بسم الله الرحمن الرحيم

Chronic Obstructive Pulmonary Disease (COPD)

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COPD

- characterized by **persistent** respiratory symptoms and **airflow limitation** that is **not fully reversible**

- COPD includes
  - ***Emphysema*** → an **anatomically** defined condition characterized by **destruction of the lung alveoli with air space enlargement**;
  - ***chronic bronchitis*** → a **clinically** defined condition with **chronic cough** and **phlegm**
  - ***small airway disease*** → a condition in which small bronchioles are narrowed and reduced in number.

- ***The classic definition of COPD*** requires the presence of **chronic airflow obstruction**, determined by **spirometry**, that usually occurs in the setting of noxious **environmental exposures**—most commonly cigarette **smoking.**

- **Emphysema**, **chronic bronchitis**, and **small airway disease** are present in varying degrees in different COPD patients.

- Patients with a history of cigarette smoking **without** *chronic airflow obstruction* may have chronic bronchitis, emphysema, and dyspnea.
- Although these patients are not included within the classic definition of COPD, they may have similar disease processes.

- Respiratory symptoms and other features of COPD can occur in subjects who do not meet a definition of COPD based only on airflow obstruction determined by spirometric thresholds of normality.

- COPD is the **third leading cause of death** and affects >10 million persons in the United States.

- COPD will rise to the third most common cause of death worldwide by 2020.

PATHOGENESIS

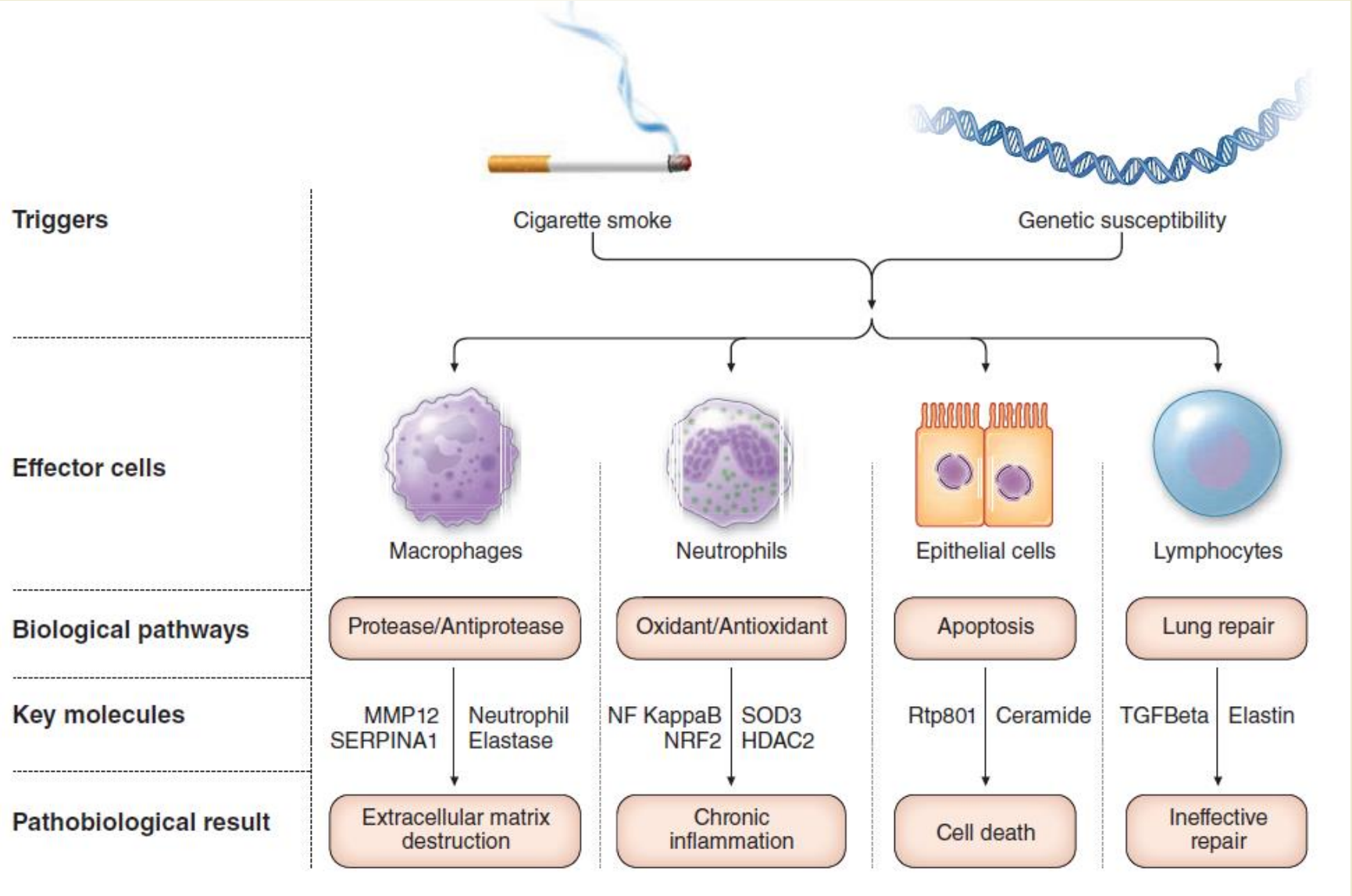
- **Airflow limitation**, a major physiologic change in COPD, can result from small airway disease and/or emphysema.
- Small airways may become narrowed by **cells** (hyperplasia and accumulation), **mucus,** and **fibrosis**,
- ***extensive small airway destruction has been demonstrated to be a hallmark of advanced COPD.***

