COPD Update: 2019

Philip T. Diaz, MD OSU Pulmonary and Critical Care Medicine

You see a new patient for shortness of breath. He is a former smoker (50 pack years) and has had progressive DOE, such that he has some trouble keeping up with people his own age walking on level ground. In the office, spirometry shows an FEV1/FVC of 0.55 and an FEV1 of 60% of predicted. Room air oxygen saturation is 94% at rest and while walking. What is the diagnosis? Why is he dyspneic without significant oxygen desaturation?

Presentation Outline

- Diagnosis/pathophysiology/pathogenesis
- Management of stable COPD
  - Pharmacologic treatment
  - COPD as a systemic disease
  - Oxygen therapy
- Management of exacerbations
- Surgical and bronchoscopic management

Definition of Disease

- COPD, a common preventable and treatable disease, is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities that is usually caused by significant exposure to noxious particles or gases.

Global Initiative for Chronic Obstructive Lung Disease: “GOLD” guidelines 2019 update.

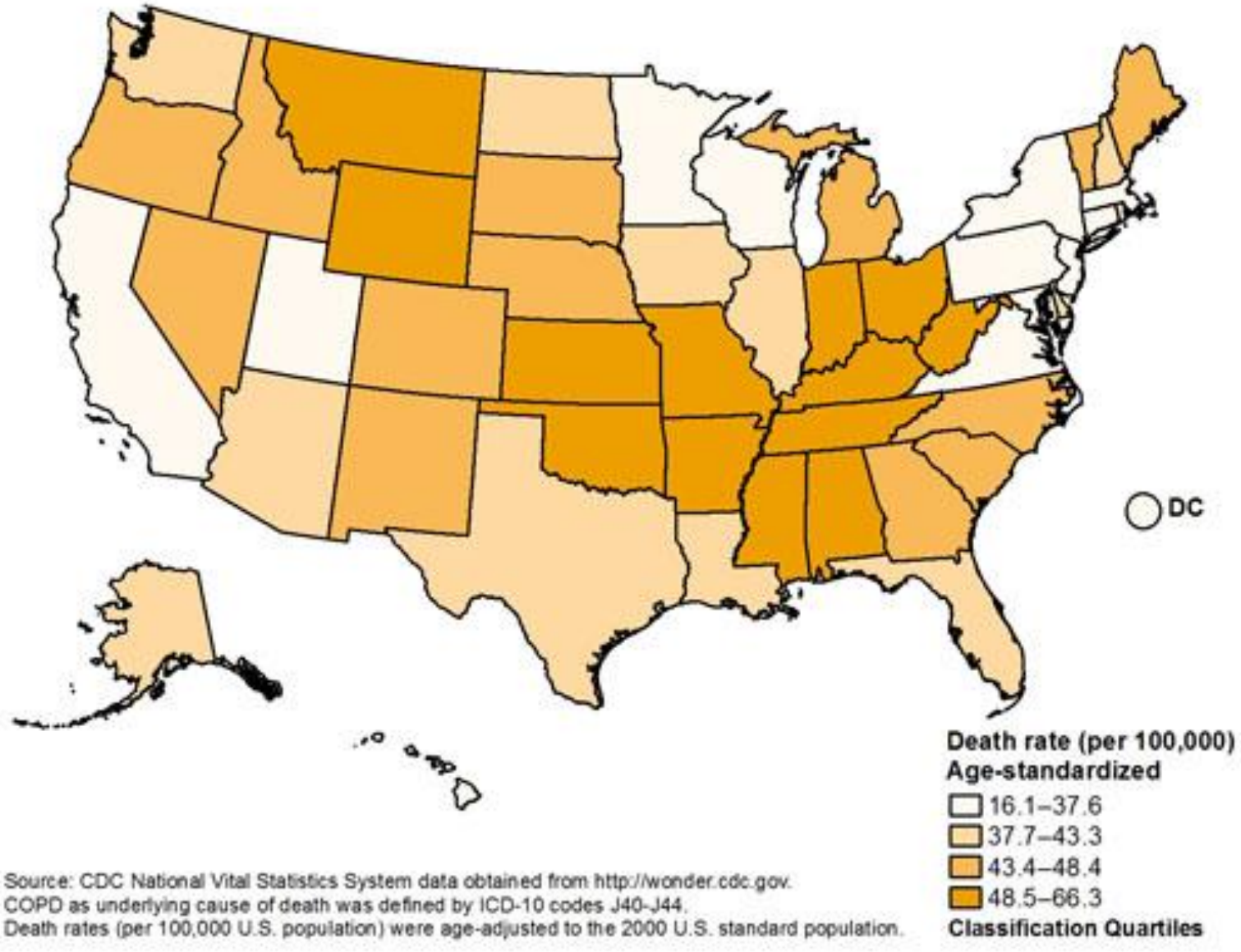
COPD: major diagnostic criteria

- Symptoms: dyspnea on exertion, cough
- Exposure
  - Cigarette smoking: generally > 20 pack years
- Air-flow obstruction
  - Reduced ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC)

COPD Epidemiology

- 6.3% of US adults have COPD (CDC 2011)
- Leading cause of mortality
  - In US: 3rd leading cause
  - Worldwide: projected to be 3rd in 2020
- Annual cost in US
  - 29.5 billion direct
  - 20.4 billion indirect

Age-Standardized Death Rate (Per 100,000 U.S. Population) for Chronic Obstructive Pulmonary Disease (COPD)— United States, 2010

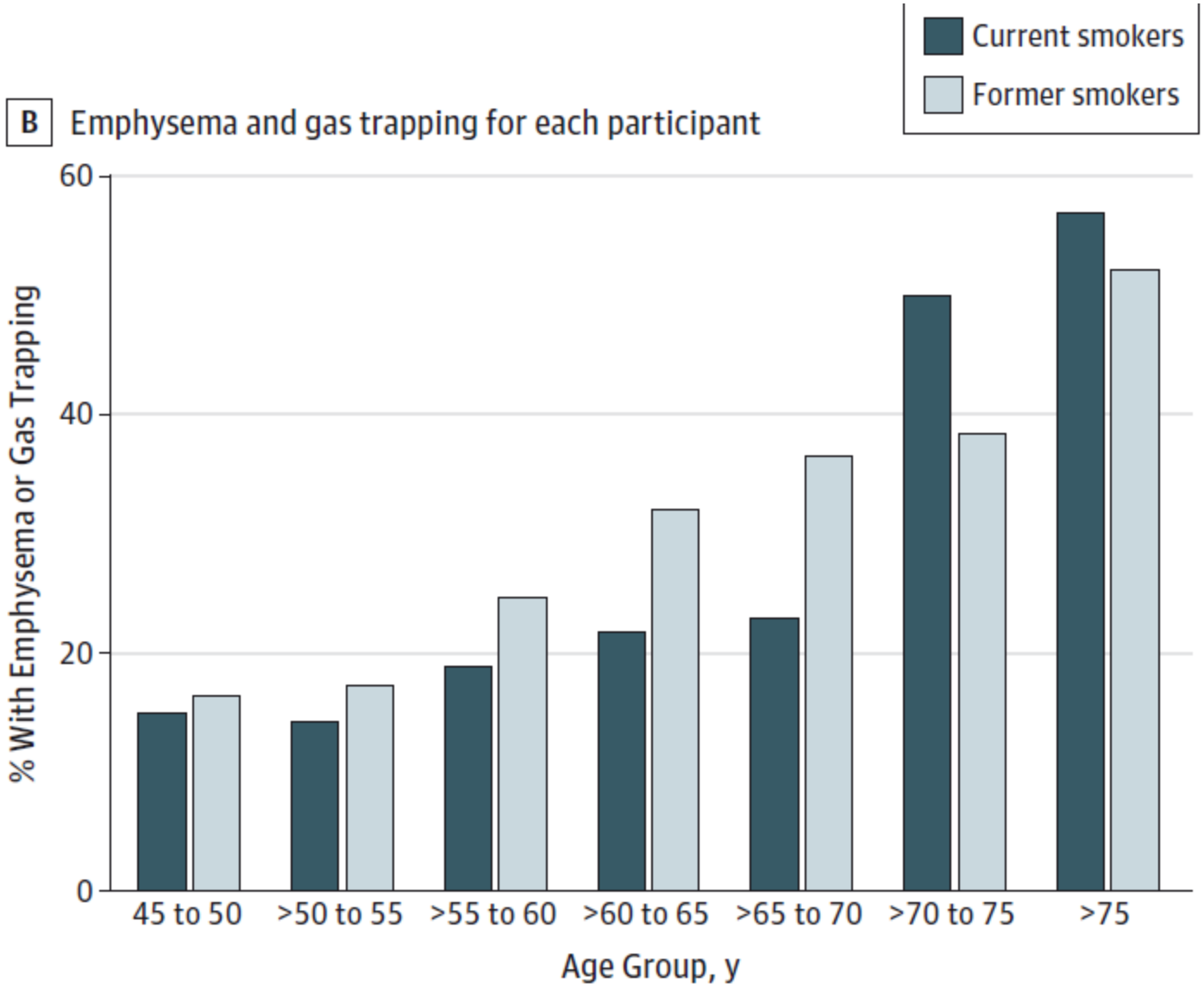


Source: CDC National Vital Statistics System data obtained from http://wonder.cdc.gov.
COPD as underlying cause of death was defined by ICD-10 codes J40-J44.
Death rates (per 100,000 U.S. population) were age-adjusted to the 2000 U.S. standard population.

Lung disease in smokers with normal spirometry

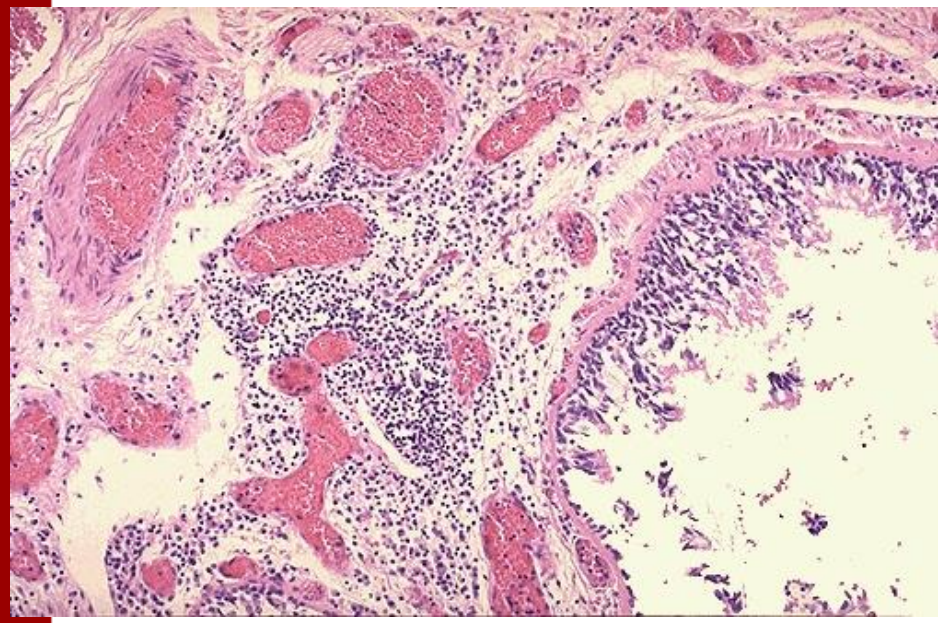
- Clinical significance of symptoms in smokers with normal pulmonary function **(NEJM 2016)**
  - High prevalence of symptoms, chest CT airways disease and “COPD” treatment among current/former smokers with normal spirometry
- Clinical and radiologic disease in smokers with normal spirometry **(JAMA 2015)**
  - High prevalence of symptoms, chest CT emphysema among current former smokers with normal spirometry
  - “35 million smokers in US with unrecognized disease”

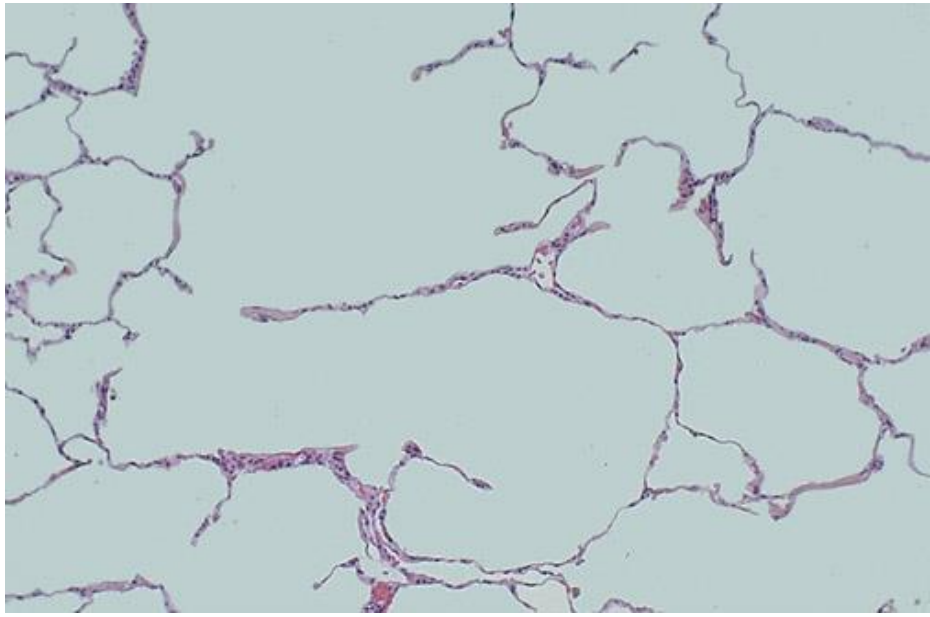
High prevalence of HRCT abnormalities in subjects with normal spirometry, Regan et al. JAMA 2015



COPD: pulmonary pathophysiology

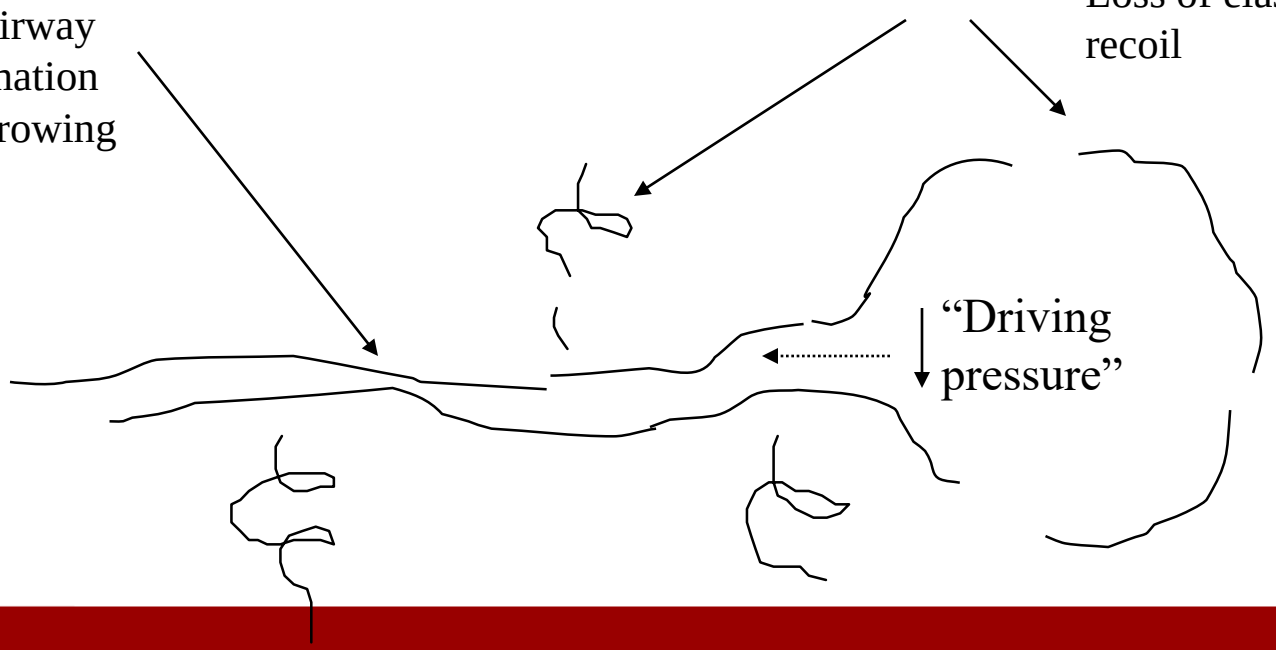
- Expiratory air-flow limitation
- Ventilation-perfusion mismatch
- Hyperinflation





