

Respiratory

“Whenever I feel blue, I start breathing again.”

—L. Frank Baum

“Until I feared I would lose it, I never loved to read. One does not love breathing.”

—Scout, *To Kill a Mockingbird*

“Love is anterior to life, posterior to death, initial of creation, and the exponent of breath.”

—Emily Dickinson

“Love and a cough cannot be concealed.”

—Anne Sexton

Group key respiratory, cardiovascular, and renal concepts together for study whenever possible. Respiratory physiology is challenging but high yield, especially as it relates to the pathophysiology of respiratory diseases. Develop a thorough understanding of normal respiratory function. Get familiar with obstructive vs restrictive lung disorders, ventilation/perfusion mismatch, lung volumes, mechanics of respiration, and hemoglobin physiology. Lung cancers and other causes of lung masses are also high yield. Be comfortable reading basic chest x-rays, CT scans, and PFTs.

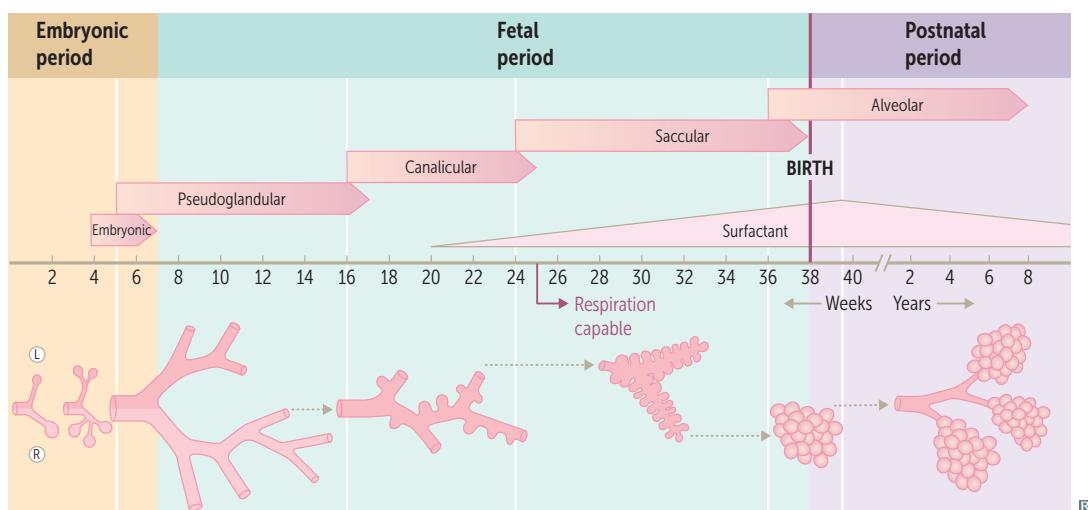
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► RESPIRATORY—EMBRYOLOGY

Lung development

Occurs in five stages. Begins with the formation of lung bud from distal end of respiratory diverticulum during week 4 of development. Every pulmonologist can see alveoli.

STAGE	STRUCTURAL DEVELOPMENT	NOTES
Embryonic (weeks 4–7)	Lung bud → trachea → bronchial buds → mainstem bronchi → secondary (lobar) bronchi → tertiary (segmental) bronchi.	Errors at this stage can lead to tracheoesophageal fistula.
Pseudoglandular (weeks 5–17)	Endodermal tubules → terminal bronchioles. Surrounded by modest capillary network.	Respiration impossible, incompatible with life.
Canalicular (weeks 16–25)	Terminal bronchioles → respiratory bronchioles → alveolar ducts. Surrounded by prominent capillary network.	Airways increase in diameter. Pneumocytes develop starting at week 20. Respiration capable at week 25.
Saccular (week 24–birth)	Alveolar ducts → terminal sacs. Terminal sacs separated by 1° septae.	
Alveolar (week 36–8 years)	Terminal sacs → adult alveoli (due to 2° septation).	In utero, “breathing” occurs via aspiration and expulsion of amniotic fluid → ↑ pulmonary vascular resistance through gestation. At birth, air replaces fluid → ↓ pulmonary vascular resistance.

**Choanal atresia**

Blockage of posterior nasal opening. Often associated with bony abnormalities of the midface. Most often unilateral. When bilateral, represents an emergency and presents with upper airway obstruction, noisy breathing, and/or cyanosis that worsens during feeding and improves with crying. Diagnosed by failure to pass nasopharyngeal tube and confirmed with CT scan.