- The pathogenesis of emphysema is more clearly defined than the pathogenesis of small airway disease.

- **Pulmonary vascular destruction** occurs in concert with small airway disease and emphysema.

- paradigm for the pathogenesis of emphysema:

- (1) Chronic exposure to **cigarette smoke** in **genetically susceptible** individuals triggers **inflammatory and immune cell recruitment** within large and small airways and in the terminal air spaces of the lung.
- (2) Inflammatory cells release **proteinases** that damage the extracellular matrix supporting airways, vasculature, and gas exchange surfaces of the lung.
- (3) Structural **cell death** occurs through oxidant-induced damage→ extensive **loss of smaller airways**, vascular pruning, and alveolar destruction.
- (4) **Disordered repair of elastin and other extracellular matrix** components contributes to air space enlargement and emphysema.



Pathogenesis of emphysema

INFLAMMATION AND EXTRACELLULAR MATRIX PROTEOLYSIS

- **Elastin**, the principal component of elastic fibers
- The **elastase:antielastase** hypothesis: 1960
- based on the clinical observation that patients with genetic **deficiency in a1AT,** were at increased risk of emphysema, and that instillation of elastases, including neutrophil elastase, into experimental animals, results in emphysema.
- The ***elastase:antielastase*** hypothesis remains a **prevailing mechanism for the development of emphysema.**

- immune and inflammatory cells
- proteinases
- exposure to oxidants → macrophages and epithelial cells activated → producing proteinases & chemokines → attract other inflammatory and immune cells.

- **Oxidative stress** is a key component of COPD pathobiology

oxidative stress

- **Mitochondrial dysfunction** in COPD may worsen oxidative stress.
- inactivation of **histone deacetylase-2**
- proinflammatory cytokines such **as interleukin 8 (IL-8)** and **tumor necrosis factor a (TNF-a)**; this leads to neutrophil recruitment.
- Smolking →CD8+ T cells → macrophage elastase (matrix metalloproteinase-12 [MMP-12]).

- There is some evidence that **autoimmune mechanisms** may promote the progression of disease.
- Increased B cells and lymphoid
- Antibodies against elastin fragments
- autoantibodies with avidity for pulmonary

- Concomitant **cigarette smoke**–induced loss of cilia in the airway epithelium and **impaired macrophage phagocytosis** predispose to bacterial infection with neutrophilia.

- **In end-stage lung disease**, **long after smoking cessation**, **there remains an exuberant inflammatory response**, suggesting that cigarette smoke–induced inflammation both initiates the disease and, in susceptible individuals, establishes a chronic process that **can continue disease progression even after smoking cessation.**

Cell Death

- Cigarette smoke → leading to cell death as well as inflammation and proteolysis.
- emphysema resembles **premature aging of the lung**.