Chronic bronchitis

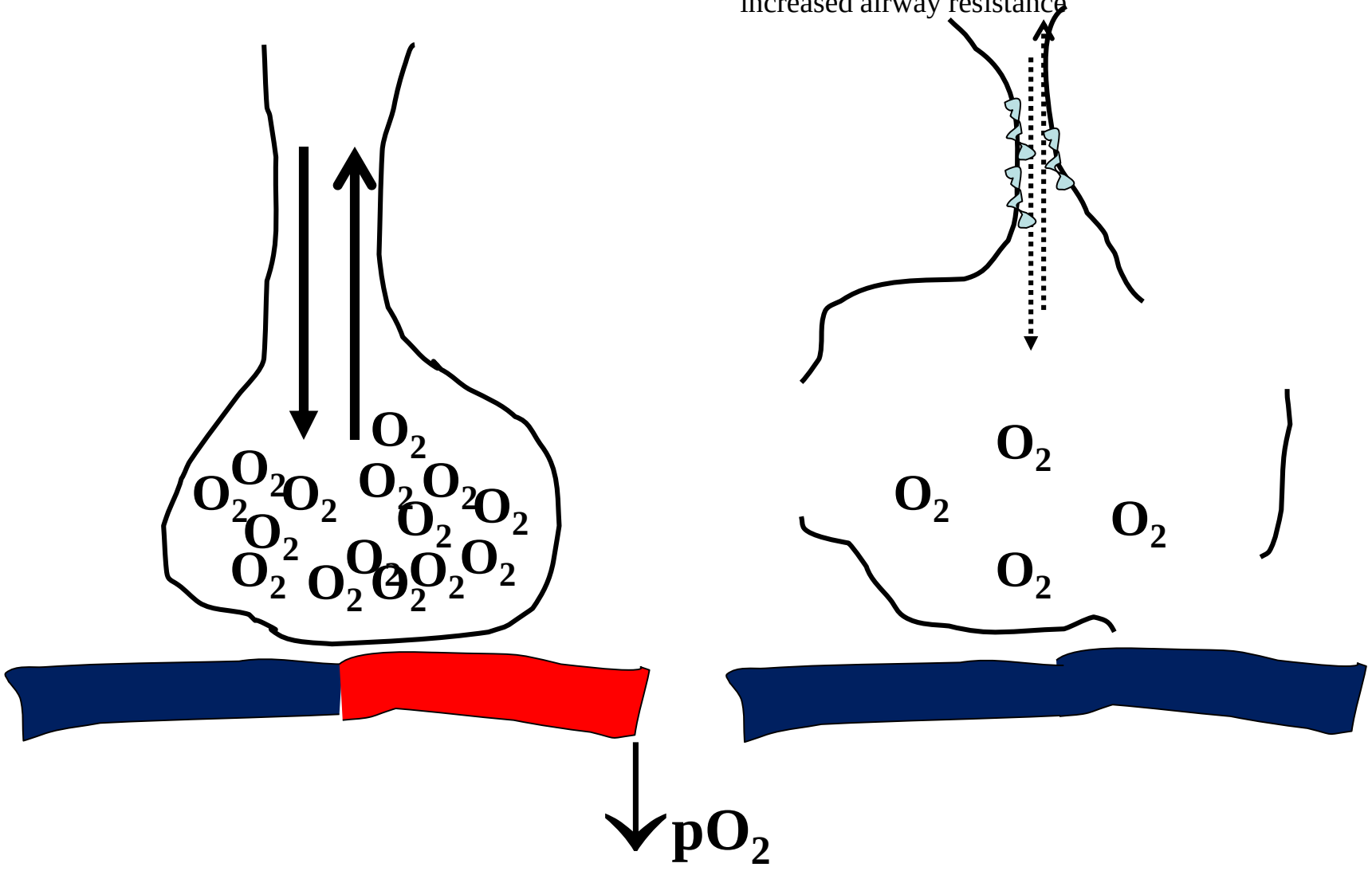
Emphysema



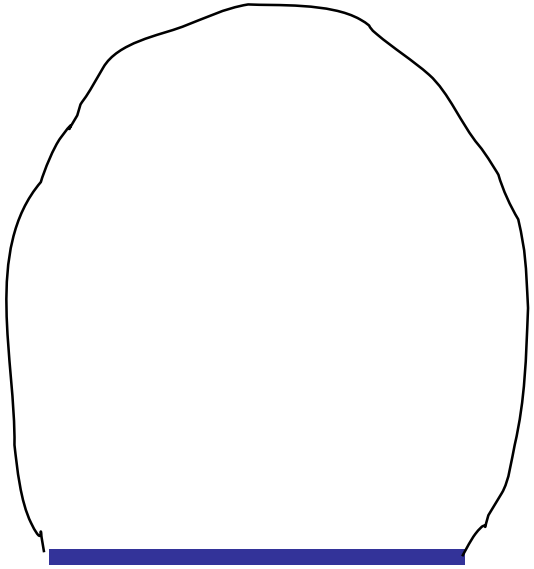
Emphysema: lung units with increased compliance fill and empty more slowly

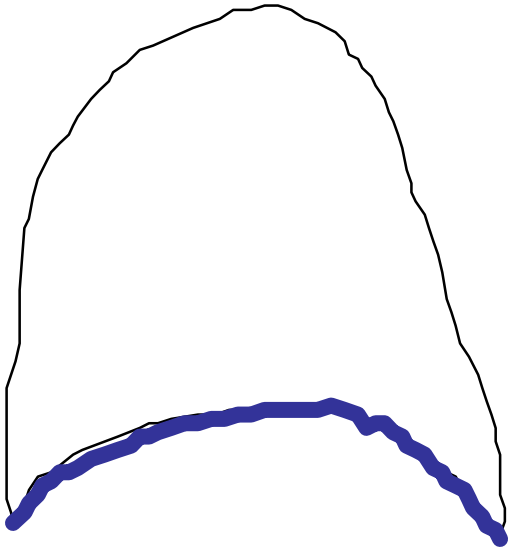
Chronic bronchitis: airway inflammation/mucous production leads to increased airway resistance

Normal



Hyperinflation and respiratory muscle weakness





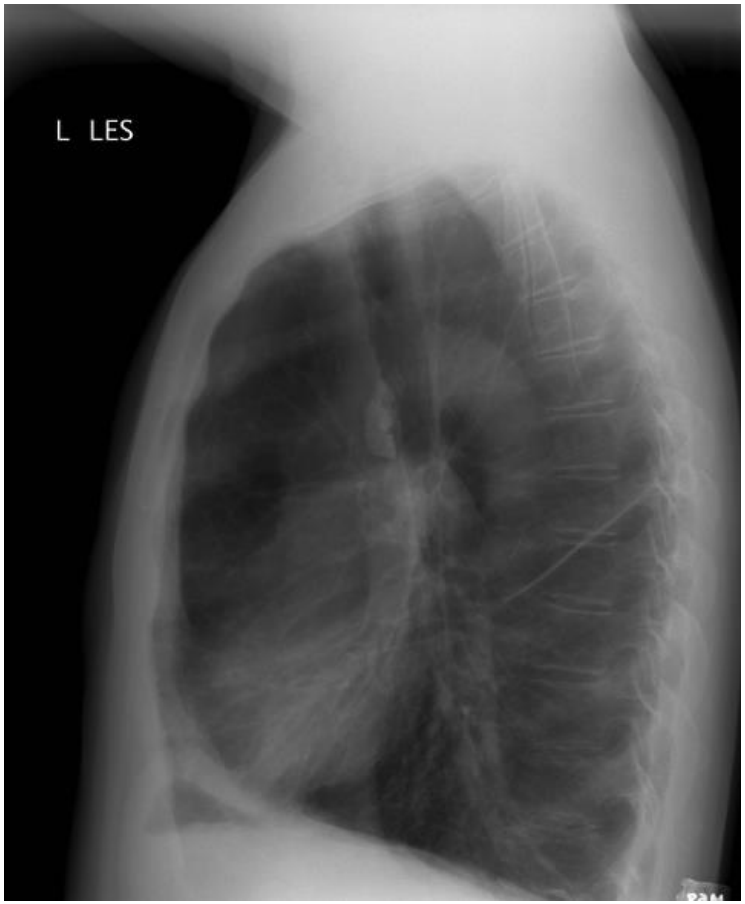
Shorter muscle length - less actin, myosin overlap

