebo group (n=470)	Dupilumab group (n=469)
Blood eosinophil count, cells per µL		
Baseline	335·0 (240·0 to 460·0)	340·0 (250·0 to 460·0)
Week 52		
Percentage change from baseline	−9·4% (−39·0 to 17·5)	−12·0% (−42·5 to 26·3)
Mean (SD)	−0·7 (82·7)	4·2 (91·3)
Change from baseline	−30·0 (−140·0 to 50·0)	−30·0 (−160·0 to 70·0)
Mean (SD)	−66·8 (280·7)	−24·7 (370·0)
Least squares mean (SE)	−70·7 (16·9)	−37·8 (17·1)
Least squares mean difference *vs* placebo (95% CI)	..	32·9 (−10·0 to 75·8)
p value *vs* placebo	..	0·13
Total serum IgE, IU/mL*		
Baseline	4·8 (3·7 to 6·0)	4·8 (3·8 to 6·0)
Week 52		
Percentage change from baseline	−0·9% (−6·5 to 4·8)	−22·5% (−30·4 to −16·5)
Change from baseline	0 (−0·3 to 0·2)	−1·1 (−1·5 to −0·7)
Least squares mean (SE)	0 (0)	−1·1 (0)
Least squares mean difference *vs* placebo (95% CI)	..	−1·1 (−1·1 to −1·0)
p value *vs* placebo	..	<0·0001
FeNO, ppb		
Baseline	17·0 (11·0 to 30·0)	17·0 (10·0 to 31·0)
Week 52		
Percentage change from baseline	−6·9% (−35·7 to 25·0)	−28·6% (−57·1 to 0)
Change from baseline	−1·0 (−8·0 to 3·0)	−4·0 (−16·0 to 0)
Least squares mean (SE)	−3·8 (0·9)	−11·1 (0·9)
Least squares mean difference *vs* placebo (95% CI)	..	−7·3 (−9·7 to −5·0)
p value *vs* placebo	..	<0·0001
Plasma eotaxin-3, pg/mL*		
Baseline	5·0 (4·7 to 5·4)	5·0 (4·7 to 5·4)
Week 52		
Percentage change from baseline	−0·4% (−5·6 to 5·0)	−8·8% (−15·6 to −2·9)
Change from baseline	0 (−0·3 to 0·3)	−0·4 (−0·8 to −0·1)
Least squares mean (SE)	−0·1 (0)	−0·6 (0)
Least squares mean difference *vs* placebo (95% CI)	..	−0·5 (−0·6 to −0·4)
p value *vs* placebo	..	<0·0001
Serum PARC, ng/mL		
Baseline	72·1 (54·0 to 94·9)	72·4 (54·9 to 97·8)
Week 52		
Percentage change from baseline	−0·8% (−13·9 to 17·2)	−14·4% (−29·2 to 2·1)
Change from baseline	−0·4 (−10·2 to 11·3)	−10·0 (−21·0 to 1·0)
Least squares mean (SE)	0·5 (2·1)	−15·4 (2·1)
Least squares mean difference *vs* placebo (95% CI)	..	−16·0 (−21·2 to −10·7)
p value *vs* placebo	..	<0·0001

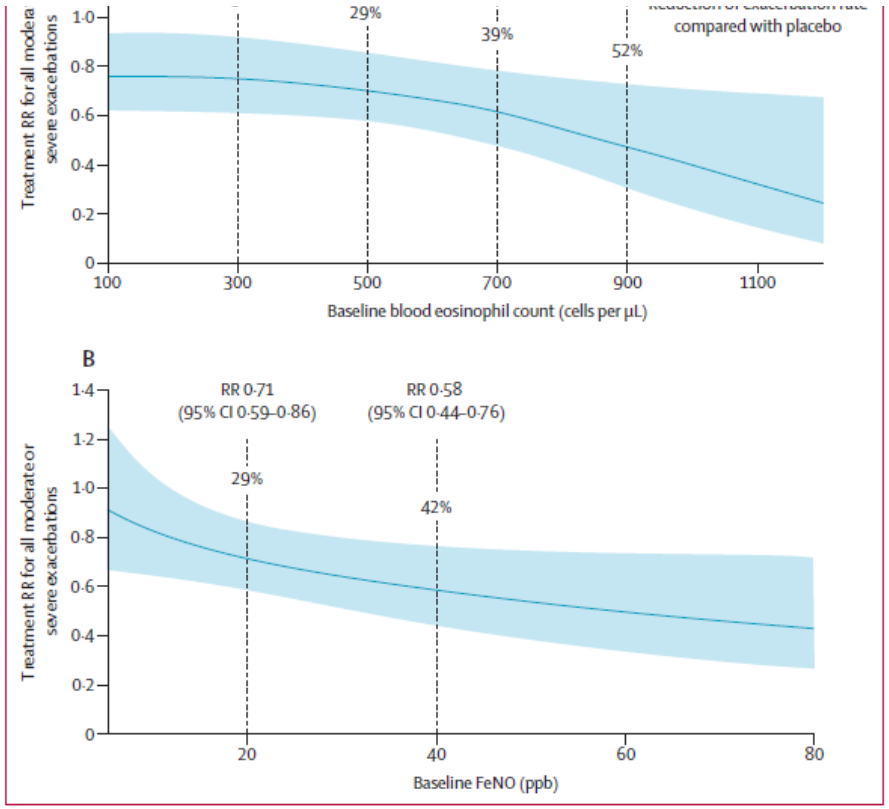


Figure 3: **Treatment rate of moderate or severe exacerbations by continuous baseline blood eosinophil count (A) and continuous baseline FeNO concentration (B)**
Percentages refer to reduction of exacerbation rate compared with placebo, which is shown by the solid blue line. The blue area curves indicate 95% CI. FeNO=fractional exhaled nitric oxide. ppb=parts per billion. RR=rate ratio.

Inflammatory mediators

- Lipid mediators
  - significant increase in PGE2 and PGF2a, LTB4 concentrations
- Cytokines
  - TNF-a
- Chemokines
  - CXCL8 ↑ exacerbations, CCL2, CXCR3 expression
- Protease
  - MMP-9 elastolytic enzyme in COPD and is secreted from macrophages, neutrophils, and epithelial cells.