Often part of multiple malformation syndromes, such as **CHARGE** syndrome:

- Coloboma of eye
- Heart defects
- Atresia of choanae
- Restricted growth and development
- Genitourinary defects
- Ear defects

Lung malformations

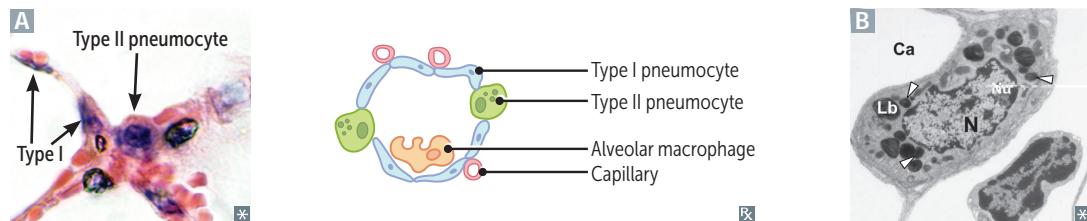
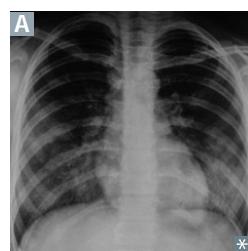
Pulmonary hypoplasia	Poorly developed bronchial tree with abnormal histology. Associated with congenital diaphragmatic hernia (usually left-sided), bilateral renal agenesis (Potter sequence).
Bronchogenic cysts	Caused by abnormal budding of the foregut and dilation of terminal or large bronchi. Discrete, round, sharply defined, fluid-filled densities on CXR (air-filled if infected). Generally asymptomatic but can drain poorly → airway compression, recurrent respiratory infections.

Club cells

Nonciliated; low columnar/cuboidal with secretory granules. Located in bronchioles. Degrade toxins via cytochrome P-450; secrete component of surfactant; progenitor cells for club and ciliated cells.

Alveolar cell types

Type I pneumocytes	Squamous. 97% of alveolar surfaces. Thinly line the alveoli A for optimal gas exchange.	Pores of Kohn —anatomical communications between alveoli that allow for passing of air, fluid, phagocytes, and bacteria (in pneumonia).
Type II pneumocytes	Cuboidal and clustered B . 2 functions: 1. Serve as stem cell precursors for 2 cell types (type I and type II pneumocytes); proliferate during lung damage. 2. Secrete surfactant from lamellar bodies (arrowheads in B). Application of Law of Laplace in alveoli–alveoli have ↑ tendency to collapse on expiration as radius ↓.	Surfactant —↓ alveolar surface tension, ↓ alveolar collapse, ↓ lung recoil, and ↑ compliance. Composed of multiple lecithins, mainly dipalmitoylphosphatidylcholine (DPPC). Synthesis begins ~20 weeks of gestation and achieves mature levels ~35 weeks of gestation. Glucocorticoids important for fetal surfactant synthesis and lung development. Collapsing pressure = 2 (surface tension)/radius
Alveolar macrophages	Phagocytose foreign materials; release cytokines and alveolar proteases.	Hemosiderin-laden macrophages may be found (eg, pulmonary edema, alveolar hemorrhage).

**Neonatal respiratory distress syndrome**

Surfactant deficiency → ↑ surface tension → alveolar collapse (“ground-glass” appearance of lung fields) **A**.

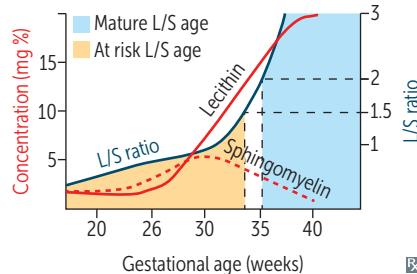
Risk factors: prematurity, diabetes during pregnancy (due to ↑ fetal insulin), C-section delivery (↓ release of fetal glucocorticoids; less stressful than vaginal delivery).

Treatment: maternal glucocorticoids before birth; exogenous surfactant for infant.