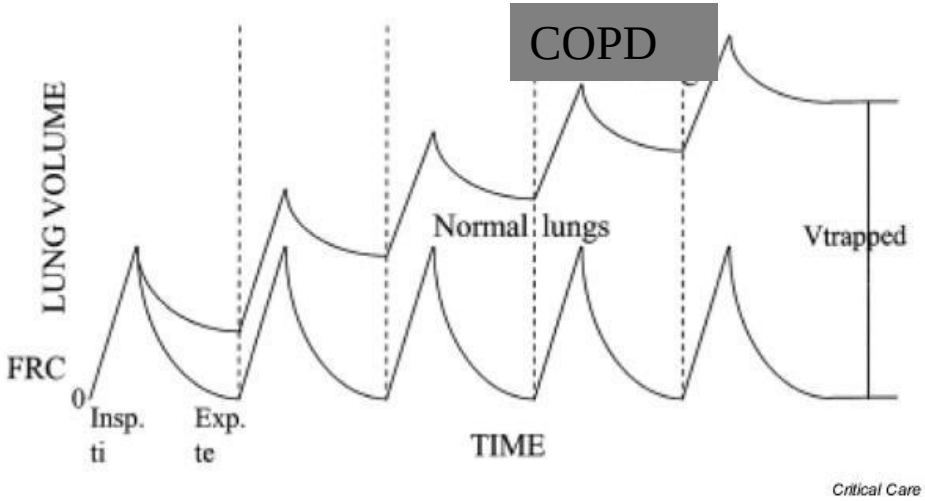
Decreased zone of apposition

Emphysema

Normal

Dynamic hyperinflation in COPD

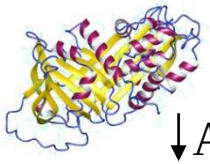




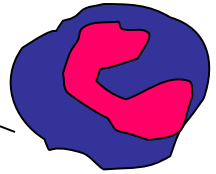
COPD Pathogenesis

54 y.o. non-smoker with severe air-flow obstruction

Protease – Antiprotease hypothesis of emphysema pathogenesis

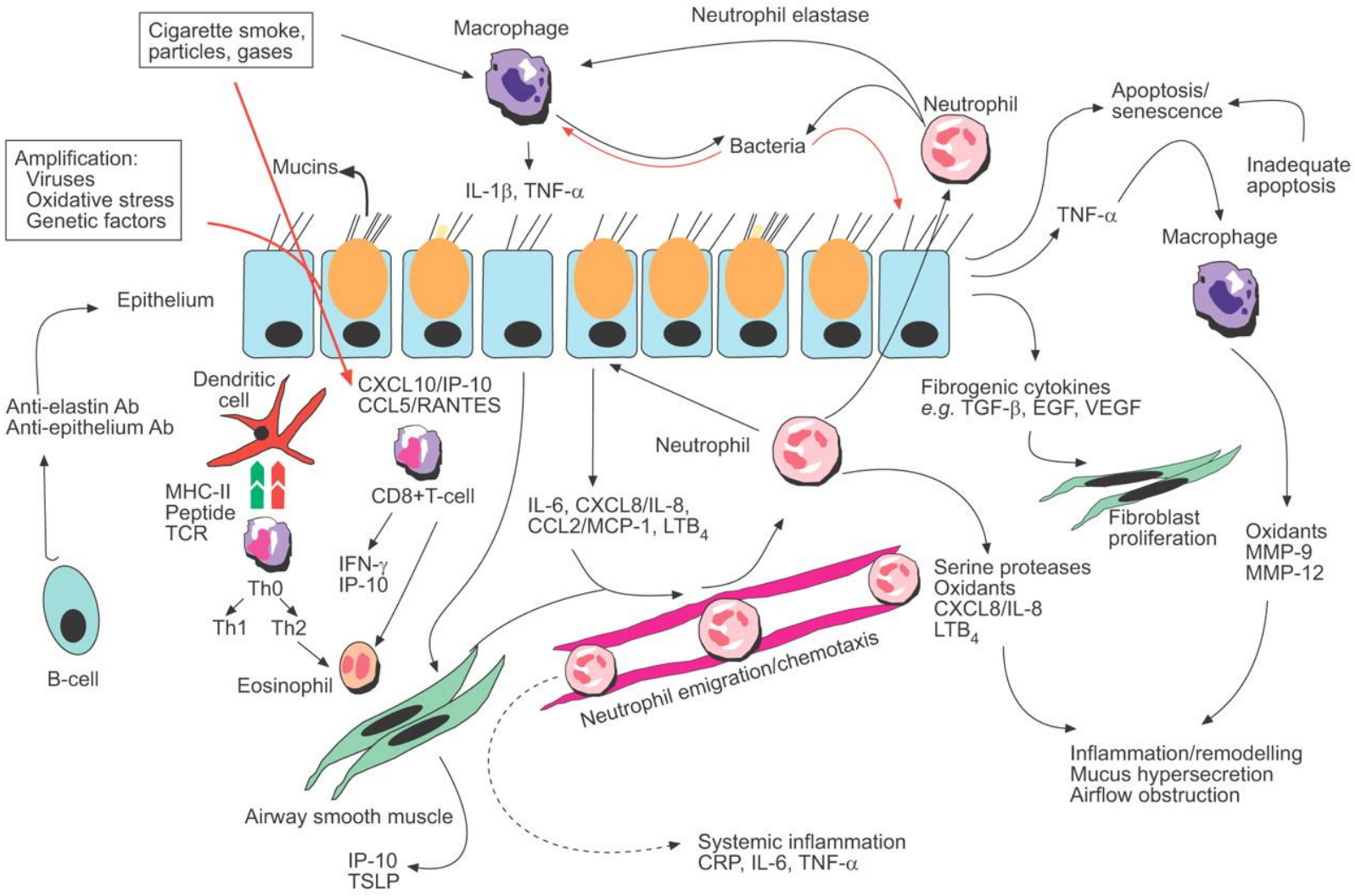


↓Alpha-1 antitrypsin



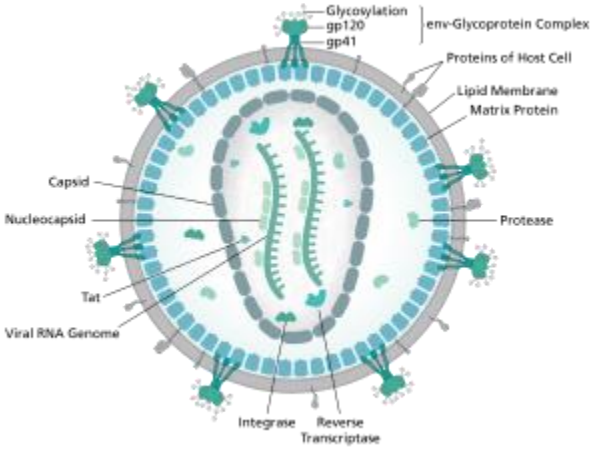
↑Neutrophil elastase

Inflammation, immunity, tissue repair and destruction in COPD

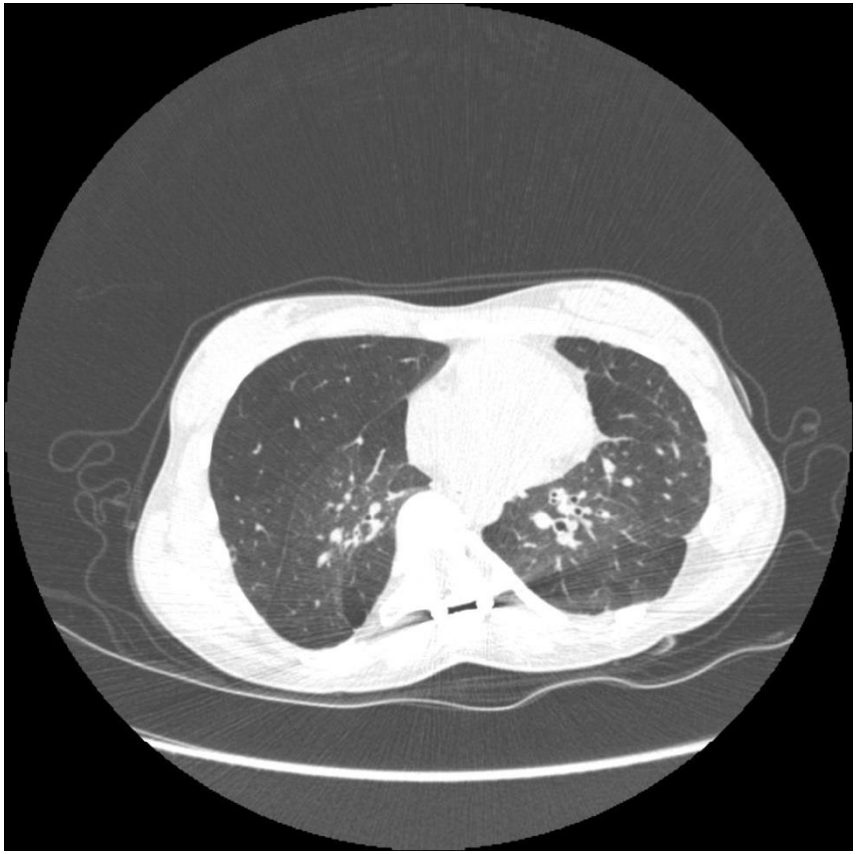


Fare, Eur Respir J, 2008

Risk factors for COPD development



HIV+



24 y.o. female never smoker with severe air-flow obstruction

34 y.o. female never smoker with severe air-flow obstruction

Presentation Outline

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1. Inhaled corticosteroid (ICS)
2. Inhaled corticosteroid/long acting beta agonist combination (ICS/LABA)
3. Long acting muscarinic antagonist (LAMA)
4. Whatever the insurance company tells you to do…

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COPD Assessment

- "GOLD" Categories based on:
  - Severity of spirometric abnormality
  - Symptoms
  - Future risk of exacerbations
- Other assessment considerations
  - CXR
  - Pulse oximetry; consider ABG if $\leq$ 92%
  - Alpha-1 anti-trypsin if age < 45 or strong family history

GOLD COPD “phenotyping” based on degree of air-flow obstruction

FEV1/FVC less than 0.7

- **GOLD 1** FEV1 ≥ 80% predicted
- **GOLD 2** 50% ≤ FEV1 > 80%
- **GOLD 3** 30% ≤ FEV1 > 50%
- **GOLD 4** FEV1 < 30% predicted

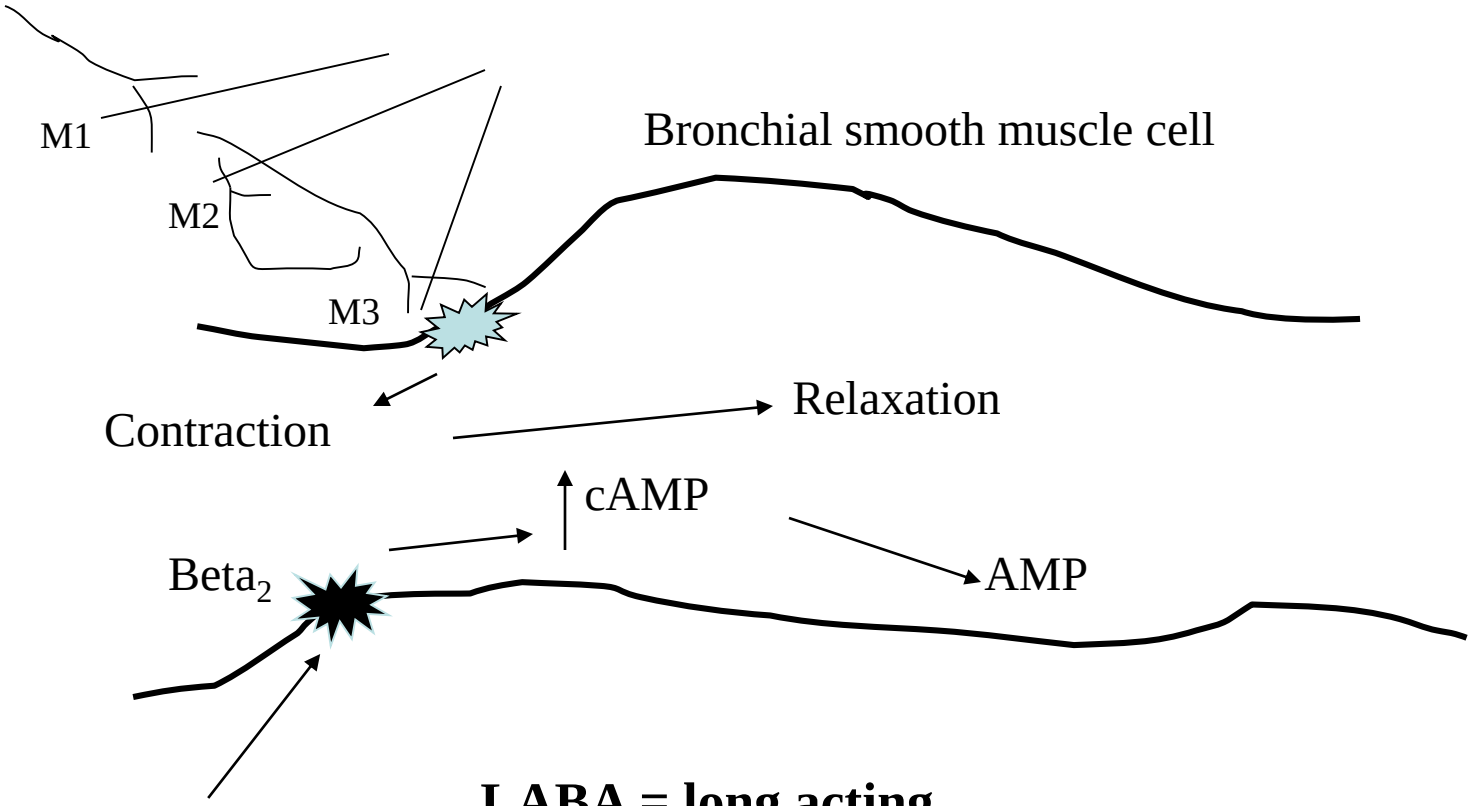
Additional GOLD “COPD phenotyping” – based on exacerbation risk and symptoms

- **C , D** = Increased Risk of Exacerbations
  - 2 or more exacerbations in the previous year (or 1 requiring hospitalization)
- **B**, **D** = Increased Breathlessness/Dyspnea
  - Walk slower than a similar age person on level ground (MRC stage 2)
  - COPD Assessment Test (CAT) score $\geq$ 10

Bronchodilator therapy in COPD

LAMA = long acting muscarinic antagonist

Muscarinic Antagonists (anticholinergic)



Beta$_2$-Agonists

LABA = long acting beta-agonist

Combination inhalers for COPD

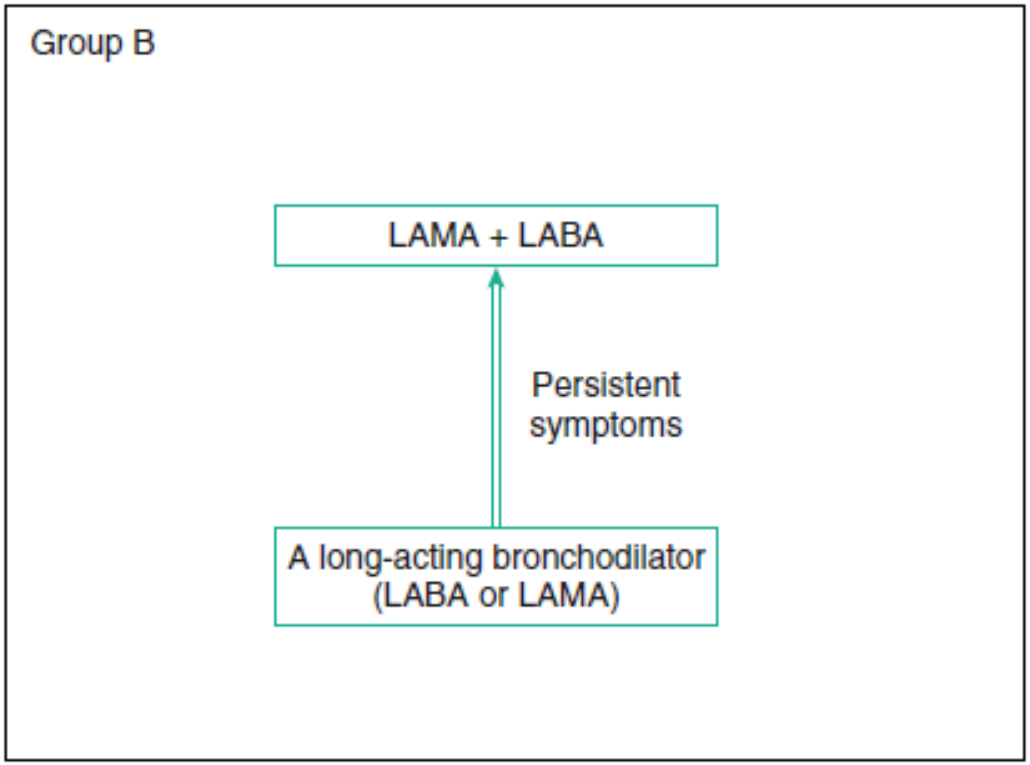
- **LAMA/LABA**
  - Umeclidinium/Vilanterol
    - ***Anoro***
  - Tiotropium/Olodaterol
    - ***Stiolto***
  - Glycopyrrolate/Formoterol
    - ***Bevespi***
  - Glycopyrrolate/indacaterol
    - ***Ultibro***

- **ICS/LABA**
  - Fluticasone/Salmeterol
    - ***Advair***
  - Budesonide/Formoterol
    - ***Symbicort***
  - Mometasone/Formoterol
    - ***Dulera***
  - Fluticasone/Vilanterol
    - ***Breo***

LAMA/LABA/ICS

- Umeclidinium/Vilanterol/Fluticasone
- ***Trelegy***

COPD patient with substantial symptoms, but no increased exacerbation risk



American Journal of Respiratory and Critical Care Medicine Volume 195 Number 5 | March 1 2017

You see a new patient for evaluation of COPD. He was hospitalized earlier in the year for an acute exacerbation but is now back to baseline. He notes significant DOE, such that he has trouble walking 100 yards without stopping. His only respiratory medication is albuterol MDI and in a nebulizer which he uses 6 times a day. Recent post-bronchodilator spirometry shows an FEV1/FVC of 0.49 and an FEV1 of 51% of predicted. He has a CAT score of 22 and his blood eosinophil count is 150. Based on the available information you should recommend the following maintenance therapy:

1. LAMA
2. ICS/LABA
3. LAMA/LABA
4. ICS

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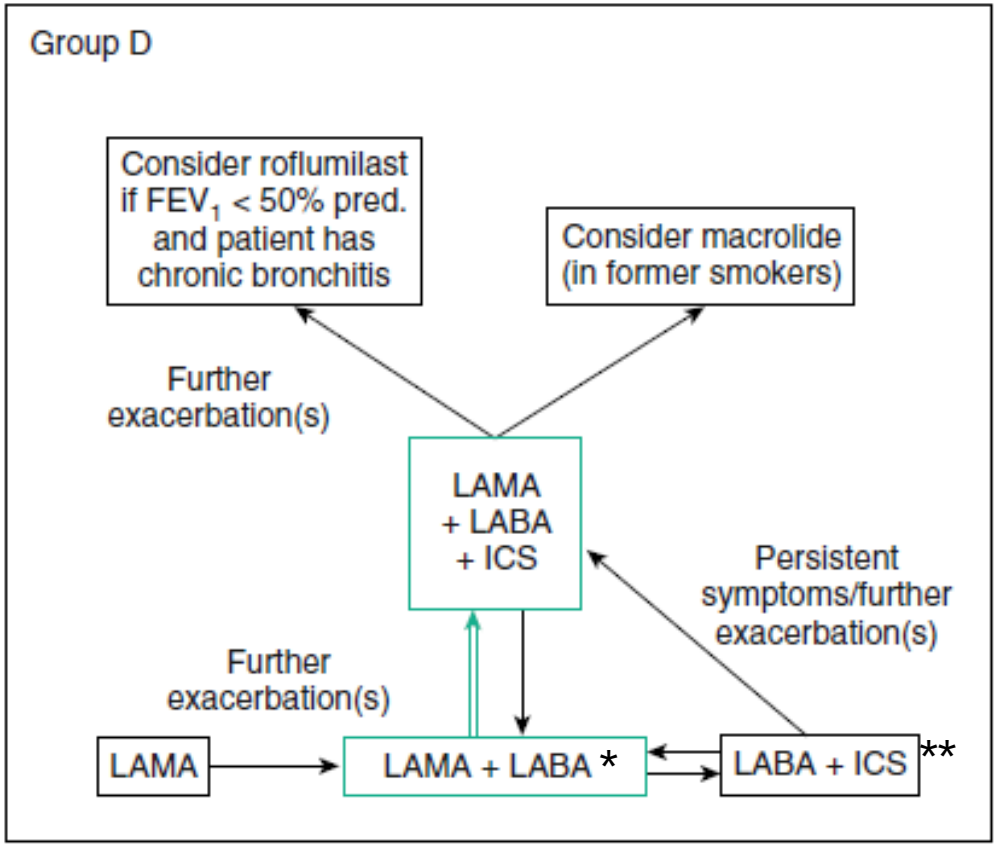
1. LAMA
2. ICS/LABA
3. LAMA/LABA
4. ICS

Drug therapy considerations based on exacerbation risk

- If increased risk of exacerbation (GOLD C,D) the regimen should contain a LAMA or ICS
- ICS therapy in COPD should be given in a combination inhaler ICS/LABA
- Increased eosinophils (≥300) may predict ICS responsiveness

COPD patient with substantial symptoms, and increased exacerbation risk



*if highly symptomatic

** if blood eos ≥300

American Journal of Respiratory and Critical Care Medicine Volume 195 Number 5 | March 1 2017