Pathophysiology

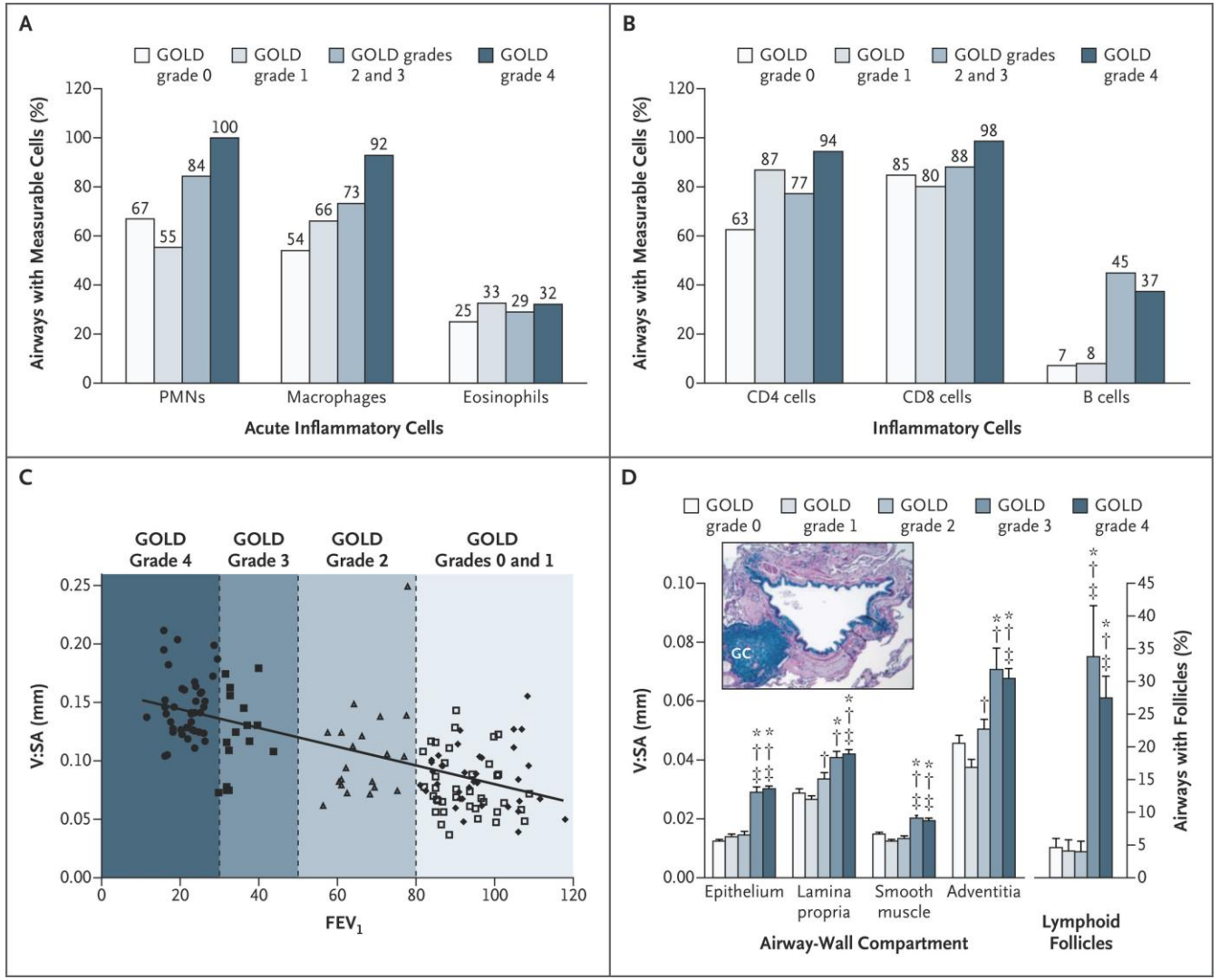
- Airflow obstruction and gas trapping
- Hyperinflation
- Pulmonary gas exchange abnormalities
- Pulmonary hypertension
- Exacerbation
- Multimorbidity

Airflow obstruction and gas trapping

- Cause
  - small airways disease (airway resistance ↑) + parenchymal destruction (emphysema, elastic recoil ↓)

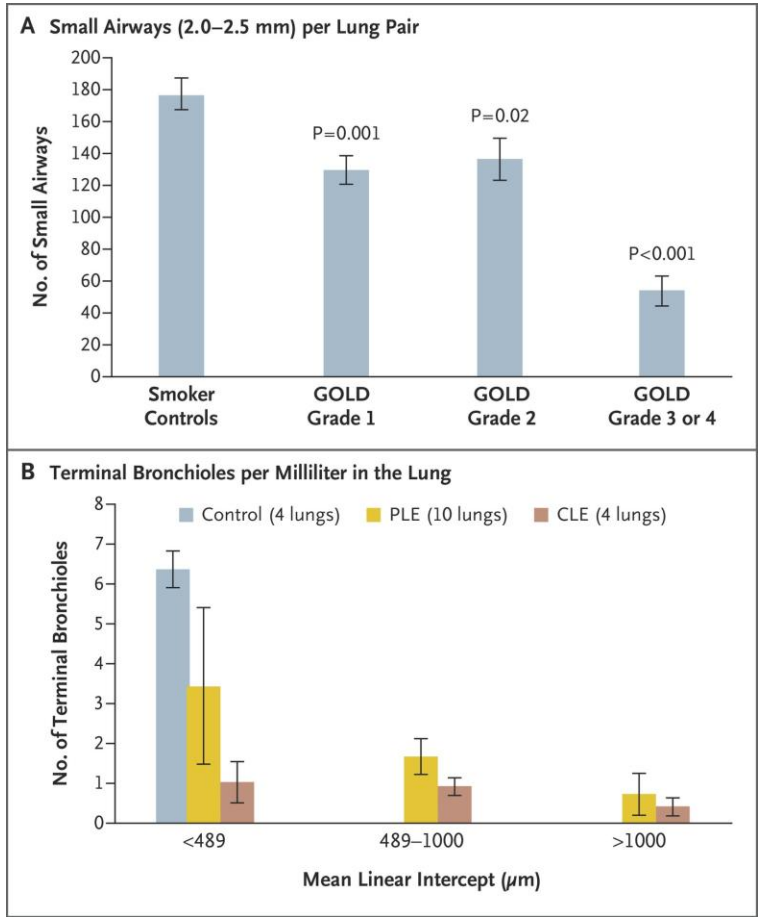
- Chronic inflammation
  - Narrowing small airways → luminal exudateds, low of alveolar attachments to the small airways
  - lung elastic recoil ↓ + ↓ FEV1 and FEV1/FVC ratio (Expiratory flow limitation) → gas trapping, hyperinflation

Pathological Features of COPD According to the Severity of Airflow Limitation.



Agustí A, Hogg JC. N Engl J Med2019;381:1248-1256

Number of Small Airways According to Severity of Airflow Limitation and Amount of Emphysema.