Ineffective Repair

- Cigarette smoke **impairs macrophage uptake of apoptotic cells**, limiting repair.

PATHOLOGY

- Cigarette smoke exposure may affect the **large airways**, **small airways (≤2 mm diameter)**, and **alveoli.**

- Changes in large airways → **cough** and **sputum production**
- changes in small airways and alveoli → **physiologic alterations**.

- Airway inflammation, destruction, and the development of emphysema are present in most persons with COPD.

- The early stages of COPD → **medium and small airway disease** with the **GOLD 1** or **GOLD 2** subjects demonstrating little or no emphysema.
- The early development of chronic airflow obstruction is driven by **small airway disease.**

- Advanced stages of COPD (**GOLD 3 and 4**) are typically characterized by **extensive emphysema**,

- there are a small number of subjects with very severe (GOLD 4) obstruction with virtually no emphysema.

TABLE 286-1 GOLD Criteria for Severity of Airflow Obstruction in COPD

GOLD STAGE	SEVERITY	SPIROMETRY
I	Mild	$FEV_1/FVC < 0.7$ and $FEV_1 \geq 80\%$ predicted
II	Moderate	$FEV_1/FVC < 0.7$ and $FEV_1 \geq 50\%$ but $< 80\%$ predicted
III	Severe	$FEV_1/FVC < 0.7$ and $FEV_1 \geq 30\%$ but $< 50\%$ predicted
IV	Very severe	$FEV_1/FVC < 0.7$ and $FEV_1 < 30\%$ predicted

- finding **emphysema** (by chest CT) → suggests enhanced risk for disease progression.

LARGE AIRWAYS

- Cigarette smoking → **mucus gland** enlargement and **goblet cell** hyperplasia → cough and mucus production → chronic bronchitis
- these abnormalities are not related to airflow limitation.

- **goblet cells**: increase in number & extent through the bronchial tree.

- **squamous metaplasia**, predisposing to carcinogenesis and disrupting mucociliary clearance.

- **smooth-muscle hypertrophy** and **bronchial hyperreactivity** leading to airflow limitation → not as prominent as in asthma

SMALL AIRWAYS

- The **major site of increased *resistance*** in most individuals with COPD is in ***airways ≤2 mm*** diameter.
- **goblet cell metaplasia**, with these mucus-secreting cells replacing surfactant-secreting Club cells.
- **Smooth-muscle hypertrophy** may also be present.
- **Luminal narrowing** → by fibrosis, excess mucus, edema, and cellular infiltration.
- **Reduced surfactant** → airway narrowing or collapse.

- Narrowing and drop-out of small airways precede the onset of emphysematous destruction.

- **Advanced COPD** → loss of many of the smaller airways and a similar significant loss of the lung microvasculature.

LUNG PARENCHYMA

- **Emphysema** is characterized by destruction of gas-exchanging air spaces, i.e., the *respiratory bronchioles*, *alveolar ducts*, and *alveoli*.
- alveolar structure → large emphysematous air spaces.
- Large numbers of macrophages accumulate in respiratory bronchioles of essentially all smokers. (**five times as many macrophages as lavage from nonsmokers.**)
- **Neutrophils** and **T lymphocytes**, particularly **CD8+ cells**, are also increased in the alveolar space of smokers.