The NEW ENGLAND JOURNAL of MEDICINE

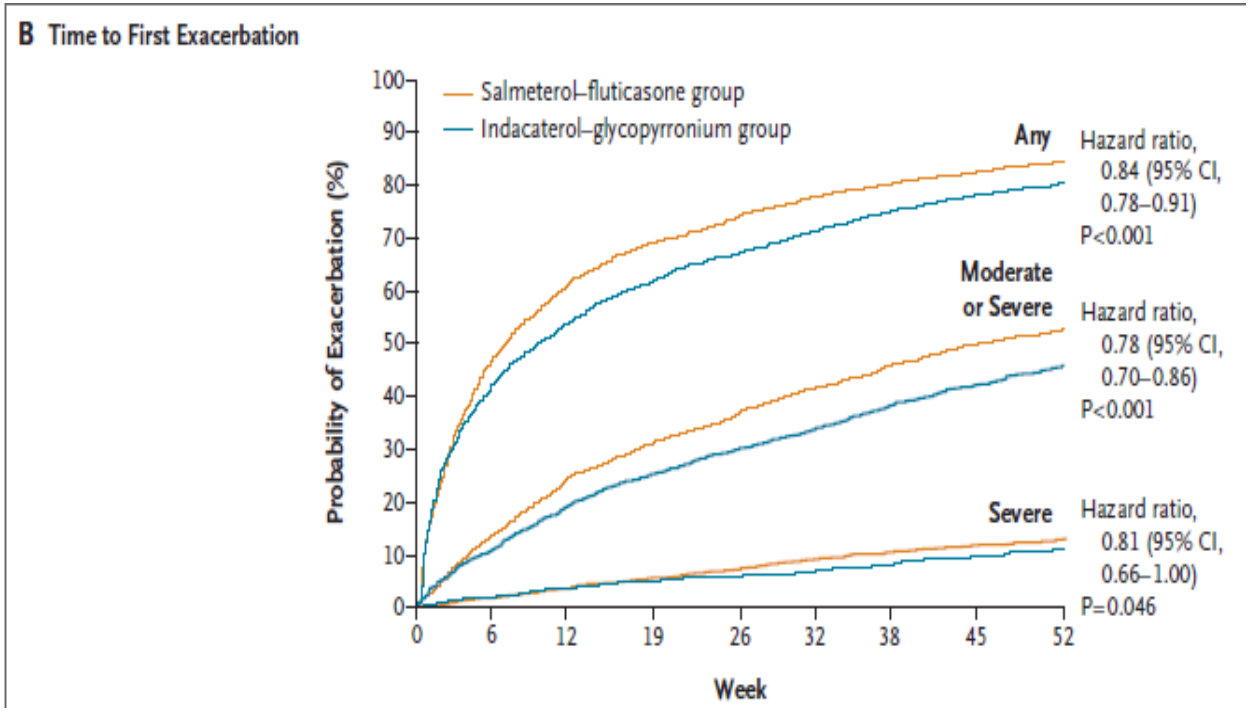
ORIGINAL ARTICLE

"Ultibro"
"Advair"

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

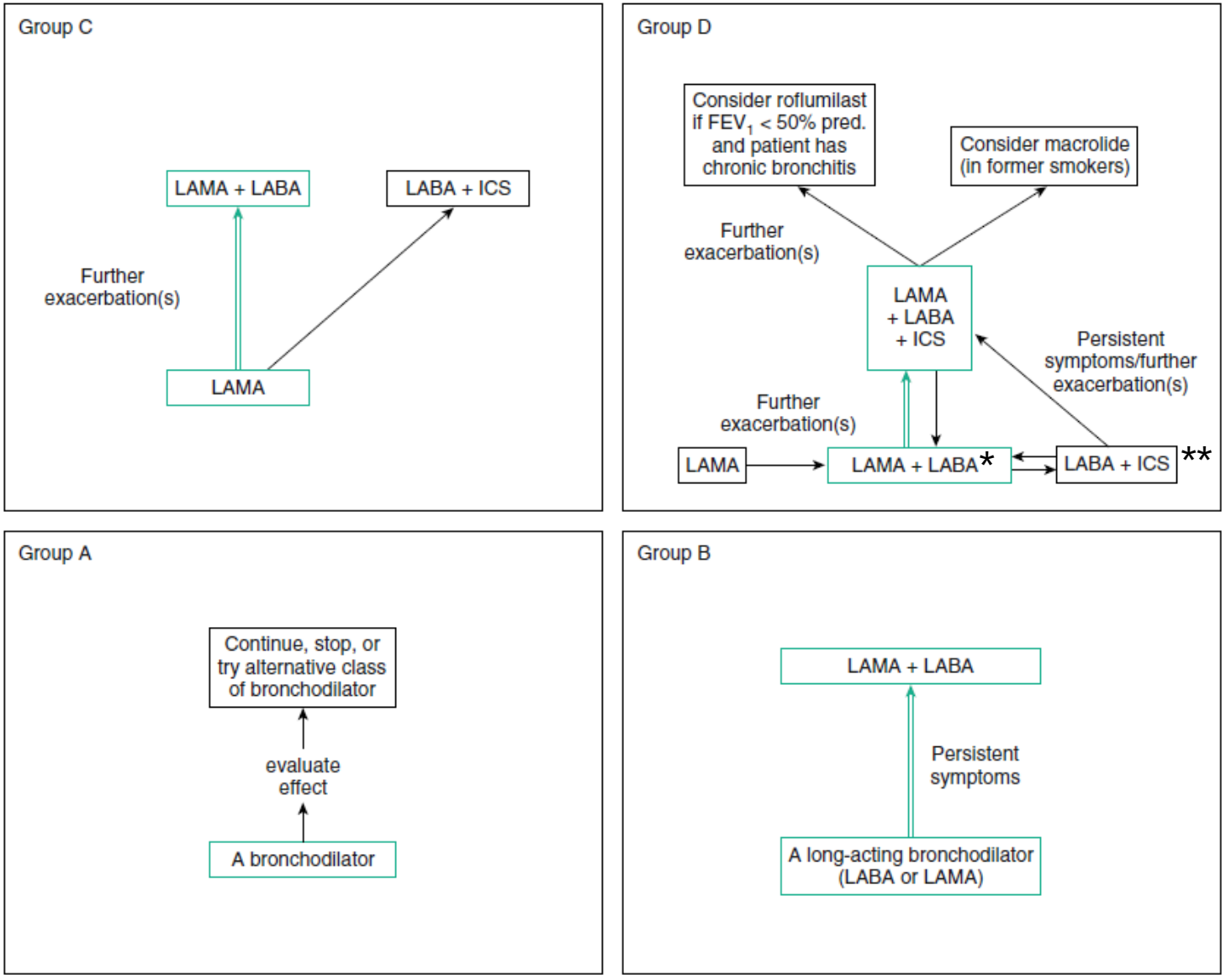
"FLAME" Trial

3200 COPD patients with at least one exacerbation the previous year randomized to ICS/LABA or LAMA/LABA



Wedzicha May 2016

COPD treatment algorithm based on symptoms and exacerbation history



*if highly symptomatic

** if blood eos ≥300

Preferred treatment =

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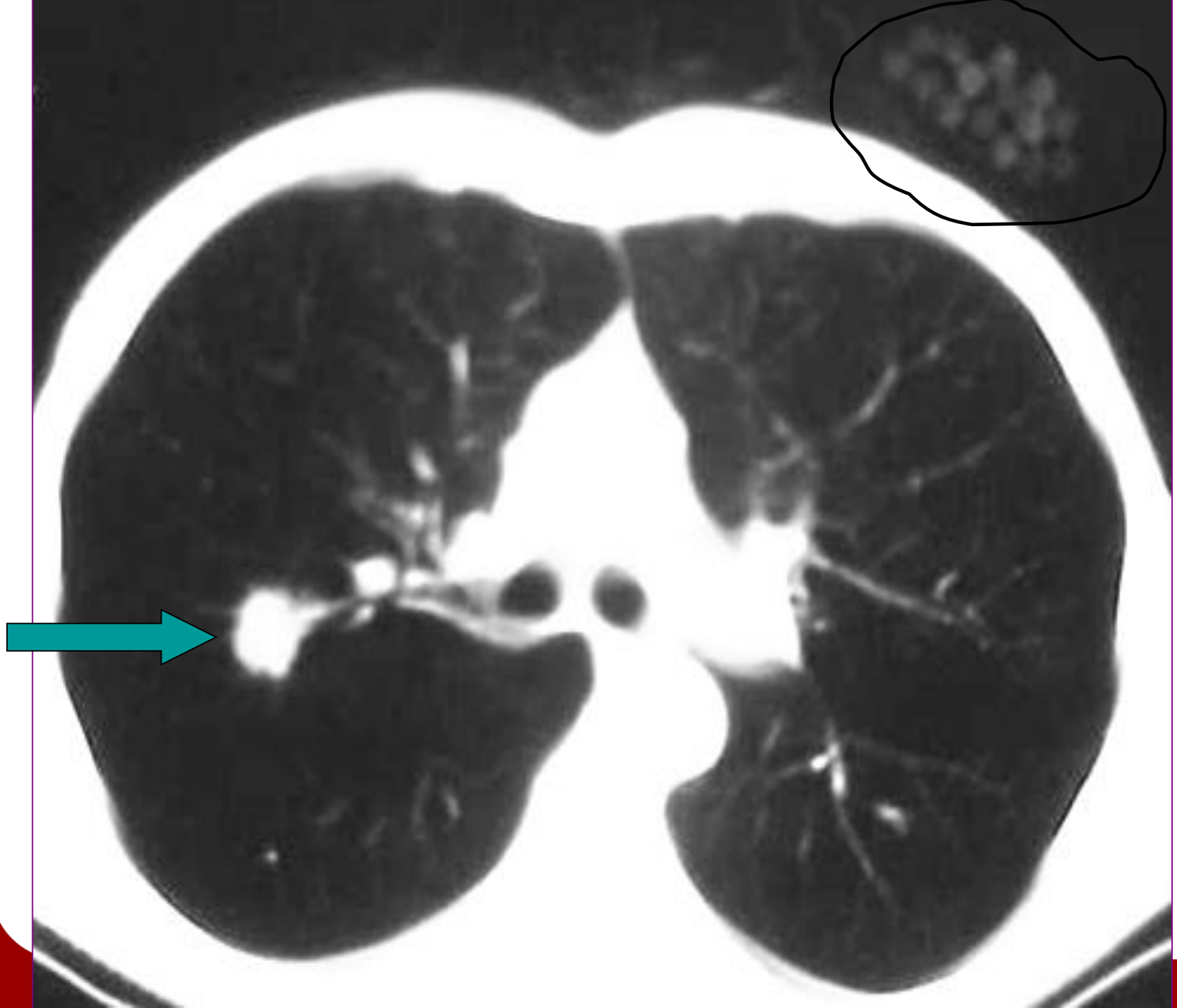
First line therapy based on letter assessment (GOLD guidelines 2019)

- Category A – a bronchodilator (short-acting or long-acting)
- Category B – LAMA or LABA
- Category C – LAMA
- Category D – LAMA or LAMA/LABA* or LABA/ICS**

- * Consider in highly symptomatic patients
- ** Consider if eosinophils > 300 cells/μL



Other Treatment Considerations

- Smoking Cessation
  - Can alter the natural history of disease
  - Intervention
    - Strong and personalized message from physician
    - Nicotine replacement
    - Varenicline
    - Buproprion
    - Smoking cessation counseling/classes
- Vaccination
  - Influenza – associated with improved outcomes in COPD
  - Pneumococcal – decreases CAP/AECOPD

Presentation Outline

- Diagnosis/pathophysiology/pathogenesis
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- Surgical and bronchoscopic management

Your patient does well with LAMA therapy for quite some time. Now, 10 years after his initial presentation he notes gradually increasing DOE, such that he trouble walking 100 yards without stopping. He had one exacerbation in the last year – 2 months ago and has had considerably more trouble after that. In the office, spirometry shows an FEV1/FVC of 0.49 and an FEV1 of 51% of predicted. Room air oxygen saturation is 93%. What treatment addition is expected to have the greatest effect of alleviating his DOE?

1. LABA
2. ICS/LABA
3. Theophylline
4. Pulmonary rehabilitation

Your patient does well with LAMA therapy for quite some time. Now, 15 years after his initial presentation he notes gradually increasing DOE, such that he trouble walking 100 yards without stopping. He had one exacerbation in the last year – 2 months ago and has had considerably more trouble after that. In the office, spirometry shows an FEV1/FVC of 0.49 and an FEV1 of 51% of predicted. Room air oxygen saturation is 93%. What treatment addition is expected to have the greatest effect of alleviating his DOE?