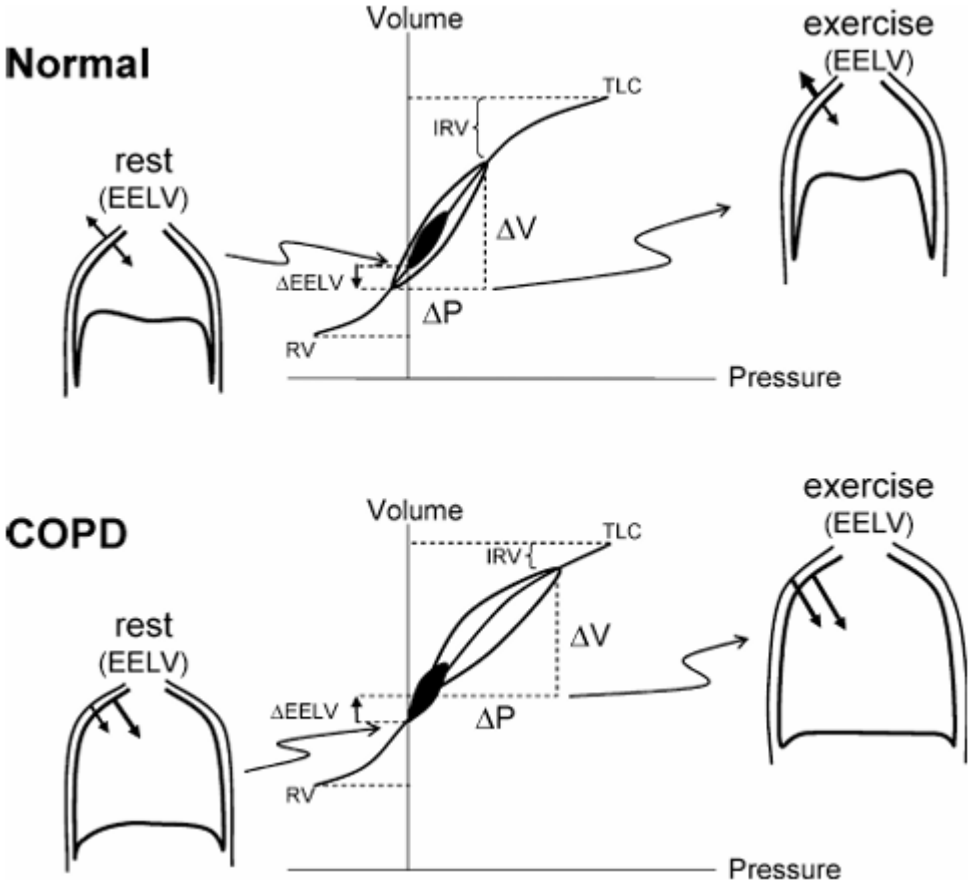
Agustí A, Hogg JC. N Engl J Med2019;381:1248-1256

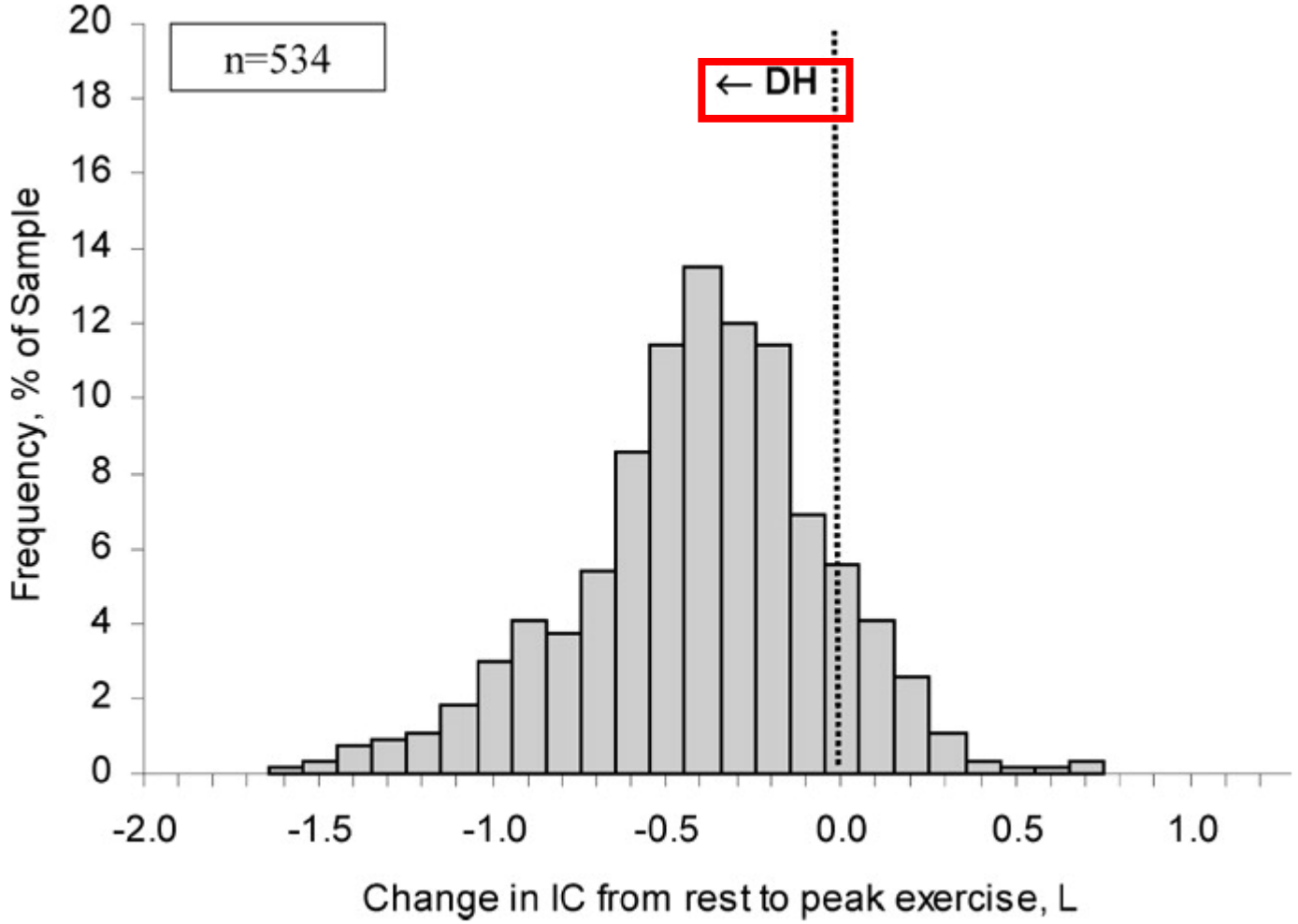
Hyperinflation

- End of expiration, Gas volume ↑

- mild obstruction at rest
  - Dyspnea
  - impaired exercise tolerance
  - increased hospitalization ↑

- Moderate to severe obstruction
  - Dynamic hyperinflation correlates severity of small airways obstruction
  - higher ventilator response to exercise