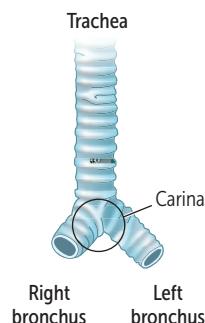
Therapeutic supplemental O₂ can result in **Retinopathy of prematurity**, **Intraventricular hemorrhage**, **Bronchopulmonary dysplasia (RIB)**.

Screening tests for fetal lung maturity: lecithin-sphingomyelin (L/S) ratio in amniotic fluid (≥ 2 is healthy; < 1.5 predictive of NRDS), foam stability index, surfactant-albumin ratio.

Persistently low O₂ tension → risk of PDA.





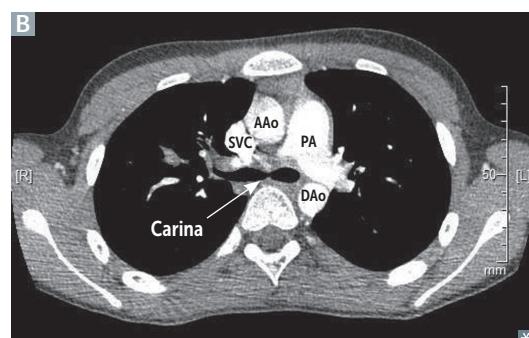
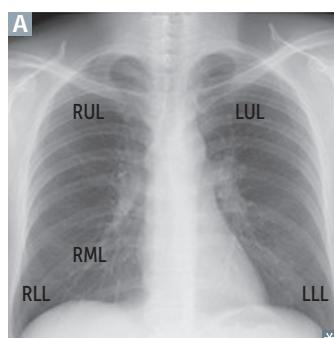
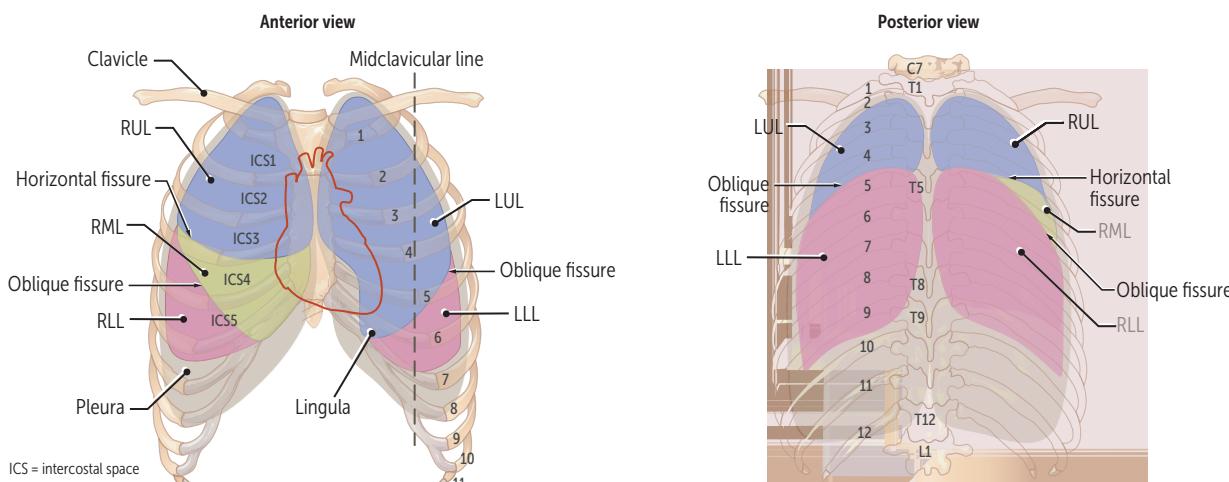
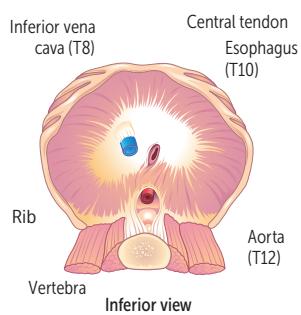
Lung anatomy

Right lung has 3 lobes; Left has less lobes (2) and Lingula (homolog of right middle lobe). Instead of a middle lobe, left lung has a space occupied by the heart **A**.

Relation of the pulmonary artery to the bronchus at each lung hilum is described by **RALS—Right Anterior; Left Superior**. Carina is posterior to ascending aorta and anteromedial to descending aorta **B**.