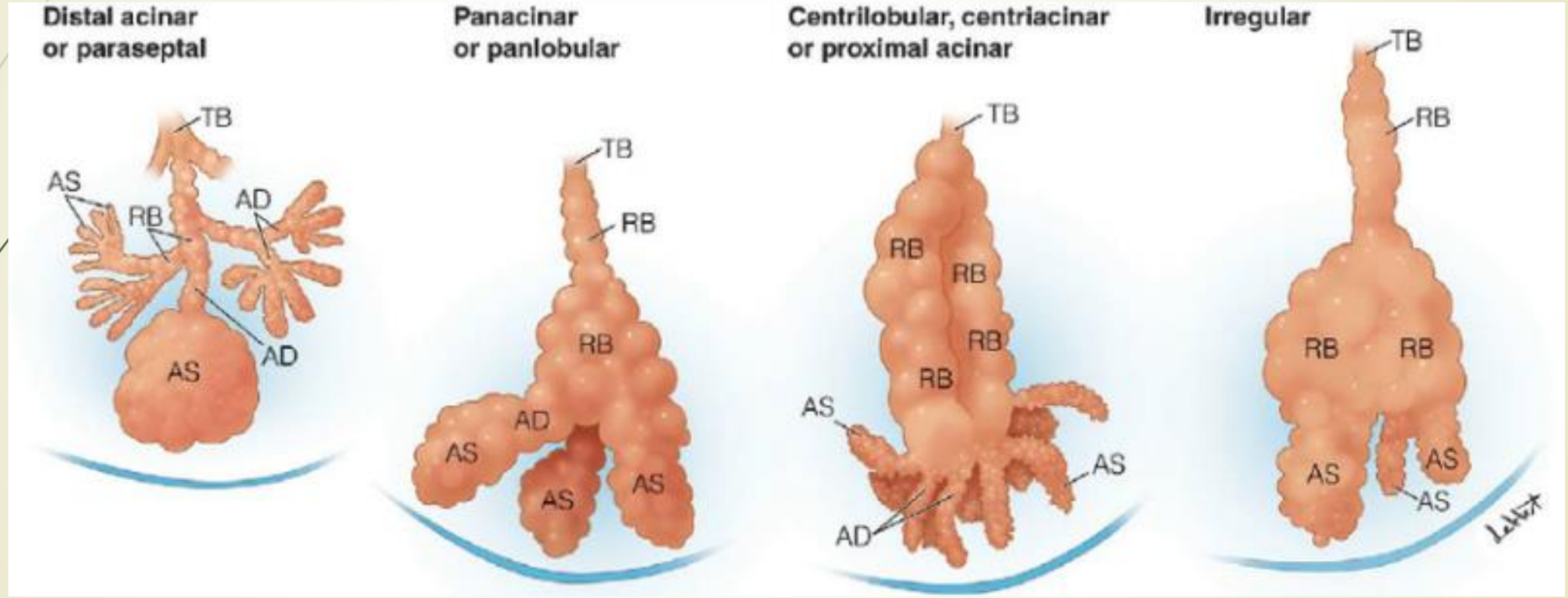
- Emphysema is classified into distinct pathologic types, which include

1. Centrilobular
2. Panlobular
3. Paraseptal

- ***Centrilobular emphysema***, → associated with **cigarette smoking**
  - characterized by enlarged air spaces found (initially) in association with respiratory bronchioles.
  - prominent in the **upper lobes** and **superior segments of lower lobes** and is often quite **focal.**

- ***Panlobular emphysema*** refers to abnormally **large air spaces** evenly distributed within and across acinar units.
- in patients with ***a1AT deficiency***,
- ***lower lobes.***

- ***Paraseptal emphysema***
- 10–15% of cases
- distributed along the **pleural margins** with relative sparing of the lung core or central regions.
- significant airway inflammation and with centrilobular emphysema