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2. ICS/LABA
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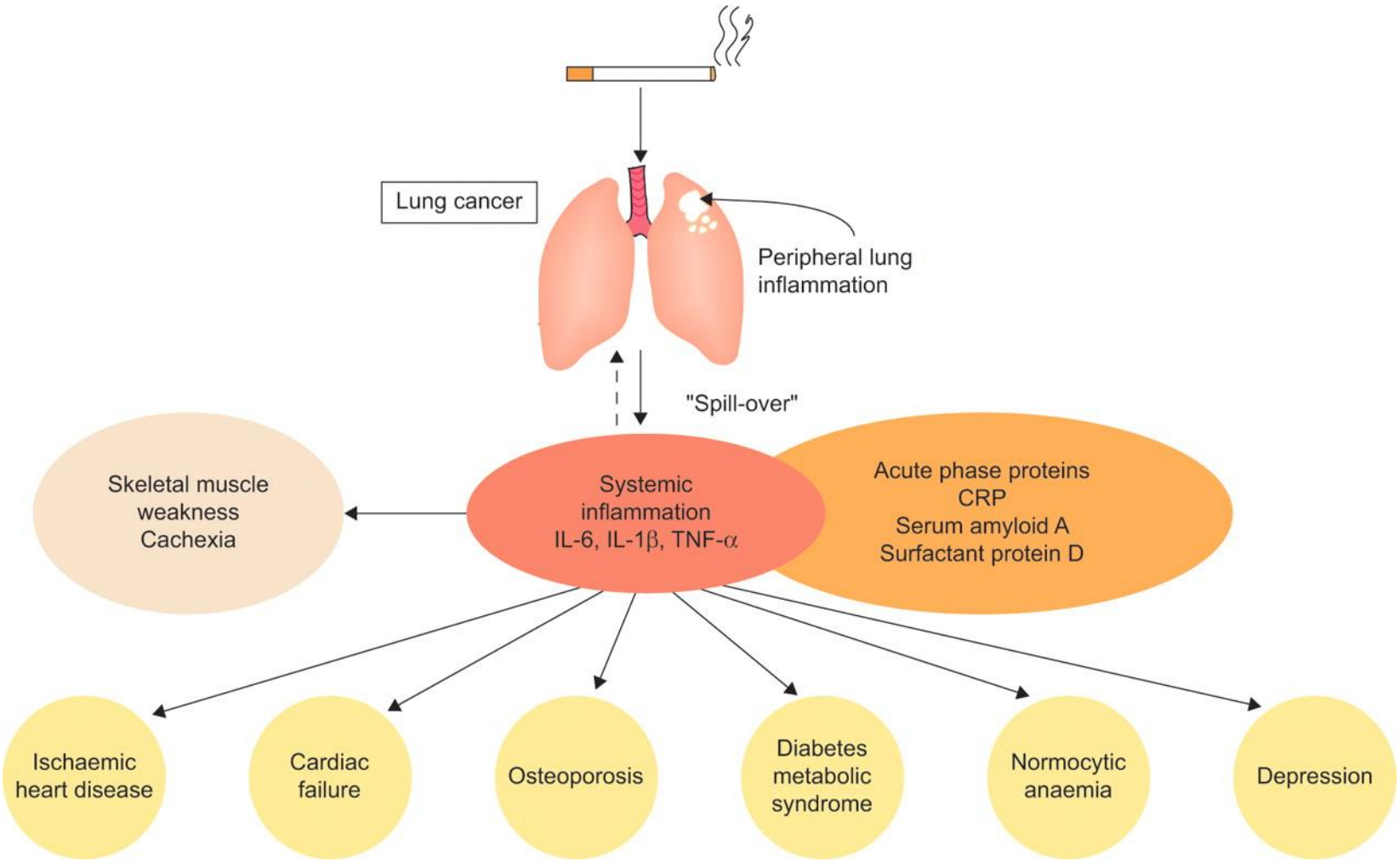
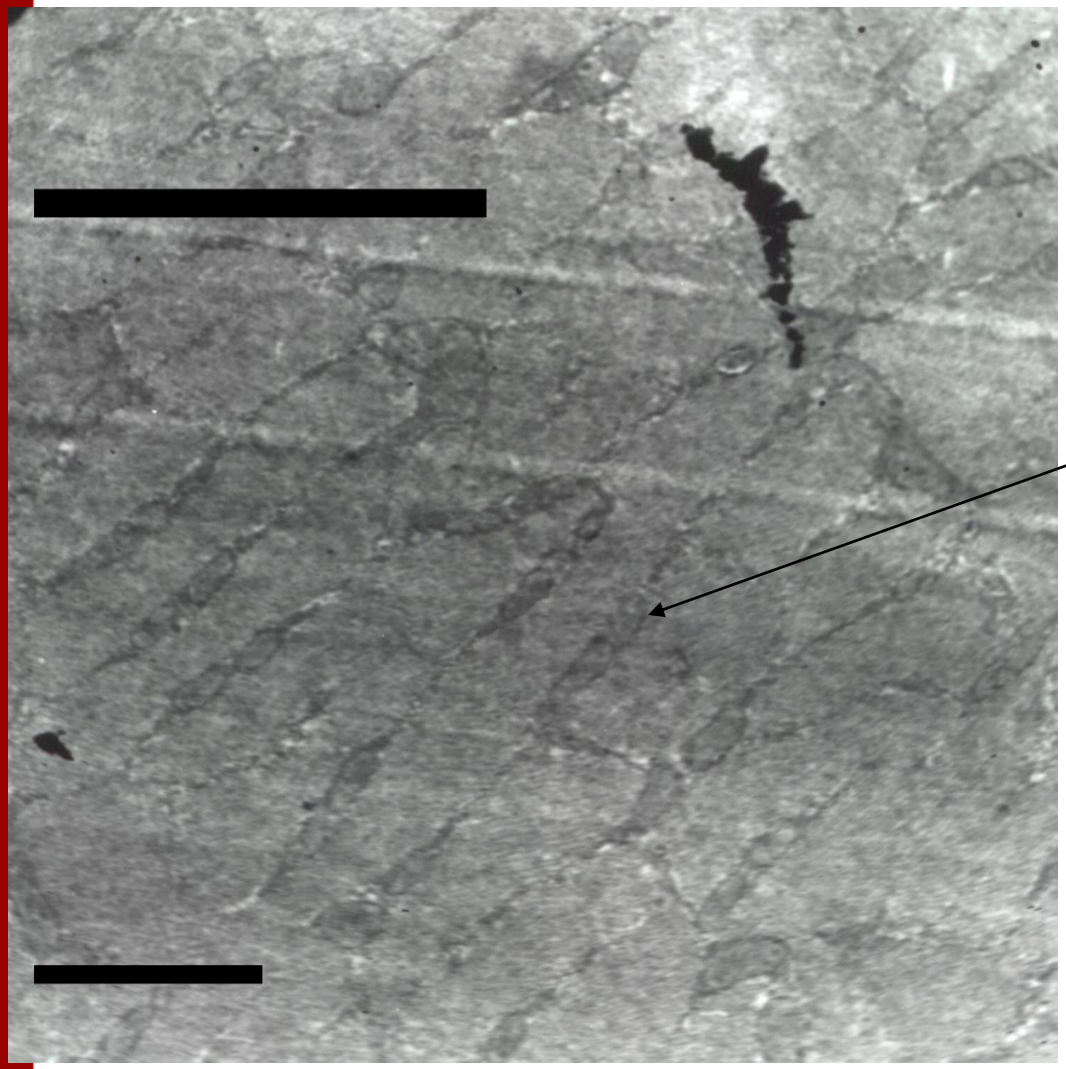
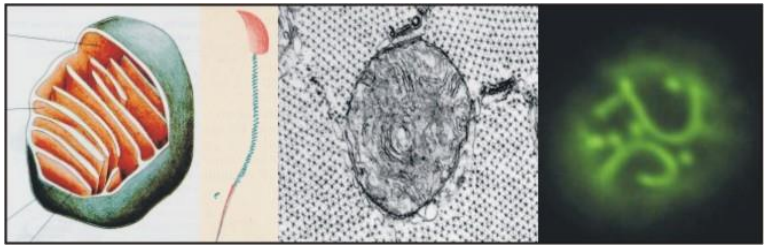
Systemic effects and comorbidities of chronic obstructive pulmonary disease (COPD).