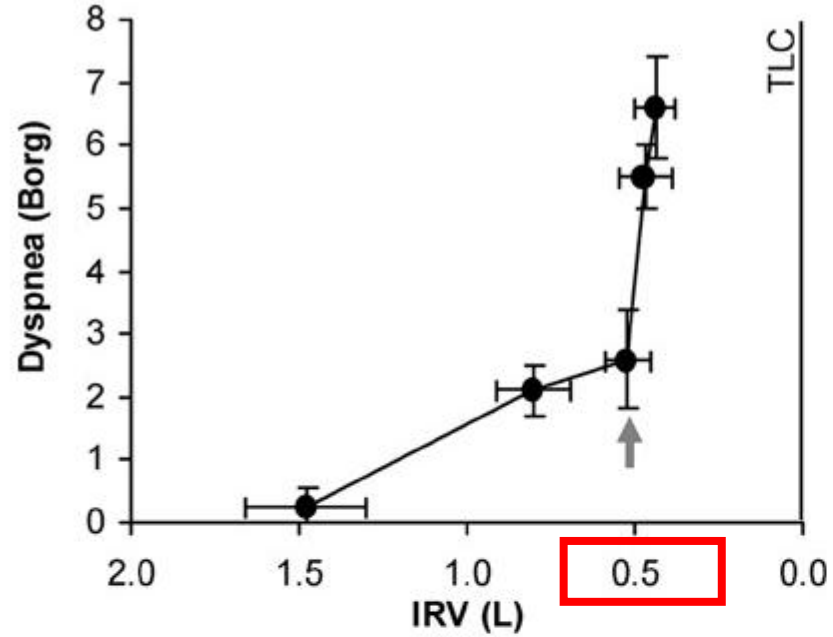


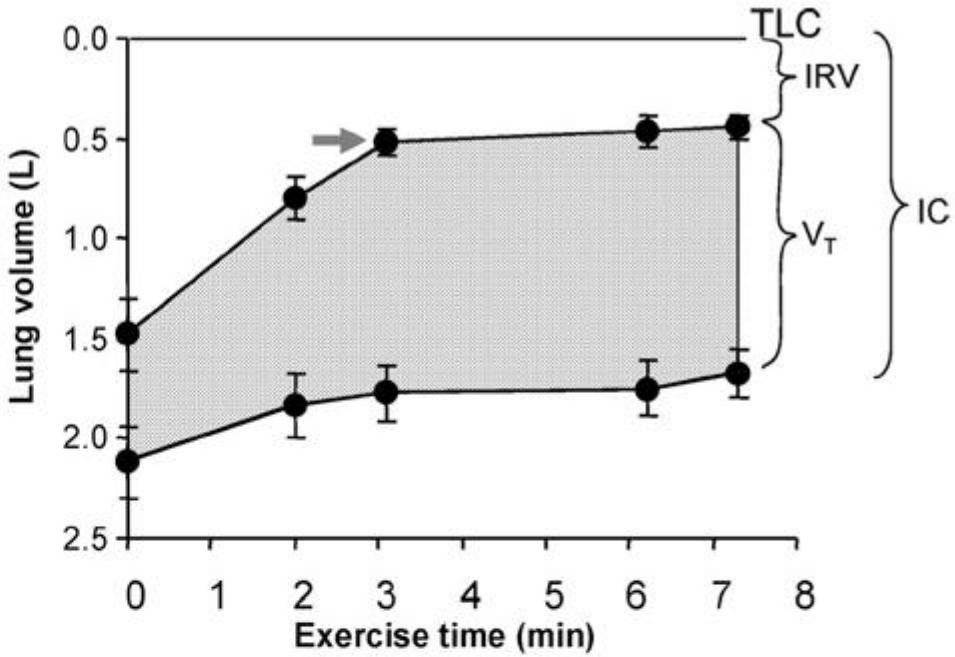


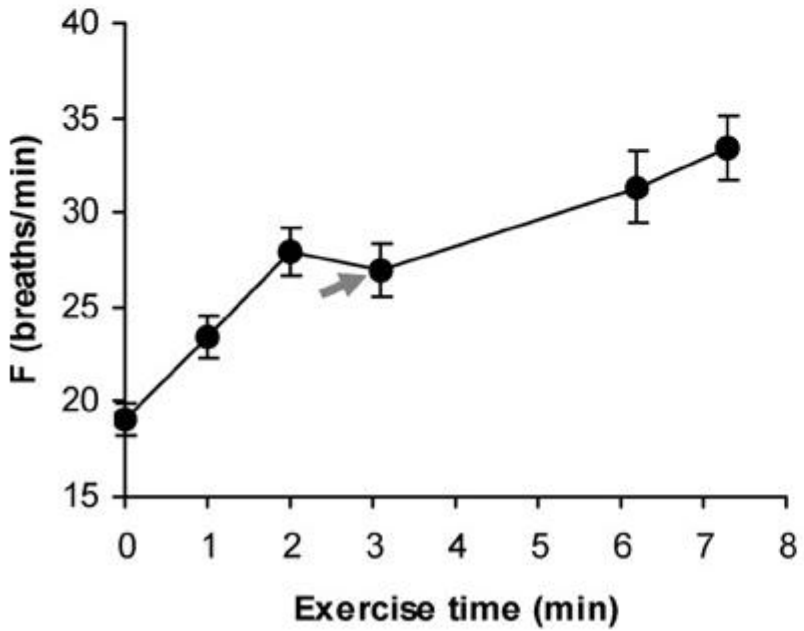
EELV : End expiratory lung volume
IRV : Inspiratory residual volume