Distal acinar
or paraseptal
TB
AS
RB
AD
AD
AS
Panacinar
or panlobular
TB
RB
RB
AD
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Centrilobular, centriacinar
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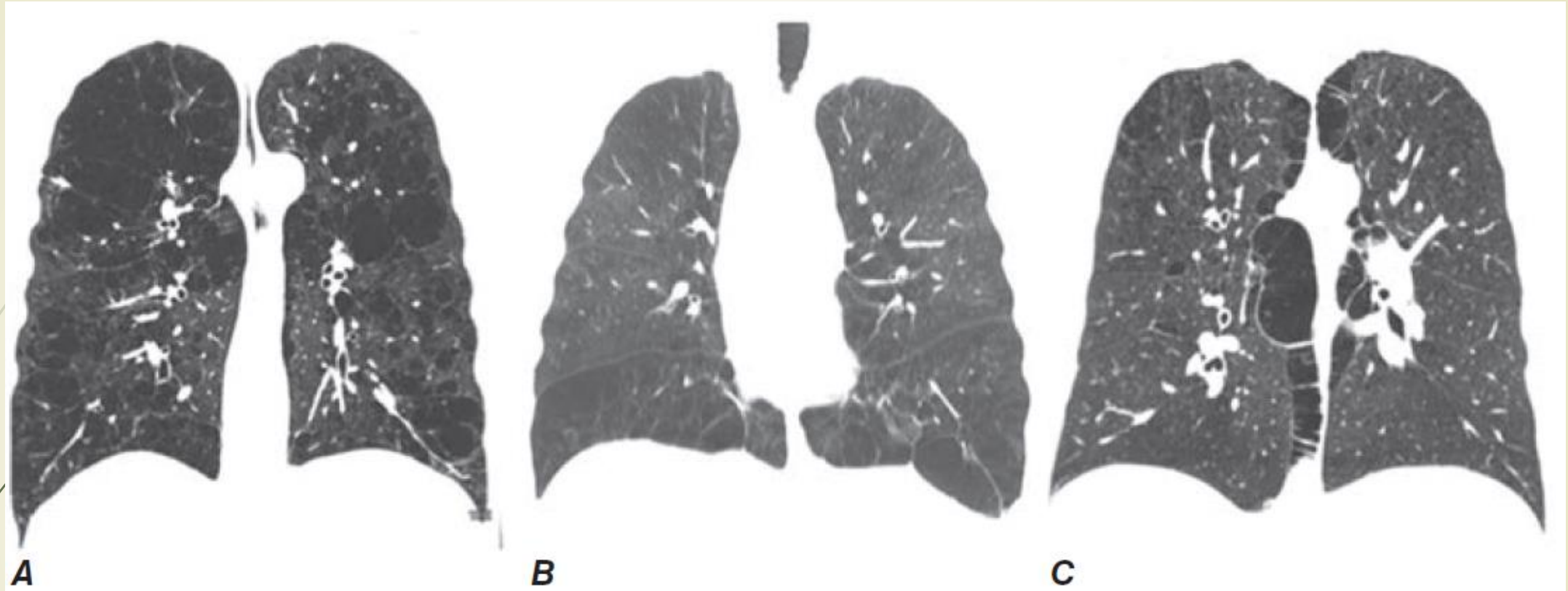


FIGURE 286-2 CT patterns of emphysema. ***A.*** Centrilobular emphysema with severe upper lobe involvement in a 68-year-old man with a 70 pack-year smoking history but forced expiratory volume (FEV_1) 81% predicted (GOLD spirometry grade 1); ***B.*** Panlobular emphysema with diffuse loss of lung parenchymal detail predominantly in the lower lobes in a 64-year-old man with severe α_1AT deficiency; and ***C.*** Paraseptal emphysema with marked airway inflammation in a 52-year-old woman with a 37 pack-year smoking history and FEV_1 40% predicted.

PATHOPHYSIOLOGY

- **Persistent** reduction in **forced expiratory flow** rates is the most typical finding in COPD.

- ↑ **residual volume (RV)** and the **residual volume/total lung capacity ratio (RV/TLC)** , **non-uniform distribution of ventilation**, and **ventilation-perfusion mismatching** also occur.

AIRFLOW OBSTRUCTION

- **Airflow limitation**, also known as **airflow obstruction**, is typically determined for clinical purposes by spirometry, which involves **forced expiratory maneuvers** after the subject has inhaled to total lung capacity.
- Key parameters → **(FEV1)** and **(forced vital capacity [FVC]).**

- Chronically reduced ratio of FEV1/FVC.