Right lung is a more common site for inhaled foreign bodies because right main stem bronchus is wider, more vertical, and shorter than the left. If you aspirate a peanut:

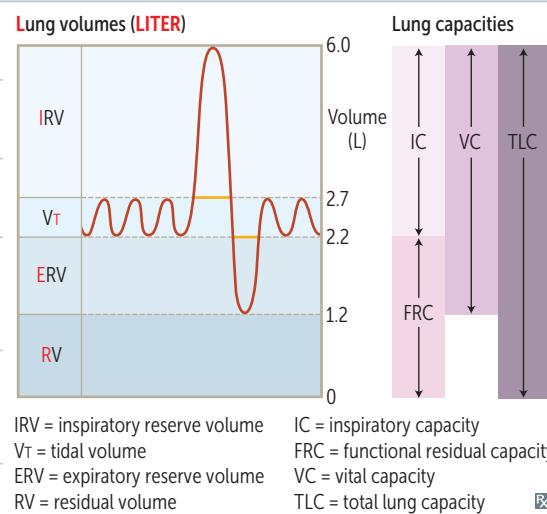
- While supine—usually enters superior segment of right lower lobe.
- While lying on right side—usually enters right upper lobe.
- While upright—usually enters right lower lobe.

**Diaphragm structures**

► RESPIRATORY—PHYSIOLOGY

Lung volumes and capacities

Tidal volume	Air that moves into lung with each quiet inspiration, 6–8 mL/kg, typically ~500 mL.
Inspiratory reserve volume	Air that can still be breathed in after normal inspiration
Expiratory reserve volume	Air that can still be breathed out after normal expiration
Residual volume	Air in lung after maximal expiration; RV and any lung capacity that includes RV cannot be measured by spirometry
Inspiratory capacity	IRV + VT Air that can be breathed in after normal exhalation
Functional residual capacity	RV + ERV Volume of gas in lungs after normal expiration; outward pulling force of chest wall is balanced with inward collapsing force of lungs
Vital capacity	IRV + VT + ERV Maximum volume of gas that can be expired after a maximal inspiration
Total lung capacity	IRV + VT + ERV + RV = VC + RV Volume of gas present in lungs after a maximal inspiration

**Work of breathing**

Refers to the energy expended or O₂ consumed by respiratory muscles to produce the ventilation needed to meet the body's metabolic demand. Comprises the work needed to overcome both elastic recoil and airway resistance (ie, work = force × distance = pressure × volume). Minimized by optimizing respiratory rate (RR) and VT. ↑ in restrictive diseases (↑ work to overcome elastic recoil achieved with ↑ RR and ↓ VT) and obstructive diseases (↑ work to overcome airway resistance achieved with ↓ RR and ↑ VT).

Determination of physiologic dead space

$$VD = VT \times \frac{Paco_2 - PECO_2}{Paco_2}$$

VD = physiologic dead space = anatomic dead space of conducting airways plus alveolar dead space; apex of healthy lung is largest contributor of alveolar dead space. VD = volume of inspired air that does not take part in gas exchange.

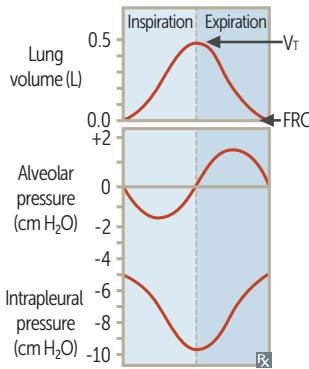
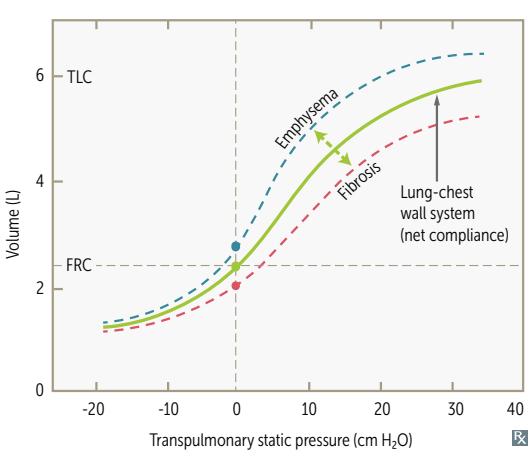
Paco₂ = arterial PCO₂.

PECO₂ = expired air PCO₂.