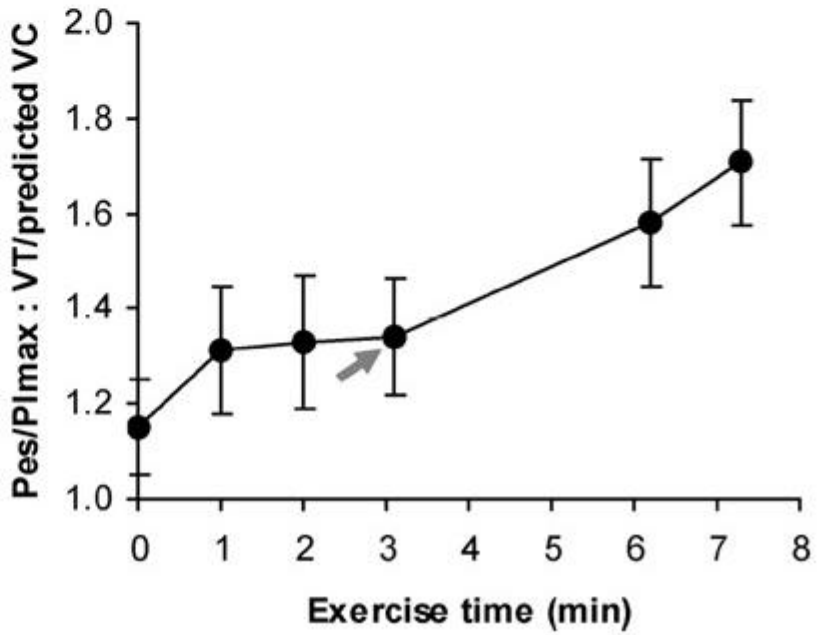
DH : Dynamic lung hyperinflation

COPD, O' Donnell et al, 2006





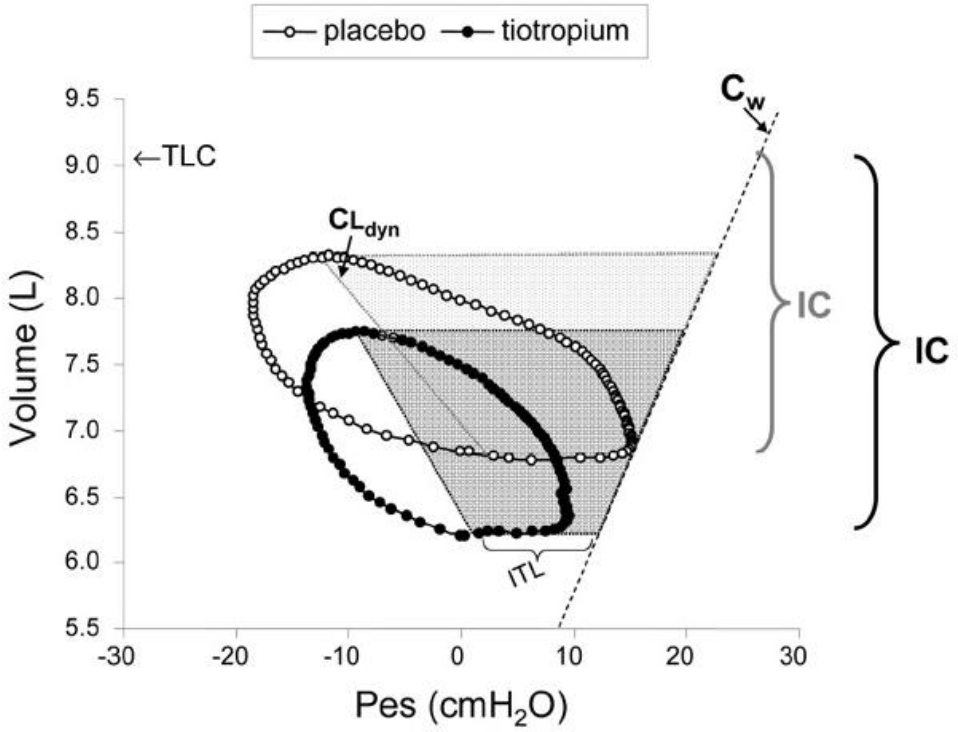


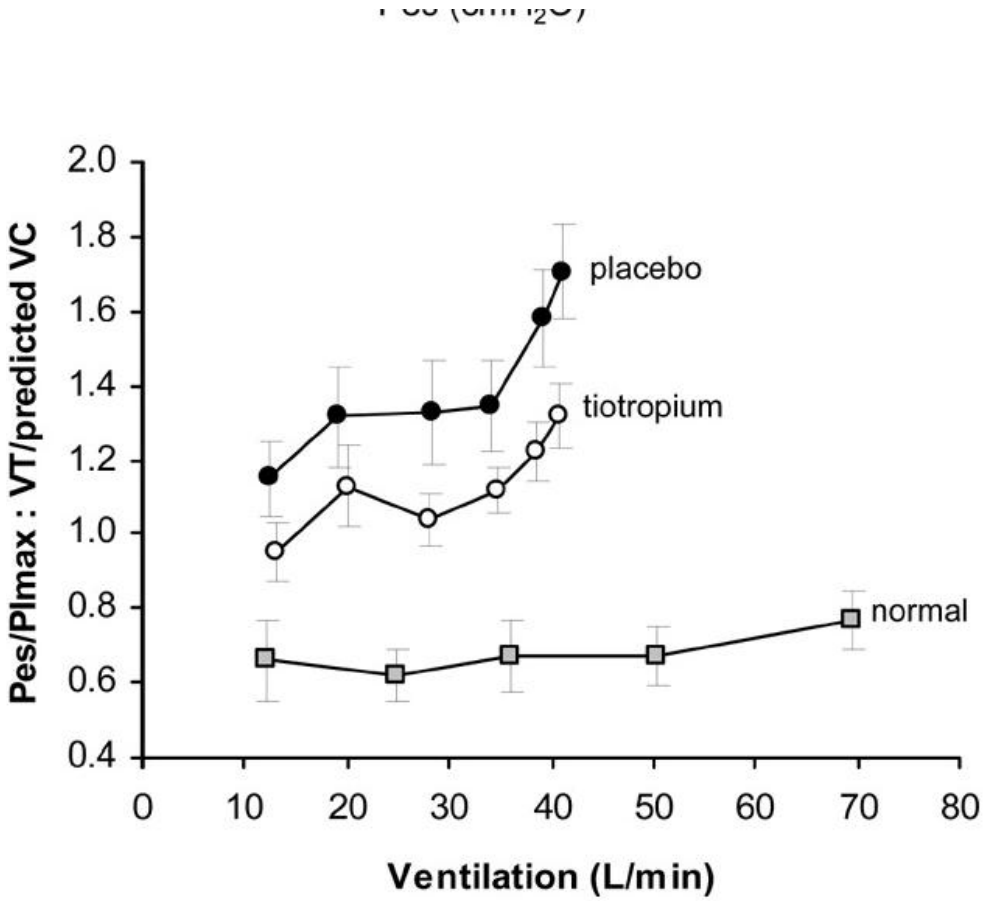


COPD, O' Donnell et al, 2006

Bronchodilator

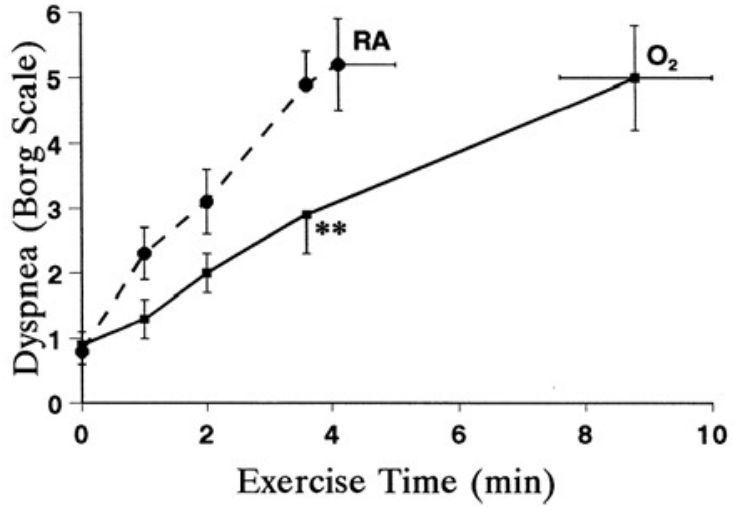
A

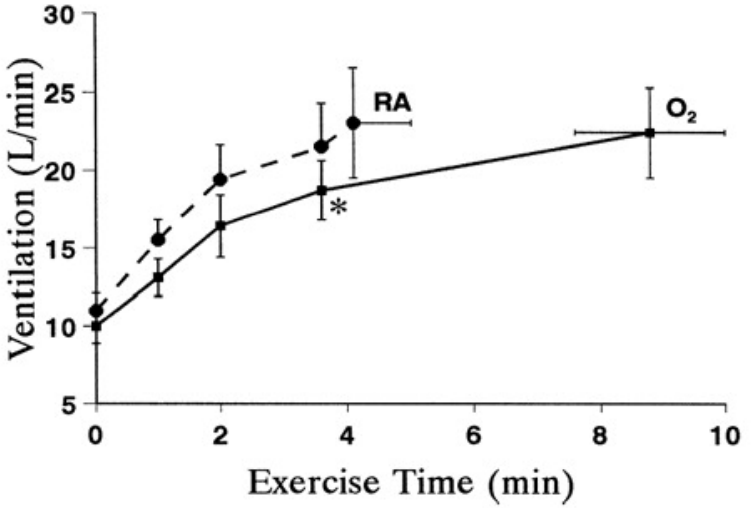


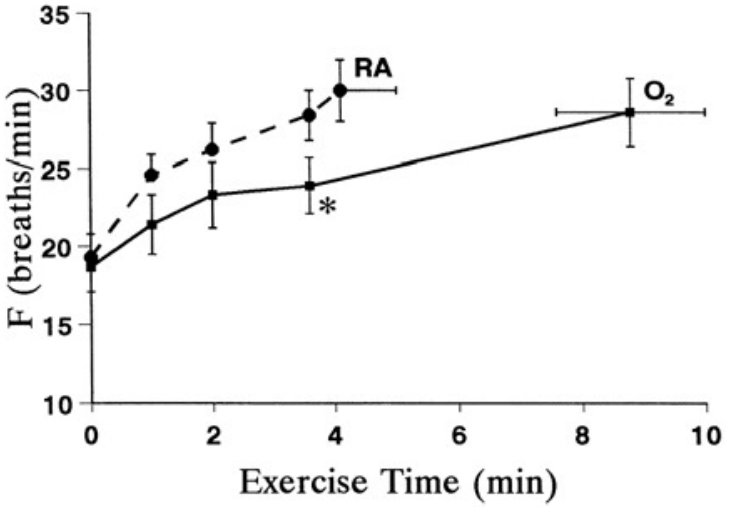


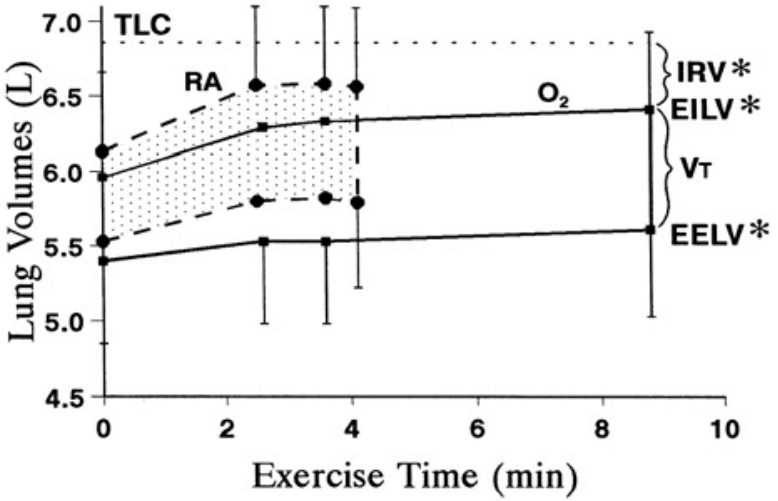
COPD, O' Donnell et al, 2006

Oxygen


Dyspnea (Borg Scale)
RA
O2
**
Exercise Time (min)


Ventilation (L/min)
RA
O2
*
Exercise Time (min)


F (breaths/min)
RA
O2
*
Exercise Time (min)


Lung Volumes (L)
TLC
RA
O2
IRV*
EILV*
VT
EELV*
Exercise Time (min)

Pulmonary gas exchange abnormalities

- Structural abnormality → alter V/Q distribution
- Reduced ventilation (d/t sed
  hypercapnic respiratory failu
- Parencymal destruction → de

Table 3. *Percentages of abnormalities of the principal pulmonary gas exchange descriptors according to the GOLD stage of COPD*

Characteristic	GOLD Stages 1	2	3	4
Pa_{O_2}, < 80 mmHg	40%	60%	72%	97%
Pa_{CO_2}, ≥ 50 mmHg	0	0	1%	21%
$AaPo_2$, ≥ 15 mmHg	87%	90%	94%	100%
Log SDQ, > 0.60	67%	73%	91%	95%
Log SDV, > 0.65	60%	90%	100%	95%
Log SDQ and/or Log SDV	73%	95%	100%	98%
DISP R-E*, > 3.0	93%	95%	100%	100%

Ventilation-perfusion indexes are dimensionless. To convert millimeters of mercury to kilopascals, multiply by 0.133.

Table 2. *Ventilation-perfusion distributions of the patients grouped according to the GOLD stage of COPD*

Characteristic	GOLD Stage 1, Mild	GOLD Stage 2, Moderate	GOLD Stage 3, Severe	GOLD Stage 4, Very Severe	*P* Value*