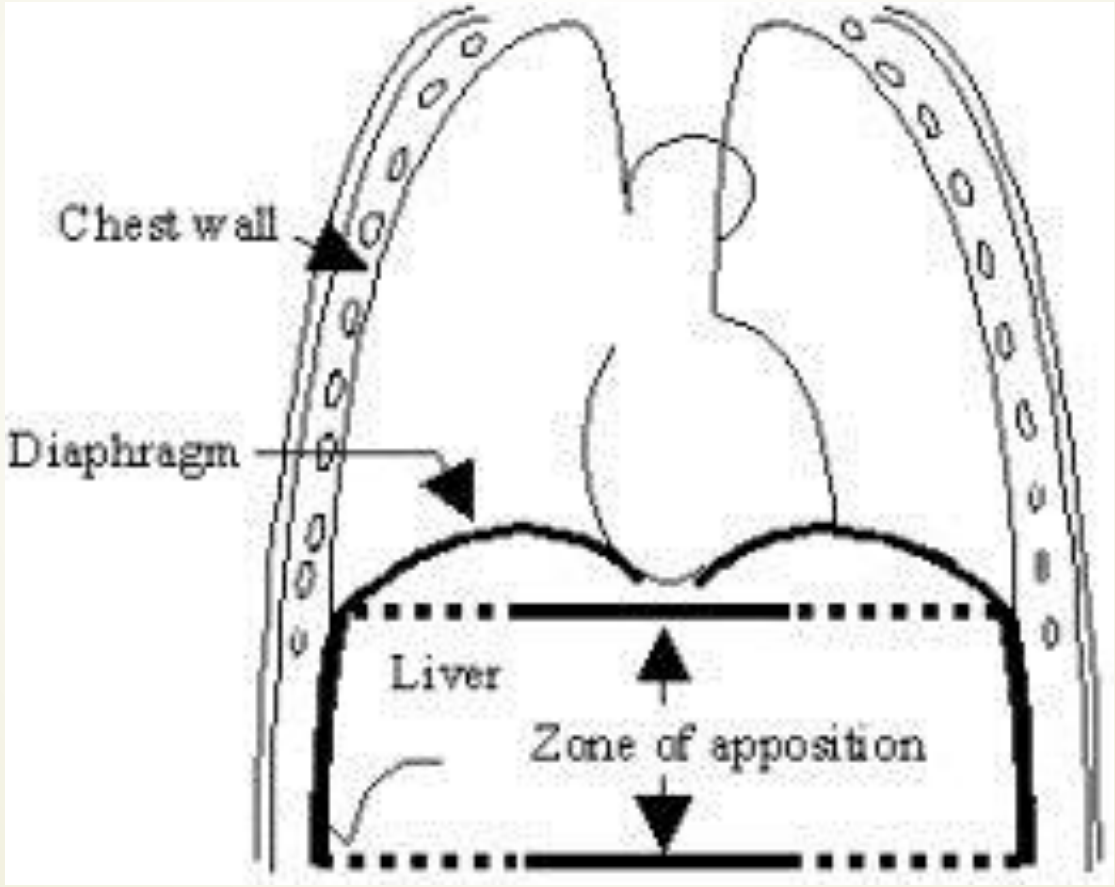
- **In contrast to asthma**, the reduced FEV1 in COPD seldom shows large responses to inhaled bronchodilators, although improvements up to 15% are common.

HYPERINFLATION

- In COPD there is often "air trapping" (**residual volume** ↑ and **RV/TLC**↑)
- progressive hyperinflation (**TLC**↑) late in the disease.
- Hyperinflation of the thorax during tidal breathing preserves maximum expiratory airflow
  - lung volume ↑ → elastic recoil pressure ↑ and airways enlarge → airway resistance ↓

- hyperinflation → diaphragm into a **flattened position** with a number of adverse effects.

- First, by decreasing the **zone of apposition** between the diaphragm and the abdominal wall, positive abdominal pressure during inspiration is not applied as effectively to the chest wall, hindering rib cage movement and impairing inspiration.
- Second, because the muscle fibers of the flattened diaphragm are shorter than those of a more normally curved diaphragm, they are less capable of generating inspiratory pressures than normal.
- Third, the flattened diaphragm must generate greater tension to develop the transpulmonary pressure required to produce tidal breathing.
- Fourth, the thoracic cage is distended beyond its normal resting volume and during tidal breathing the inspiratory muscles must do work to overcome the resistance of the thoracic cage to further inflation instead of gaining the normal assistance from the chest wall recoiling outward toward its resting volume.