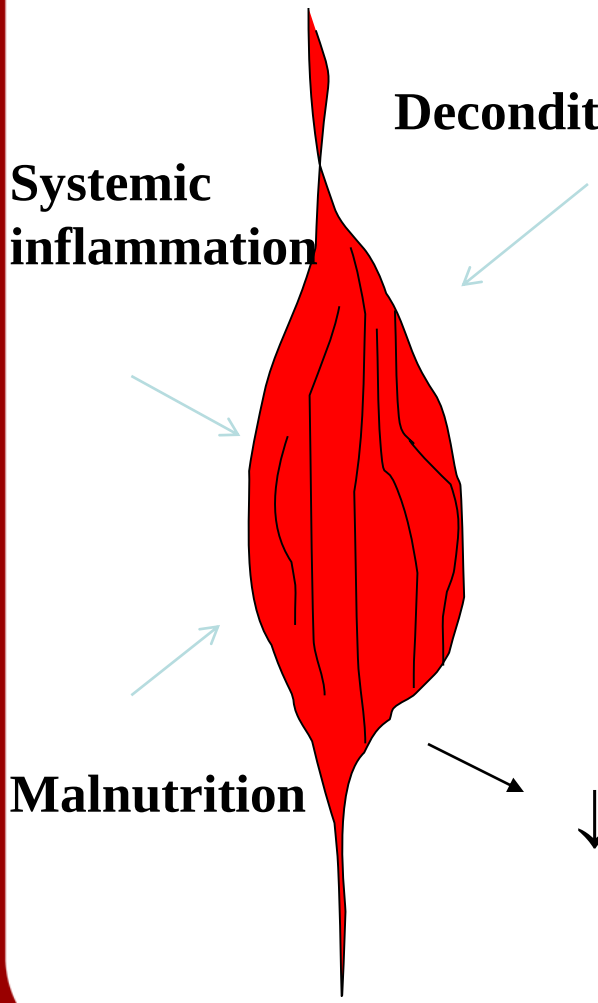


P. J. Barnes, and B. R. Celli Eur Respir J 2009;33:1165-1185





Skeletal muscle dysfunction and COPD



↓ Mitochondrial oxidative enzymes

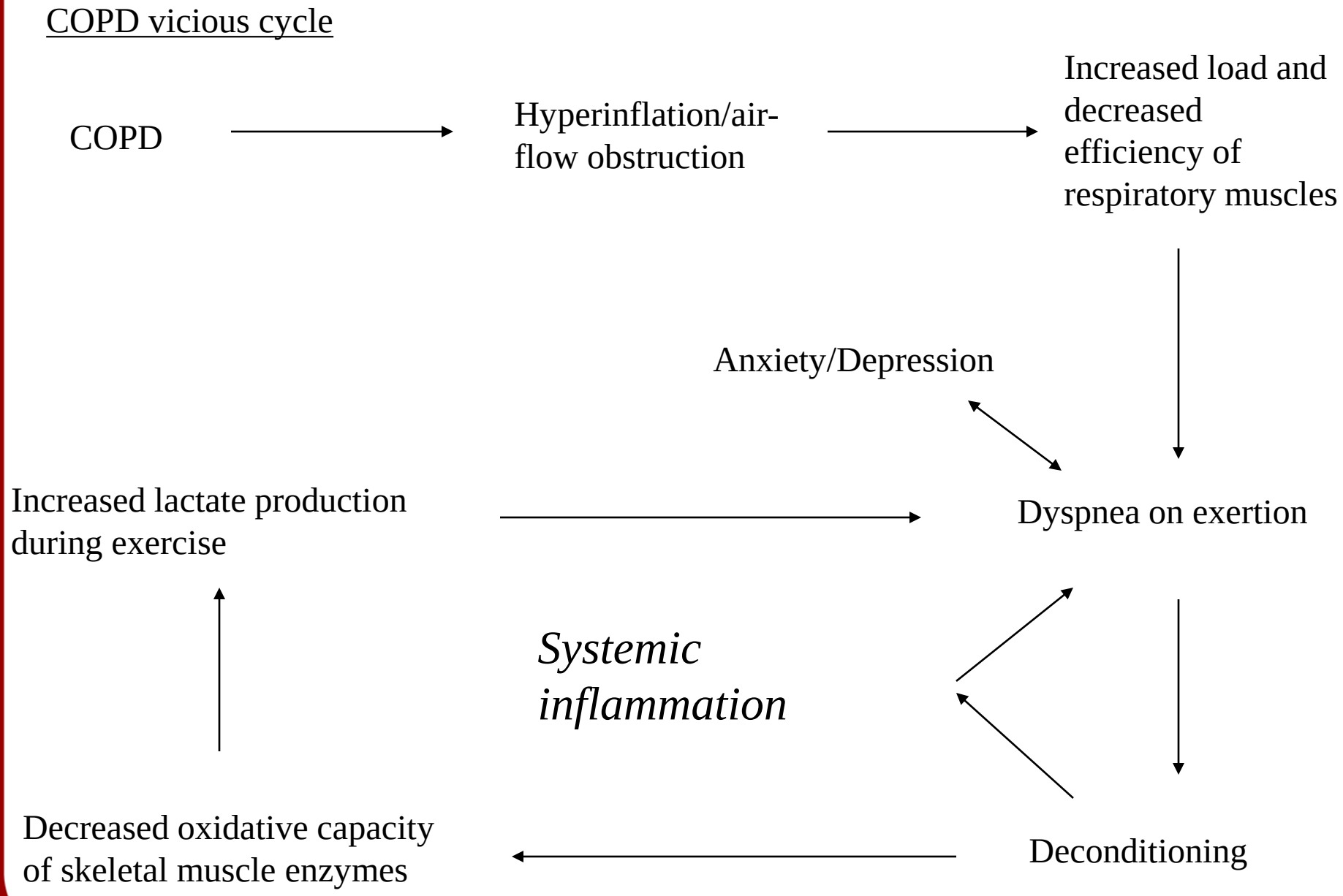
↓ Capillary density

Earlier onset anaerobic metabolism

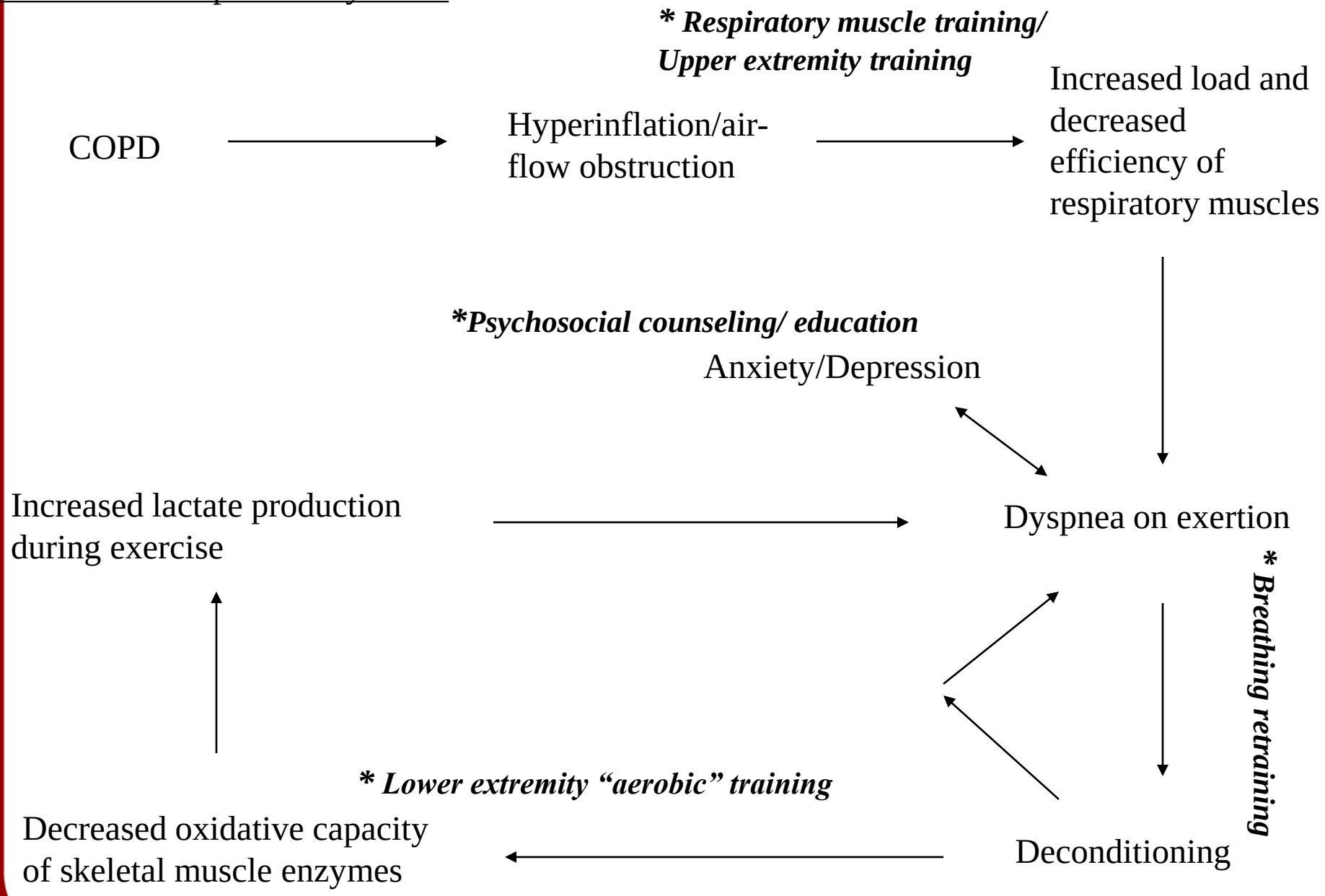
↑ Lactic acid

↑ pCO_2

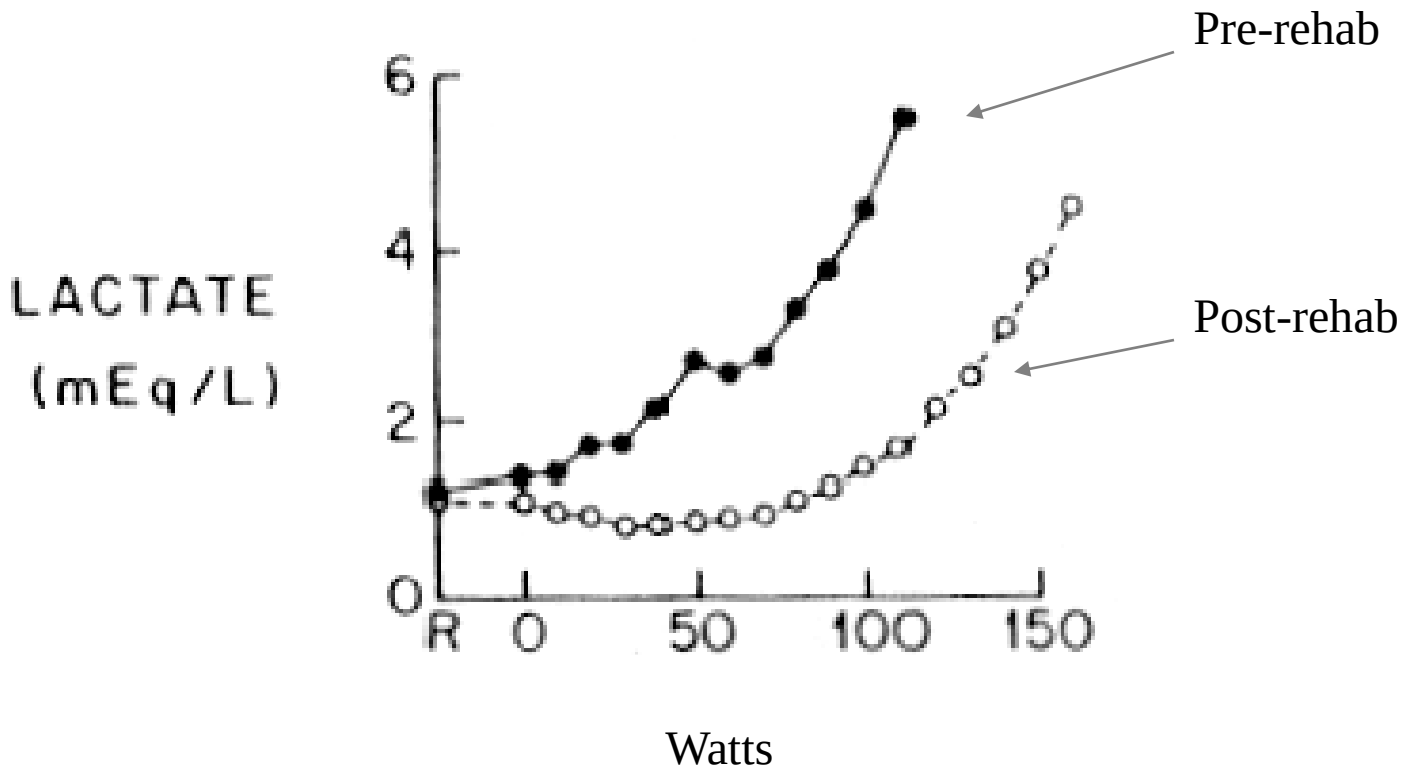
↑ DYSPNEA


COPD vicious cycle
COPD
Hyperinflation/air-flow obstruction
Increased load and decreased efficiency of respiratory muscles
Anxiety/Depression
Dyspnea on exertion
Deconditioning
Decreased oxidative capacity of skeletal muscle enzymes
Increased lactate production during exercise
Systemic inflammation

Intervention with pulmonary rehab




VIPER



Lactate production during exercise in COPD patients, Casaburi et al. Am Rev Respir Dis 1991

Ischemic heart disease in COPD

- Ischemic heart disease increased in COPD
  - Shared risk factors
  - Shared inflammatory pathways
- Myocardial injury overlooked in COPD (Respir Med 2008)
- In general, treatment of IHD should be similar to guidelines for the non-COPD population

Ischemic heart disease in COPD

- Dietary/nutrition “paradox”
  - Higher BMI even into obese range associated with improved survival in COPD
  - Hyperlipidemia associated with improved lung function and survival in COPD

“Hyperlipidemia in COPD is associated with decreased incidence of pneumonia and mortality”

Chan, Int J of COPD 2016

1491 COPD patients analyzed in a retrospective cohort study

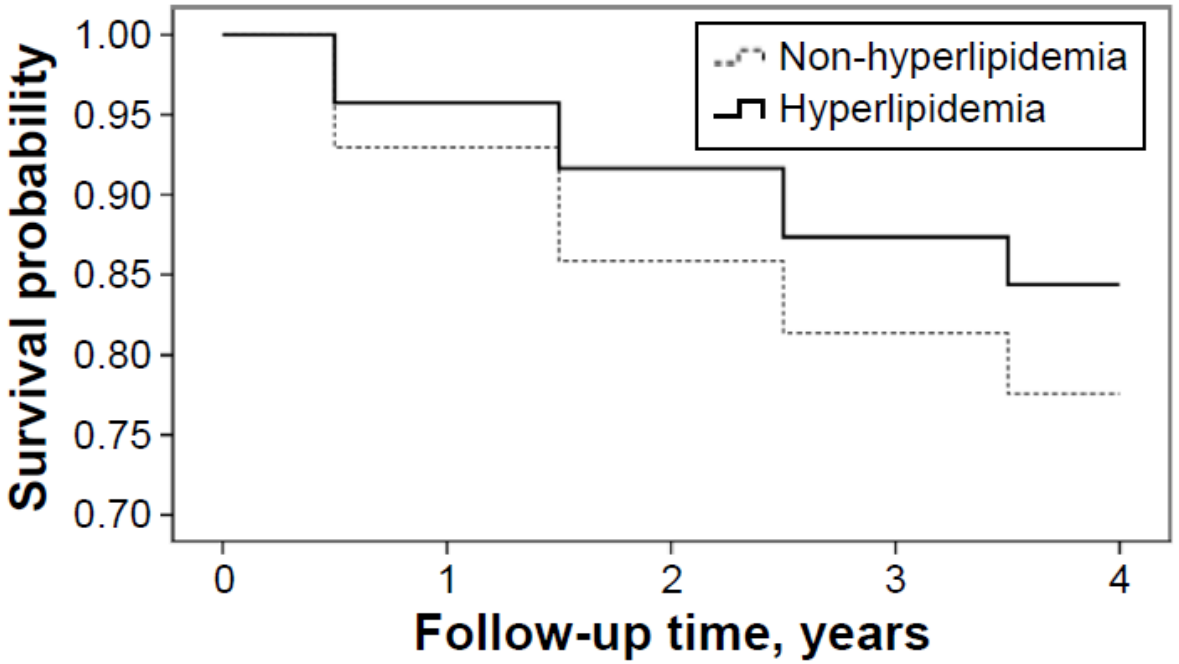


Figure 2 Kaplan–Meier survival estimates for hyperlipidemia and non-hyperlipidemia in patients with COPD.

Note: Patients with COPD having hyperlipidemia are associated with better survival ($P<0.05$).

Beta-blockers in COPD: change in attitude timeline

1983

"It has been established that no beta-blocker is entirely safe in patients with chronic obstructive lung disease."

J Cardiovasc Pharm.

2005

"…cardioselective beta-blockers should not be routinely withheld from patients with COPD."

Cochrane Review

2011

"β blockers may reduce mortality and COPD exacerbations …, independently of overt cardiovascular disease and cardiac drugs"

BMJ

2016

βLOCK COPD: placebo-controlled trial to definitively assess the impact of metoprolol succinate on the rate of COPD exacerbations.

Federally funded multi-center trial

Your patient with COPD, hospitalized with an acute exacerbation is ready for discharge. At rest on room air her O2 saturation is 94%. Walking around the nurses station several times she is not short of breath, but her O2 sat drops to 86%. As part of her discharge planning you should arrange the following outpatient therapy:

1. Supplemental oxygen 2 liters/min at rest, sleep and with exertion
2. Supplemental oxygen 2 liters/min with exertion only
3. Supplemental oxygen 2 liters/min with exertion and while sleeping
4. Discharge without oxygen; follow-up in 2 weeks

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Continuous or Nocturnal Oxygen Therapy in Hypoxemic Chronic Obstructive Lung Disease

A Clinical Trial

NOCTURNAL OXYGEN THERAPY TRIAL GROUP*

Nocturnal Oxygen Therapy Trial (NOTT): Main selection criteria

- Clinical diagnosis of COPD with FEV1/FVC < 70%
- Resting room air pO2 ≤ 55 mmHg (roughly equivalent to O2 sat of 88%)
- If cor pulmonale, polycythemia: pO2 of 56-59 (O2 of ~89%) eligible

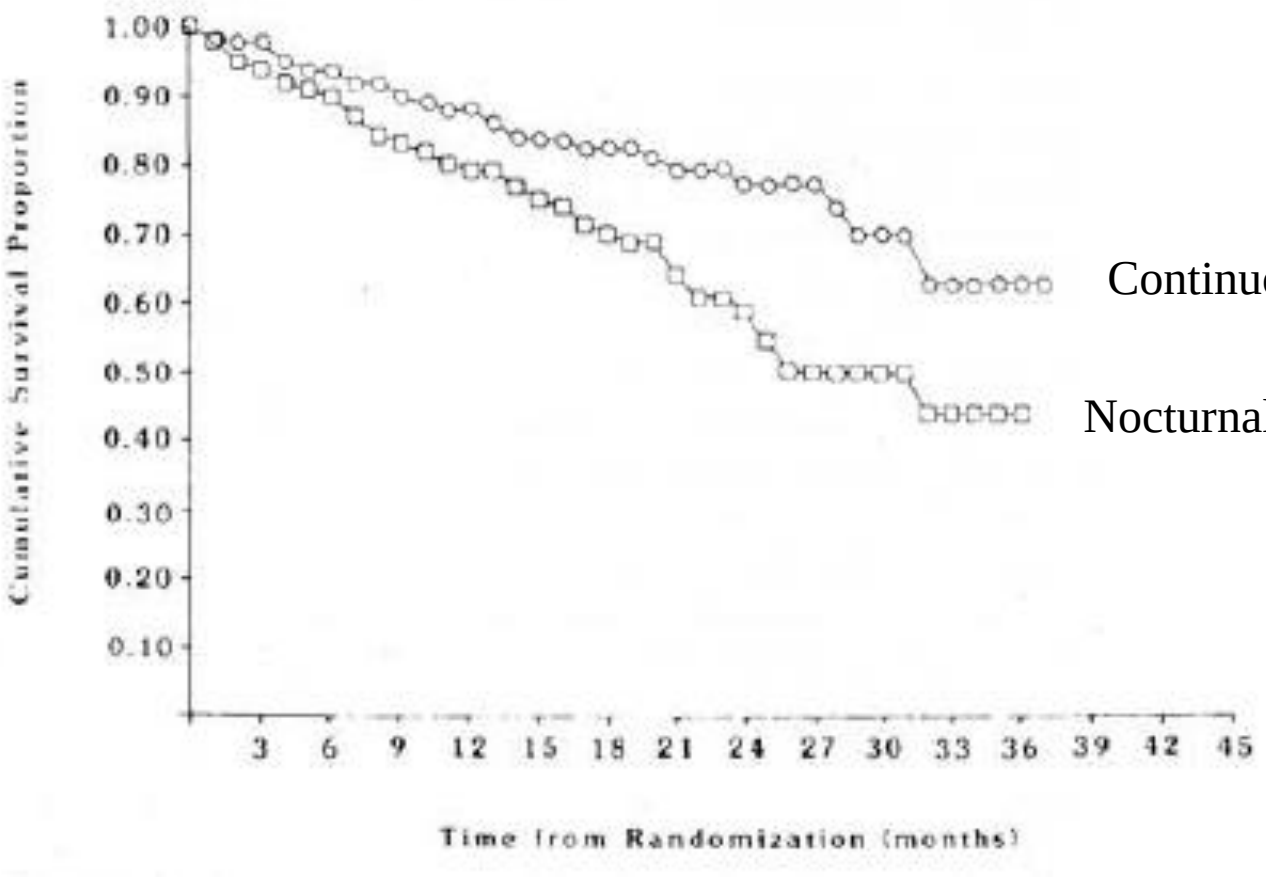
Cumulative Survival Proportion
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
Time from Randomization (months)
Continuous
Nocturnal only

TABLE 1. SUMMARY OF THE AVAILABILITY OF COVERAGE FOR LONG-TERM HOME OXYGEN TREATMENT UNDER MEDICARE

Measurement		Condition for Testing[1]		
Arterial O_2 (mm Hg)	O_2 Saturation (%)	At Rest	During Exercise	During Sleep
≤ 55	*≤ 88*	*Available*	Available[2]	Available[3]
56–59	89	*Available for dependent edema, pulmonary hypertension, or hematocrit > 56*		
≥ 60	≥ 90	Coverage available only by special approval		
Devices Covered		Stationary ± Ambulatory	Ambulatory ± Stationary	Stationary Only

Data from Reference 37. Data in *italics* represent conditions similar to the entry criteria of the NOTT and MRC studies, which showed effects of long-term oxygen treatment on survival in subjects with chronic obstructive pulmonary disease.

[1] While breathing room air in a chronic stable state or no earlier than 2 days prior to hospital discharge.

[2] Requires demonstration that supplemental O_2 improves the exercise-associated hypoxemia.

[3] Also available for subjects who show a greater than normal fall in Arterial O_2 (> 10 mm Hg) or arterial O_2 Saturation (> 5%) during sleep with associated symptoms or signs reasonably attributable to hypoxemia.

Supplemental O2 in US

- ~ 1.4 million users
- ~ 2.8 billion dollars/year
- Cost increasing by 12-13%
- ~75% of Medicare's outpatient costs for COPD

Long Term Oxygen Treatment Trial (LOTT)

- Patients randomized to supplemental O2 or no O2
- Outcomes tracked: mortality, hospitalizations, quality of life
- Eligibility
  - COPD – FEV1/FVC < 70%; FEV1 ≤ 65% of predicted
  - Age > 40
  - Resting O2 sat 89-93% or
  - O2 sat 80 – 89% with exertion

CMS Centers for Medicare & Medicaid Services

National Heart, Lung, and Blood Institute

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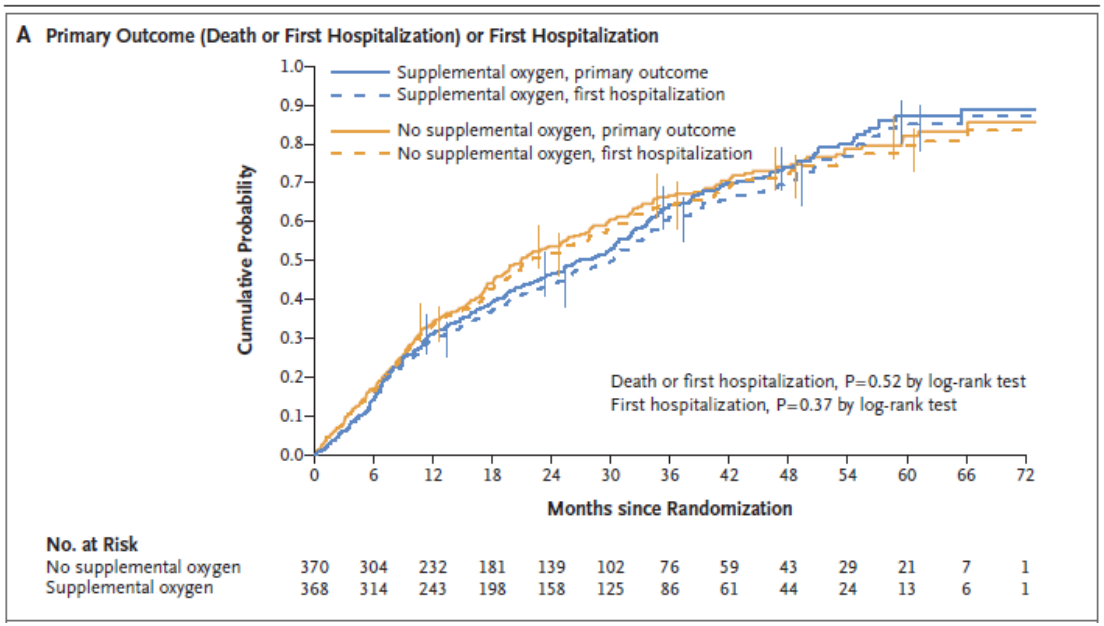
A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation

The Long-Term Oxygen Treatment Trial Research Group*

For patients with moderate hypoxemia or desaturation with exercise:

No effect of supplemental oxygen on mortality, hospitalization or quality of life



Management of stable COPD

- Take home points
  - Goals of therapy: improve quality of life, decrease symptoms, decrease acute exacerbations
  - Bronchodilators central to symptomatic management – alleviation of hyperinflation key
  - Strongly consider pulmonary rehabilitation in patients short of breath despite pharmacologic management
  - Supplemental oxygen improves survival in severe resting hypoxemia.
    - No data has demonstrated benefit of supplemental oxygen for exercise or sleep related desaturation. Consider an individualized approach in these settings.