Shunt, $\%\dot{Q}_T$	1±1	1±1	1±2	2±2§	< 0.01
Low, $\dot{V}_A/\dot{Q}$, $\%\dot{Q}_T$	1.4±3.3	2.8±4.8	4.1±7.0	3.1±7.0	NS
Mean Q	0.83±0.23	0.72±0.23	0.68±0.30	0.65±0.27	NS
Log SDQ	0.83±0.32	0.87±0.30	0.98±0.24	1.00±0.26	< 0.05
High, $\dot{V}_A/\dot{Q}$, $\%\dot{V}_E$	0.9±2.8	7.4±14.4	5.1±10.7*	6.8±11.5†	< 0.05
Mean $\dot{V}$	1.60±0.54	1.54±0.73	1.80±0.52	2.00±0.97§	§ 0.01
Log SDV	0.72±0.25	0.79±0.24	0.98±0.26*‡	1.04±0.28§	< 0.001
DISP R-E*	8.12±4.43	9.02±4.11	13.22±6.08*‡	14.20±4.57§	< 0.001
Dead space, $\%\dot{V}_E$	21±12	28±15	31±12	34±14†	< 0.01
$\dot{V}_E$, l/min	9.0±4.0	9.0±2.3	8.3±2.0	8.4±2.0	NS
$\dot{Q}_T$, l/min	5.8±1.8	6.0±1.3	5.6±1.5	5.3±1.5	NS

Values are means ± SD. Shunt, perfusion-to-alveolar units with $\dot{V}_A/\dot{Q}$ ratios <0.005; low $\dot{V}_A/\dot{Q}$, ratios between 0.005 and 0.1 (excluding shunt); $\dot{Q}_T$, cardiac output; mean Q, the mean $\dot{V}_A/\dot{Q}$ ratio of the blood flow distribution; Log SDQ, dispersion of pulmonary blood flow; mean $\dot{V}$, the mean of $\dot{V}_A/\dot{Q}$ ratio of the ventilation distribution; Log SDV, dispersion of pulmonary blood flow, $\dot{V}_A/Q$ ratio between 10 and 100; DISP R-E*, dispersion of retention minus excretion of inert gases corrected by dead space; dead space, $\dot{V}_A/\dot{Q}$ ratios >100; $\dot{V}_E$, minute ventilation. mean Q, mean $\dot{V}$, Log SDQ, Log SDV, and DISP R-E* are dimensionless. *P* values were determined by the Kruskal-Wallis test: $*P < 0.0083$, GOLD stage 1 vs. 3; $\dagger P < 0.0083$, GOLD stage 1 vs. 4; $\ddagger P < 0.0083$, GOLD stage 2 vs. 3; $\S P < 0.0083$, GOLD stage 2 vs. 4.