Chest wall
Diaphragm
Liver
Zone of apposition

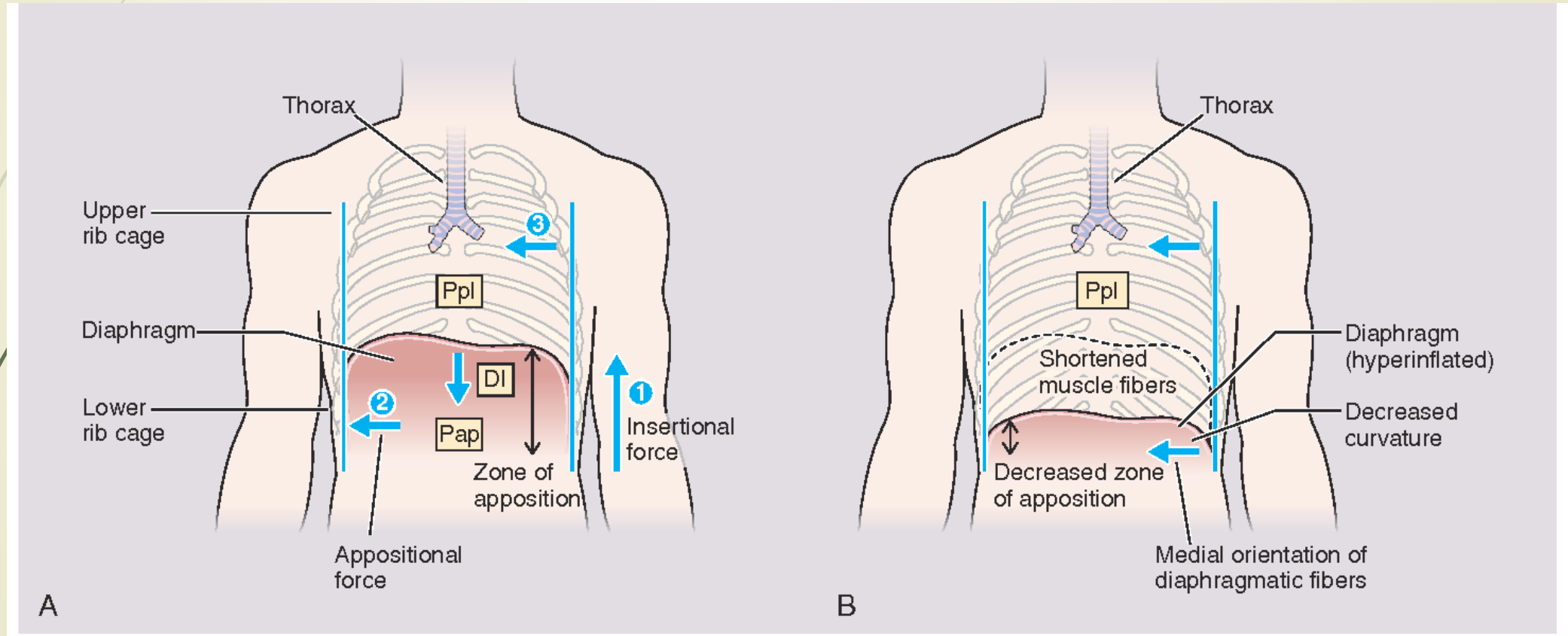


FIGURE 8-12 Consequences of hyperinflation on the diaphragm. **A,** Normal actions of the diaphragm as in Figure 8-2. **B,** Deleterious effects f

GAS EXCHANGE

- **PaO2 near normal** → until the **FEV1 <~50%** of predicted,
  - even much lower FEV1 values can be associated with a normal Pao2, at least at rest.

- ↑ **Paco2** → until the **FEV1 is <25%** of predicted and even then may not occur.

- **Pulmonary hypertension** → cor pulmonale and right ventricular failure:
  - **If** ↓ in **FEV1 <25%** of predicted and chronic hypoxemia **(Pao2 <55 mmHg)**
  - some patients → **pulmonary hypertension** independent of COPD severity

- **Non-uniform ventilation** and **ventilation-perfusion mismatching** are characteristic of COPD, → heterogeneous nature of the disease

- **Ventilation-perfusion mismatching** → Main cause of reduction in Pao2
- **shunting is minimal.**
- modest elevations of inspired oxygen in treating hypoxemia due to COPD
- consider problems other than COPD when hypoxemia is difficult to correct with modest levels of supplemental oxygen.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2010/07/30