Presentation Outline

- Diagnosis/pathophysiology/pathogenesis
- Management of stable COPD
  - Pharmacologic treatment
  - COPD as a systemic disease
  - Oxygen therapy
- Management of exacerbations
- Surgical and bronchoscopic management

Your 66 y.o. patient with COPD presents with increased productive cough, dyspnea and chest tightness following a “cold”. On exam he is in no acute distress and vital signs are stable. There is increased wheezing on chest exam and the rest of the exam is unchanged. Which of the following biomarkers has recently been shown to help guide antibiotic therapy?

A. Oxygen saturation
B. Eosinophil count
C. CRP
D. Hemoglobin

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C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations

Christopher C. Butler, F.Med.Sci., David Gillespie, Ph.D., Patrick White, M.D., Janine Bates, M.Phil., Rachel Lowe, Ph.D., Emma Thomas-Jones, Ph.D., Mandy Wootton, Ph.D., Kerenza Hood, Ph.D., Rhiannon Phillips, Ph.D., Hasse Melbye, Ph.D., Carl Llor, Ph.D., Jochen W.L. Cals, M.D., Ph.D., Gurudutt Naik, M.B., M.S., M.P.H., Nigel Kirby, M.A., Micaela Gal, D.Phil., Evgenia Riga, M.Sc., and Nick A. Francis, Ph.D.

- Randomized controlled study – primary care setting
- 653 COPD patients with acute exacerbation
  - CRP guideline used
    - < 20 antibiotics not recommended
    - 20-40 antibiotics may be beneficial
    - > 40 antibiotics likely to be beneficial
  - Usual care

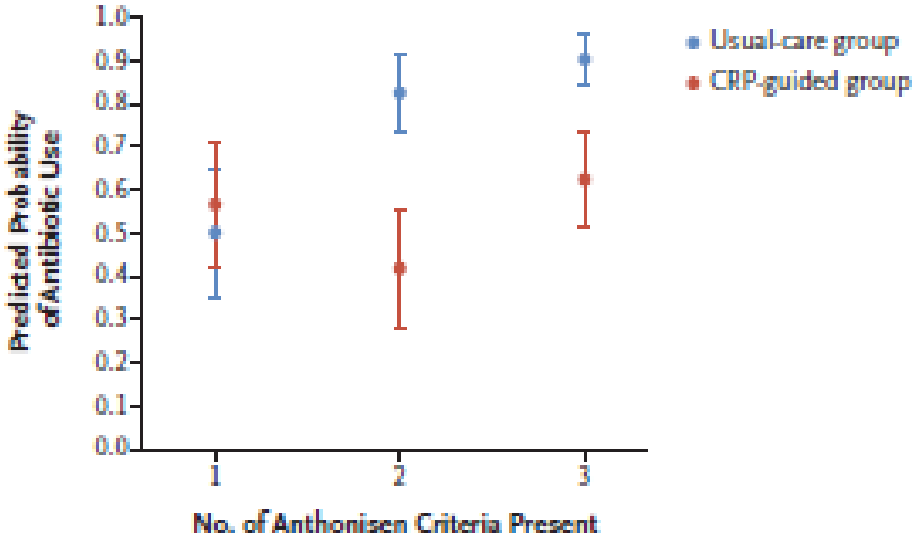


Figure 2. Differential Effect of the Interventions on the Use of Antibiotics during the First 4 Weeks.

Shown is the predicted probability of antibiotic use for acute exacerbations of COPD during the first 4 weeks according to the number of Anthonisen criteria present. The Anthonisen criteria include increased dyspnea, increased sputum volume, and increased sputum purulence. I bars denote 95% confidence intervals.[29]

- CRP guided group used less antibiotics
- No difference in outcomes between the groups

Management of COPD exacerbations

- Exacerbations are associated with:
  - Accelerated decline in lung function
  - Increased morbidity/mortality
  - High costs
- Most common causes: infection of tracheobronchial tree and air-pollution; no cause can be found in ~1/3 of cases
- Outpatient considerations
  - Inhaled bronchodilators and system glucocorticoids are effective
  - Use antibiotics if: hospitalized or increased dyspnea and increased sputum volume/color change in outpatients
    - Possible role of CRP

Global Initiative for Chronic Obstructive Lung Disease, NIH pub. #2701A;

Management of Acute Exacerbations of COPD: Inpatient considerations

- Antibiotics for inpatients:
  - Faster is better (JAMA 2010)
- Corticosteroids
  - More is not better (JAMA 2010)
- Oxygen
  - Titrate to keep sats 88-92%: improved mortality compared to high FIO2 (BMJ 2011)
- Non-invasive ventilation for respiratory acidosis

Non-invasive ventilation in COPD exacerbations: improved mortality

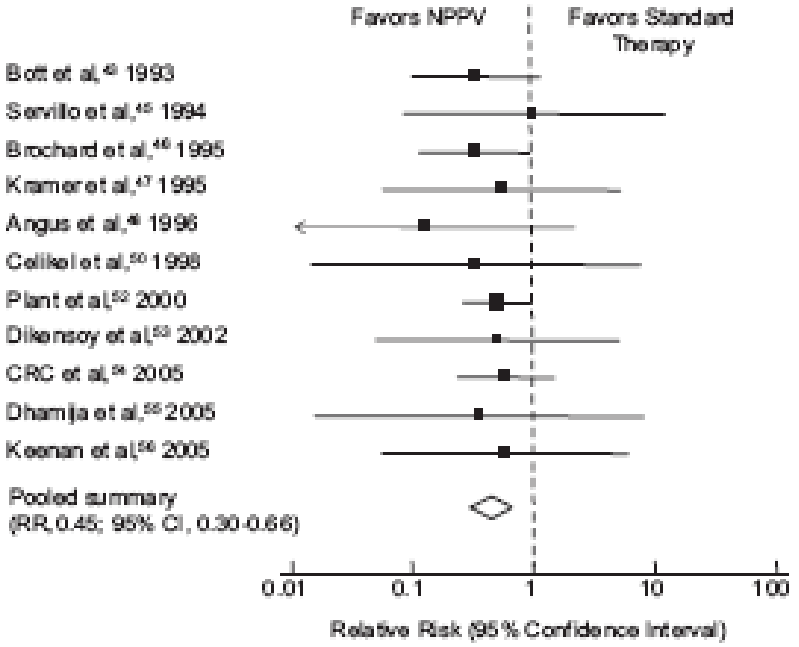
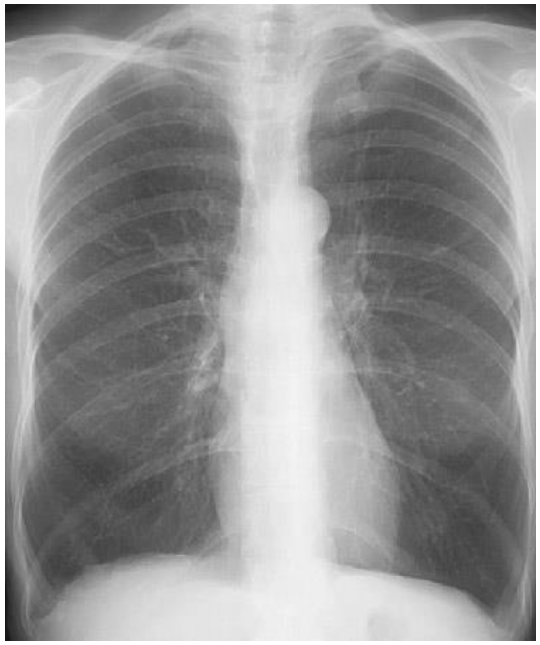


FIGURE 6. Effects of NPPV on the risk of in-hospital mortality during COPD exacerbations. See Figure 4 legend for expansion of abbreviation.

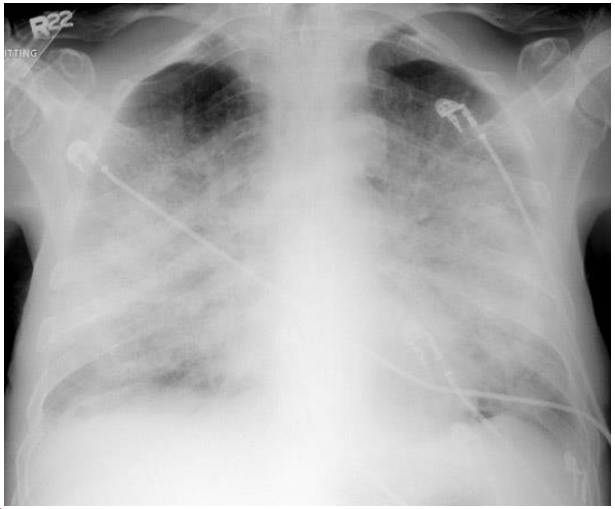
Lungs and respiratory muscle a “CO2 pump”



COPD

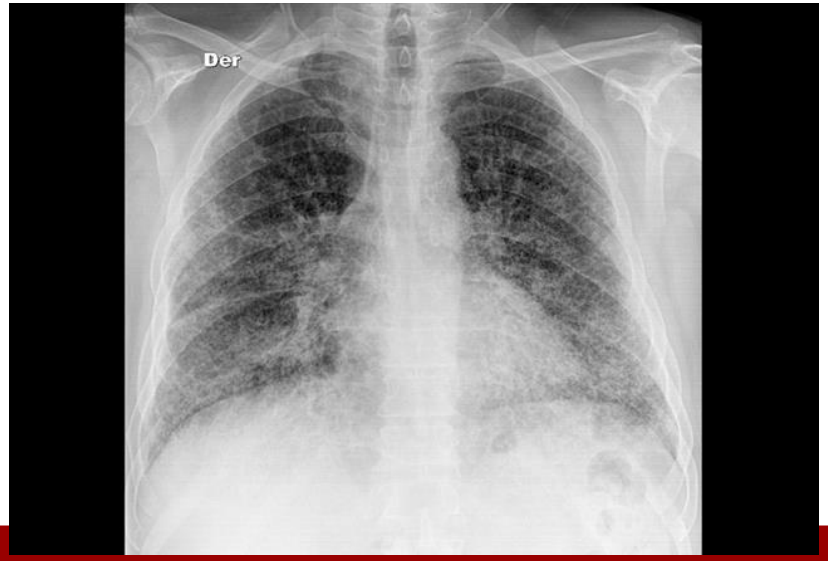
↑pCO2

Pulmonary edema



Often normal pCO2

Pulmonary fibrosis



Prevention of COPD exacerbations

- Smoking cessation, avoidance of environmental exposures
- Inhaled corticosteroids
- Inhaled long-acting bronchodilators
- Rofumilast
- Azithromycin
- Pulmonary rehab

Presentation Outline

- Diagnosis/pathophysiology/pathogenesis
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Case

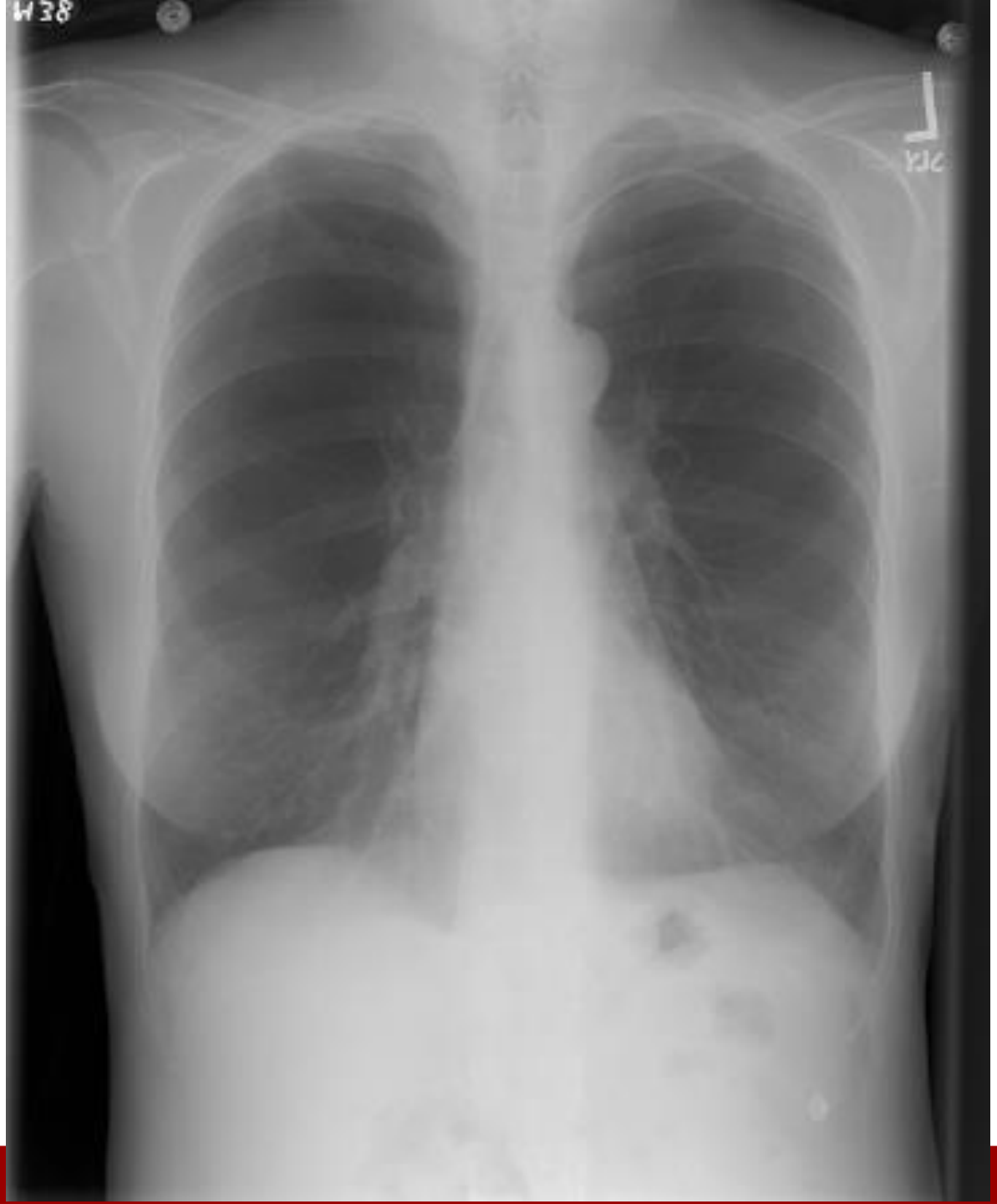
- 62 y.o. female; presents in a wheelchair; dyspneic getting dressed
- Long history of emphysema
- 40 pack year smoking history
  - No longer smoking

Pulmonary function studies 8/25/04

- *FEV_1 - 0.42 liters (17% of predicted)
- FVC – 0.91 liters (30% of predicted)
- Total lung capacity (TLC) – 8.01 liters (159% of predicted)
- Residual volume (RV) – 7.07 liters (352% of predicted)