Roterto et el, J Appl Physiol, 2009

Pulmonary hypertension

- Inflammatory response in vessel, endothelial cell dysfunction
- Progressive pulmonary hypertension → Rt ventricular hypertrophy , Rt heart failure (Cor pulmonale)
- Diameter of pulmonary artery, exacerbations ↑

Exacerbation

- Trigger : respiratory infection, environmental pollutants

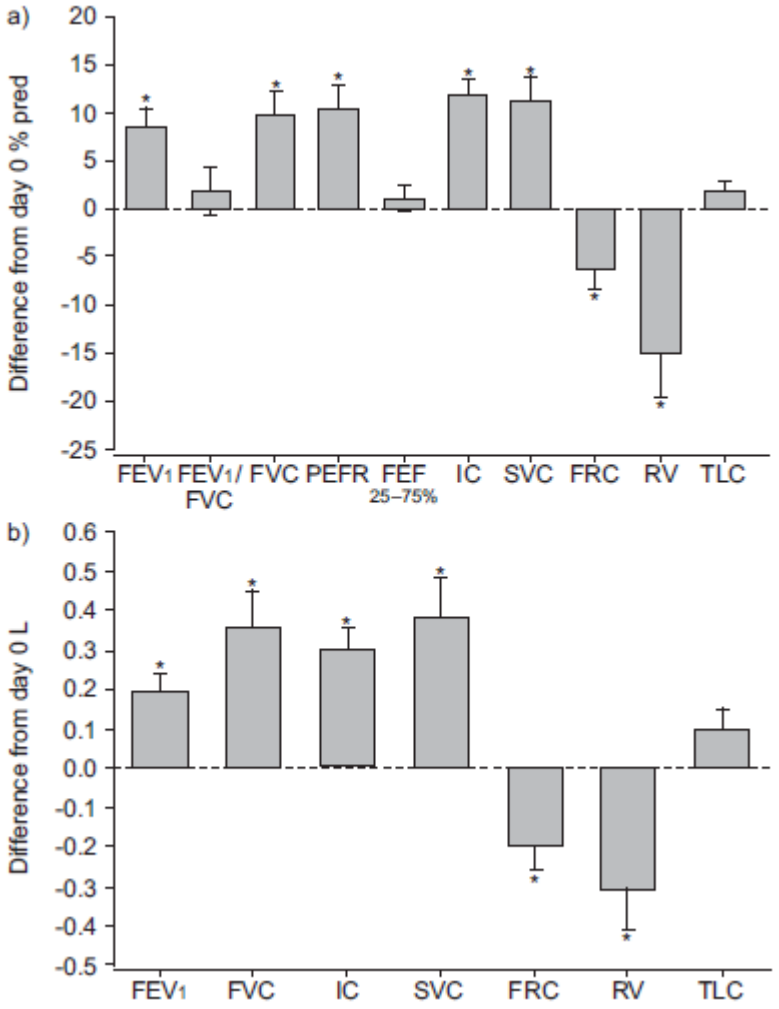
- During exacerbation
  - airway , systemic inflammation ↑
  - gas trapping ↑
  - hyperinflation with reduced expiratory flow

Eur Respir J 2005; 26: 420–428
DOI: 10.1183/09031936.05.00136304

Physiological changes during symptom recovery from moderate exacerbations of COPD

TABLE 3 Recovery from acute exacerbations of chronic obstructive disease as indicated by changes in measurements from study entry (day 0) during follow-up visits

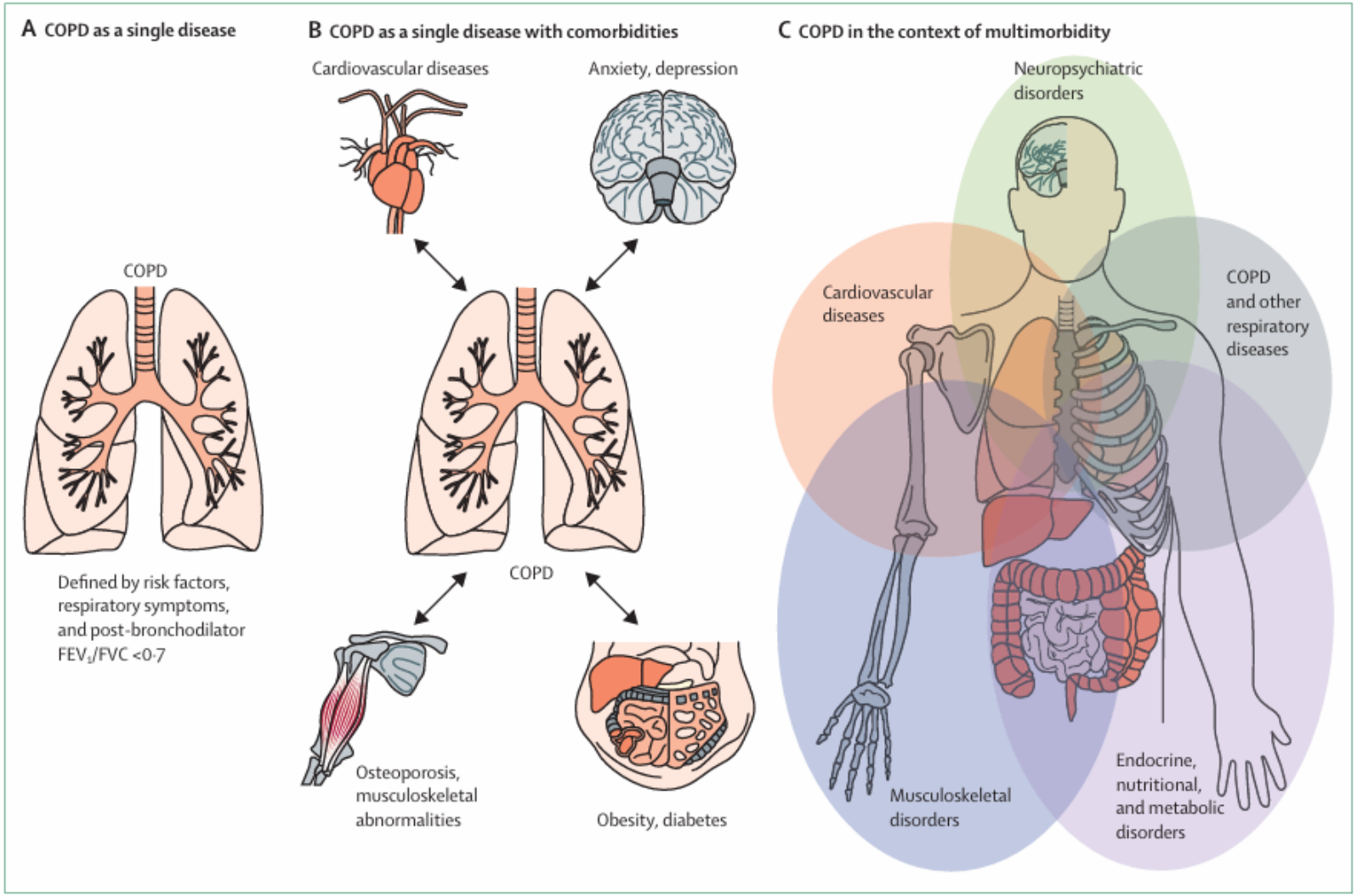
Variable	Day 7	Day 14	Day 30	Day 60	Final visit
Subjects n	8	17	15	15	20
Days post study entry	7±1	15±1	30±1	63±3	60±5 (14–92)
Symptoms					
CRQ dyspnoea	0.1±0.4	1.5±0.3**	1.4±0.4**	1.8±0.5**	1.6±0.4**
Modified MRC	-0.8±0.3*	-0.8±0.3**	-0.9±0.4**	-1.0±0.4**	-0.8±0.3*
TDI	3.0±0.7**	2.7±0.7**	2.4±1.0*	3.3±0.9*	2.8±0.8**
Dyspnoea at rest Borg	-0.2±0.6	-0.7±0.3	-1.4±0.5*	-1.1±0.5	-1.6±0.4**
Pulmonary function					
FEV_1 L	0.00±0.09	0.12±0.06*	0.13±0.06*	0.24±0.06**	0.19±0.05**
FEV_1/FVC %	-2.5±2.4	-0.2±2.1	1.2±1.8	2.0±1.9	1.4±1.8
$FEF_{25-75\%}$ L·s^{-1}	-0.07±0.04	0.01±0.04	0.04±0.03	0.04±0.04	0.03±0.03
PEFR L·s^{-1}	0.09±0.14	0.70±0.22**	0.65±0.25**	0.64±0.18**	0.60±0.14**
FVC L	0.15±0.12	0.30±0.11**	0.23±0.09**	0.40±0.11**	0.35±0.10**
IC L	0.06±0.07	0.26±0.06**	0.27±0.07**	0.30±0.06**	0.30±0.05**
SVC L	0.27±0.10*	0.34±0.11**	0.32±0.07**	0.47±0.12**	0.38±0.10**
TLC L	0.07±0.15	-0.00±0.09	0.12±0.07	0.13±0.07	0.09±0.06
FRC L	0.00±0.12	-0.28±0.09**	-0.16±0.10*	-0.17±0.07*	-0.20±0.06**
RV L	-0.21±0.11	-0.41±0.11**	-0.20±0.11*	-0.34±0.12*	-0.31±0.10*
$sRaw$ % pred	-15±50	-133±57*	-67±57	-128±51*	-102±43*
$D_{L,CO}/VA$ % pred	6±1**	2±3	-2±3	1±3	2±3
Steady-state rest (room air)					
Sa,O_2 %	0.4±0.2	1.6±0.8	1.5±0.5	2.8±0.9*	2.1±0.9**
V'_{O_2} L·min^{-1}	-0.00±0.02	0.02±0.02	0.02±0.02	0.02±0.02	0.01±0.02
V'_{CO_2} L·min^{-1}	0.00±0.01	0.01±0.02	0.02±0.02	0.02±0.02	0.01±0.02
V'_E L·min^{-1}	-1.8±1.1	-0.7±0.6	-0.1±0.5	-0.3±0.7	-0.3±0.6
Vt L	0.05±0.04	0.01±0.04	0.02±0.05	0.04±0.06	0.03±0.05
f breaths·min^{-1}	-4.0±0.7**	-1.3±1.0	-0.8±1.3	-1.6±1.1	-1.1±1.0
ti/t_{TOT}	-0.01±0.02	-0.02±0.02	-0.00±0.01	-0.00±0.02	-0.02±0.02