Arterial blood gases

- pCO2 - 57 mmHg
- pO2 - 60 mmHg

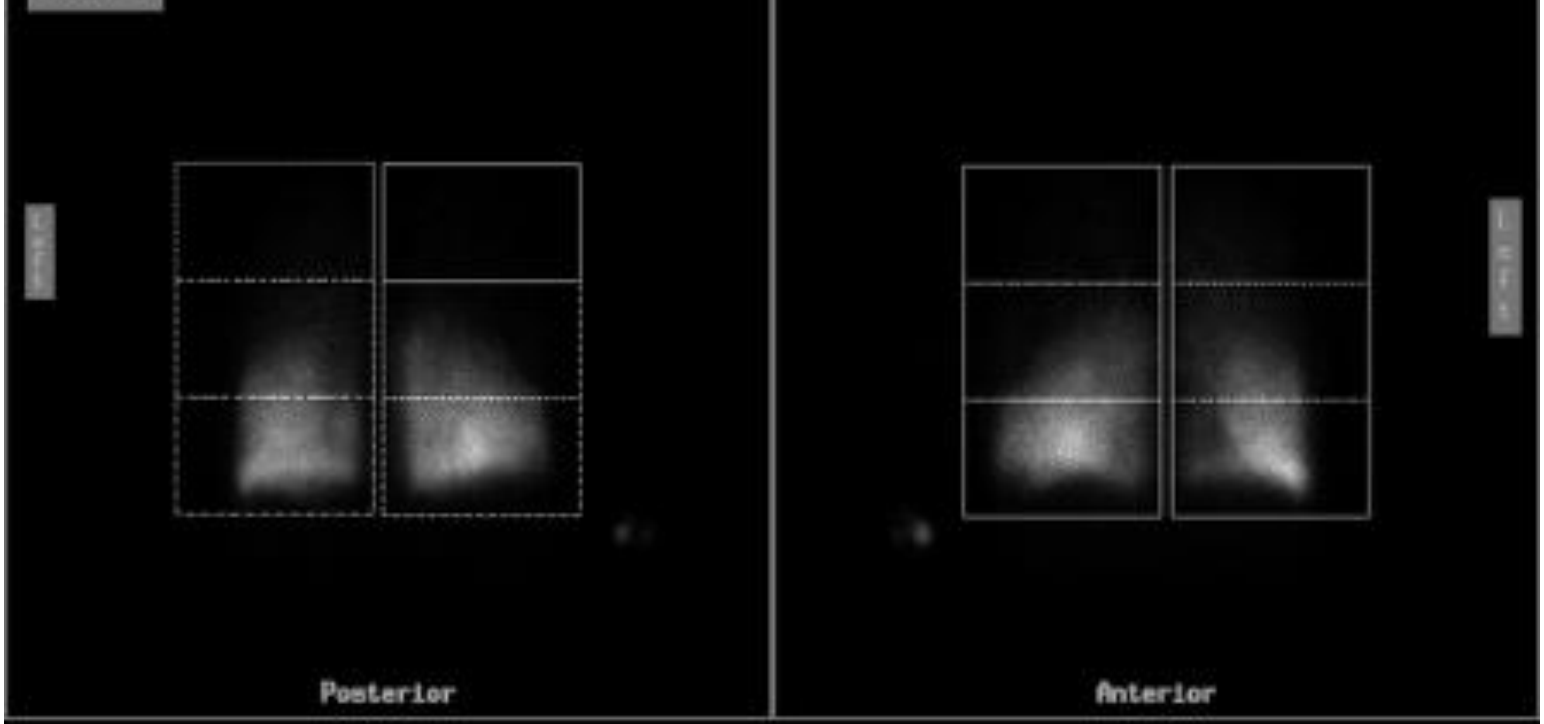


Upper lobe predilection for emphysema:

?Differences in inflammatory cell trafficking

?Differential accumulation of inhaled particulate matter, gases

?Differences in oxidant stress



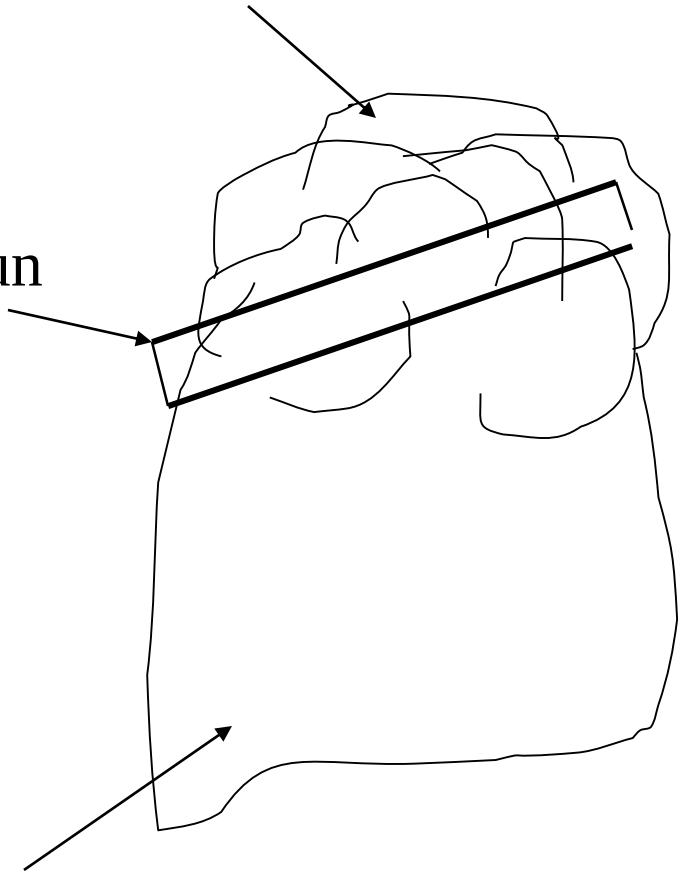
Posterior		Anterior	
Rt Upper	8116.00 cts	Rt Upper	15481.00 cts
Rt Middle	109481.00 cts	Rt Middle	124258.00 cts
Rt Lower	276495.00 cts	Rt Lower	251938.00 cts
Lt Upper	12378.00 cts	Lt Upper	21985.00 cts
Lt Middle	94517.00 cts	Lt Middle	112952.00 cts
Lt Lower	236709.00 cts	Lt Lower	202301.00 cts

	Geometric Mean	Percent
Rt Upper	11209.09 cts	1.53 %
Rt Middle	116635.72 cts	15.97 %
Rt Lower	263931.06 cts	36.13 %
Lt Upper	16496.37 cts	2.26 %
Lt Middle	103324.17 cts	14.15 %
Lt Lower	218829.77 cts	29.96 %

total cts = 730426.19

Lung volume reduction surgery (LVRS) for emphysema

Emphysematous upper lung zones

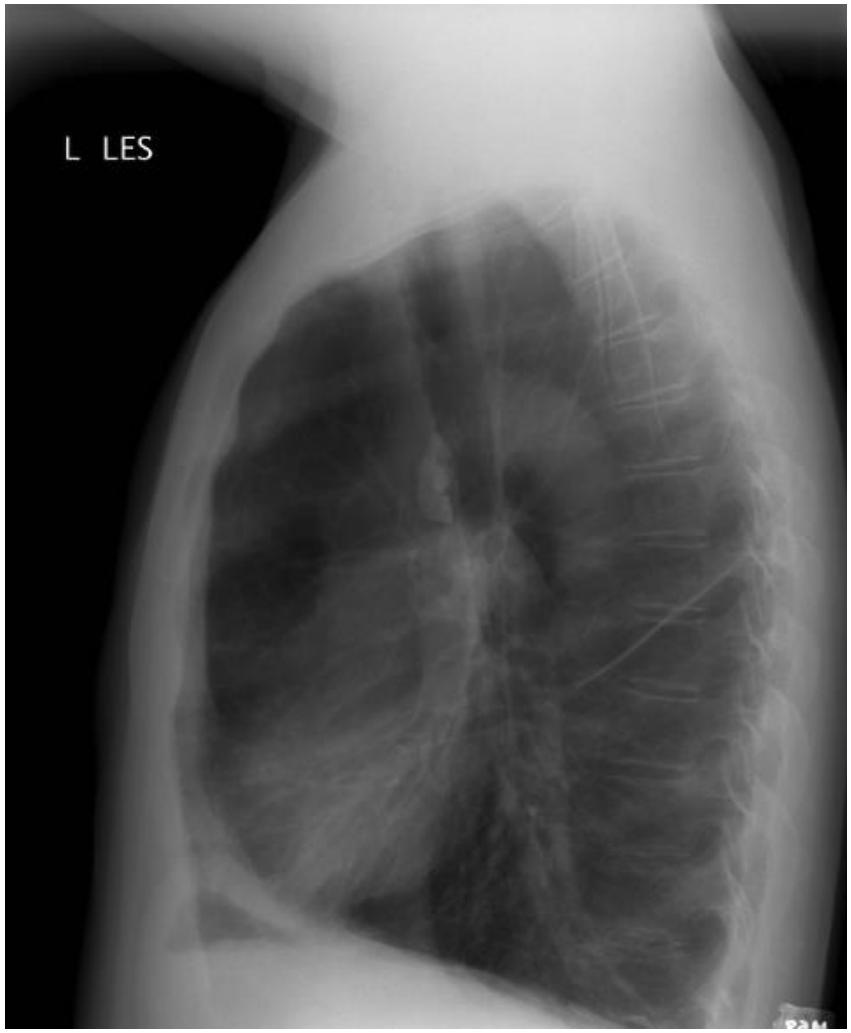


Staple gun

More normal lower lung zones

Protocol: Median sternotomy or bilatateral video-assisted thoracoscopy. Target areas identified by CT scan and perfusion scan. ~30% of each lung removed by a stapling technique.

Post-op: Improved elastic recoil and V/Q matching in remaining lung. Decreased hyperinflation.

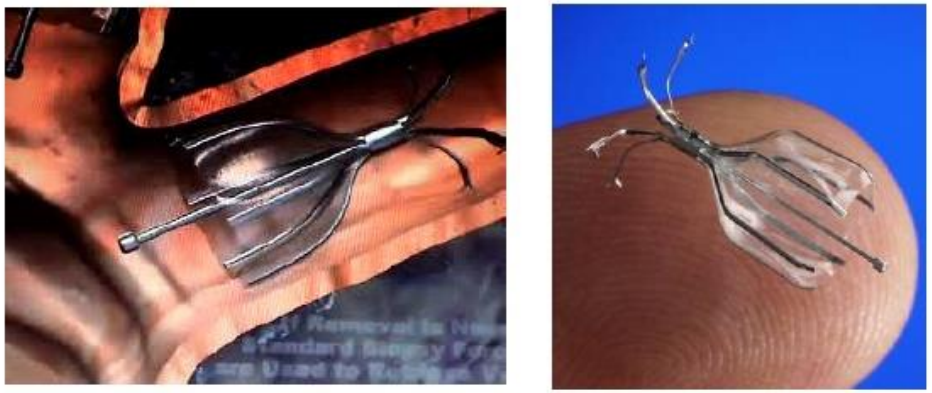

L LES

Major selection criteria for LVRS

- Severe air-flow obstruction (FEV1 < 45% predicted)
- Hyperinflation/Air-trapping
- Upper lobe predominant disease
- No longer smoking

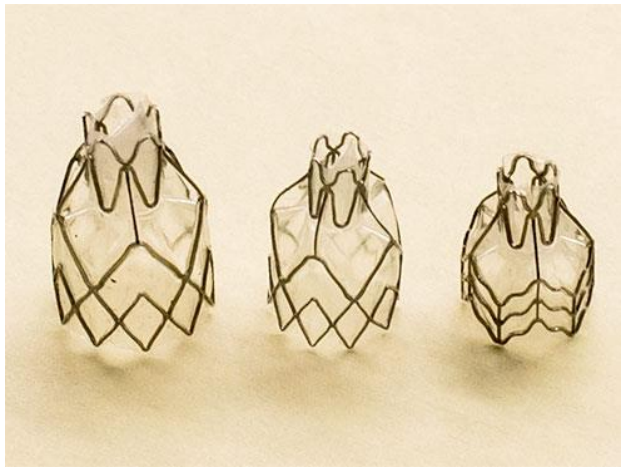
Bronchoscopic LVR with Endobronchial Valves

The use of one-way endobronchial valves in emphysematous regions of the lungs aimed at inducing atelectasis of the worst affected regions, reducing hyperinflation and possibly providing symptomatic relief.



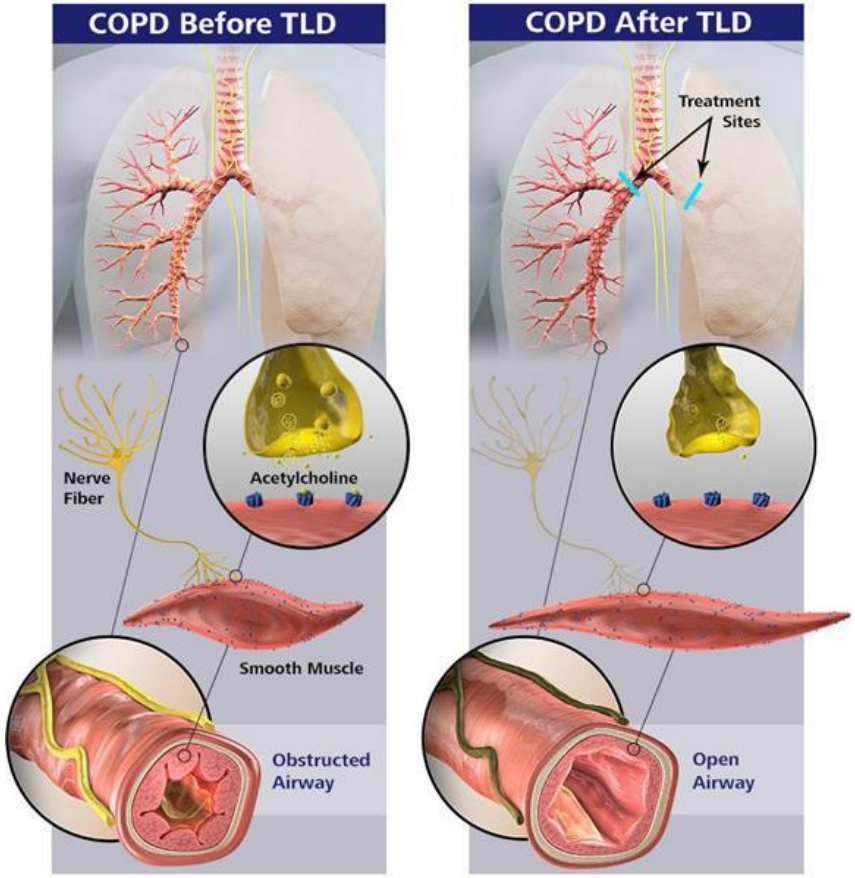
Spiration valve

Fig. (2). IBV® umbrella (Spiration Inc. Redmond USA). The valve consists of a Nitinol framework, with umbrella-shaped hooks which hold the valve in position without damaging the airway, while covered by synthetic polymer. In theory, it allows exhalation and mucus outflow from the bronchus where is placed, without allowing air entrance, thus gradually causing atelectasis of the specific lung segment.



Zephyr valve

Nuvaira study of Targeted Lung Denervation



Targeted lung denervation (TLD) uses radiofrequency ablation to ablate airway nerve trunks to decrease cholinergic signaling – less airway constriction and less secretions

Lung transplant for COPD

- **Consider referral**
  - FEV1 < 25% pred
  - Room air pO2 < 55-60
  - Hypercapnia
  - Secondary pulmonary hypertension
  - Accelerated decline in FEV1