Parker et el, ERJ (2005)

Multimorbidity

- Co-occurance of COPD with possible shared mechanisms and risk factors
- Smoking, aging, inactivity
- Inflammatory mediators – skeletal muscle wasting, cachexia, worsen comorbidity



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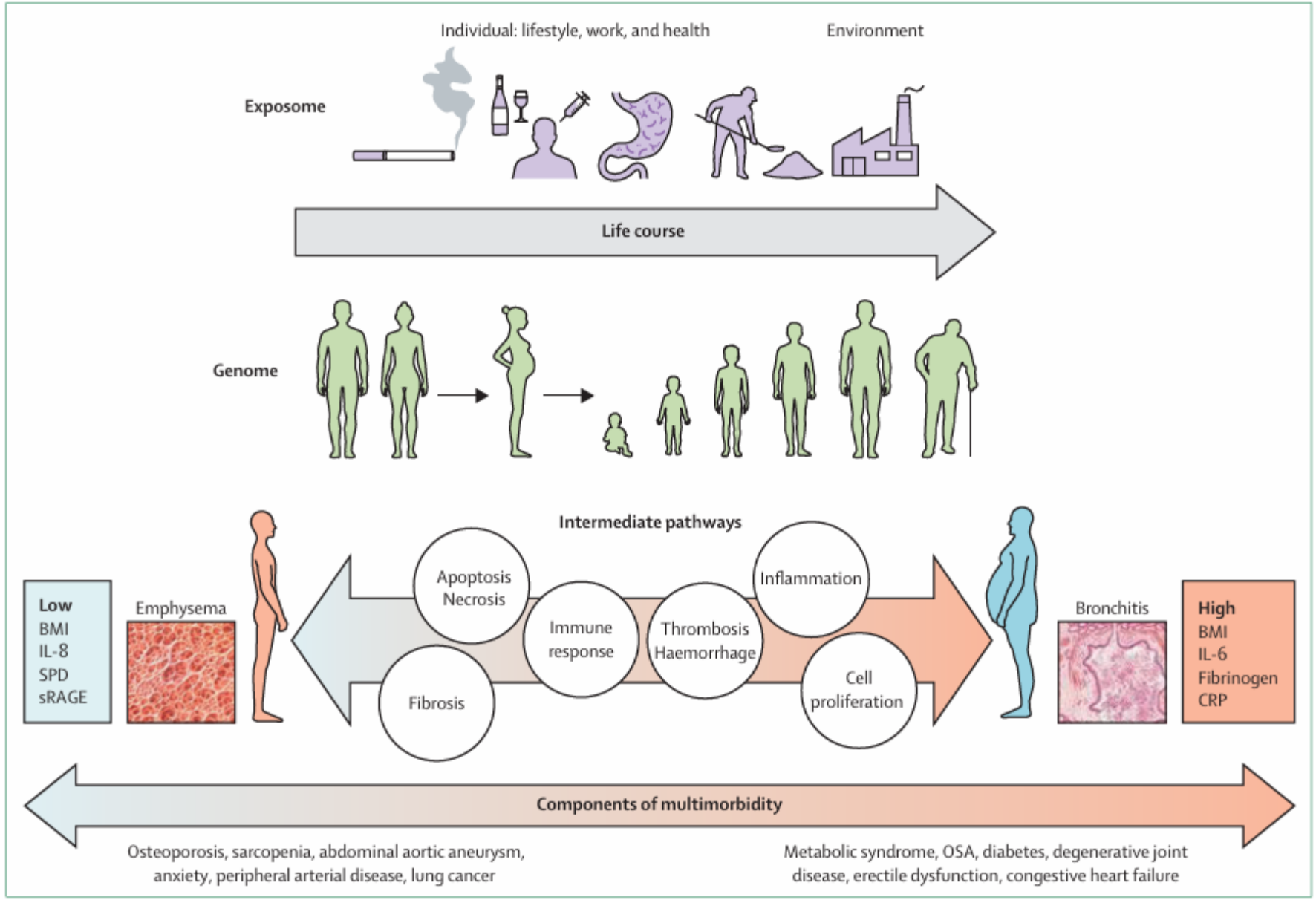

Fabbri et el. Lancet Resp Med. (2023)

Summary

- Type 2 inflammation in COPD
- Airflow obstruction and gas trapping
- Hyperinflation
- Pulmonary gas exchange abnormalities
- Pulmonary hypertension
- Exacerbation
- Multimorbidity

경청해주셔서 감사합니다.