Physiologic dead space—approximately equivalent to anatomic dead space in normal lungs. May be greater than anatomic dead space in lung diseases with ventilation/perfusion mismatch.

Ventilation

Minute ventilation	Abbreviated as VE . Total volume of gas entering lungs per minute. $VE = VT \times RR$	Normal values: ▪ $RR = 12\text{--}20$ breaths/min ▪ $VT = 500$ mL/breath ▪ $VD = 150$ mL/breath
Alveolar ventilation	Abbreviated as VA . Volume of gas that reaches alveoli each minute. $VA = (VT - VD) \times RR$	

Lung and chest wall properties	Because of historical reasons and small pressures, pulmonary pressures are always presented in $\text{cm H}_2\text{O}$.	
Elastic recoil	Tendency for lungs to collapse inward and chest wall to spring outward. At FRC, airway and alveolar pressures equal atmospheric pressure (P_B ; called zero), and intrapleural pressure is negative (preventing atelectasis). The inward pull of the lung is balanced by the outward pull of the chest wall. System pressure is atmospheric. Pulmonary vascular resistance (PVR) is at a minimum.	
Compliance	Change in lung volume for a change in pressure ($\Delta V/\Delta P$). Inversely proportional to wall stiffness and increased by surfactant. <ul style="list-style-type: none">▪ ↑ compliance = lung easier to fill (eg, emphysema, older adults)▪ ↓ compliance = lung more difficult to fill (eg, pulmonary fibrosis, pneumonia, ARDS, pulmonary edema)	
Hysteresis	Lung inflation follows a different pressure-volume curve than lung deflation due to need to overcome surface tension forces in inflation.	

Pulmonary circulation

Normally a low-resistance, high-compliance system. A ↓ in PAO_2 causes hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

Perfusion limited— O_2 (normal health), CO_2 , N_2O . Gas equilibrates early along the length of the capillary. Exchange can be ↑ only if blood flow ↑.

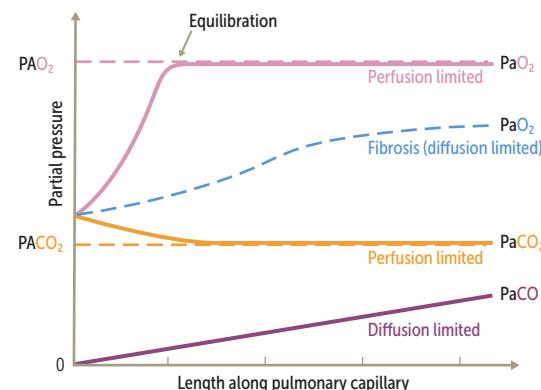
Diffusion limited— O_2 (emphysema, fibrosis), CO . Gas does not equilibrate by the time blood reaches the end of the capillary. O_2 diffuses slowly, while CO_2 diffuses very rapidly across the alveolar membrane. Disease states that lead to diffusion limitation (eg, pulmonary fibrosis) are more likely to cause early hypoxia than hypercapnia.

Chronic hypoxic vasoconstriction may lead to pulmonary hypertension +/- cor pulmonale.

$$\text{Diffusion } (J) = A \times D_k \times \frac{P_1 - P_2}{\Delta_x} \text{ where}$$

- A = area, Δ_x = alveolar wall thickness,
 D_k = diffusion coefficient of gas,
 $P_1 - P_2$ = difference in partial pressures.
 ■ $A \downarrow$ in emphysema.
 ■ $\Delta_x \uparrow$ in pulmonary fibrosis.

DLCO is the extent to which CO passes from air sacs of lungs into blood.



Pa = partial pressure of gas in pulmonary capillary blood
 PA = partial pressure of gas in alveolar air

**Pulmonary vascular resistance**

$$\text{PVR} = \frac{P_{\text{pulm artery}} - P_{\text{L atrium}}}{\dot{Q}}$$

Remember: $\Delta P = \dot{Q} \times R$, so $R = \Delta P / \dot{Q}$

$$R = \frac{8\eta l}{\pi r^4}$$

$P_{\text{pulm artery}}$ = pressure in pulmonary artery
 $P_{\text{L atrium}}$ ≈ pulmonary artery occlusion pressure
 (also called pulmonary capillary wedge pressure)
 \dot{Q} = cardiac output (mL/min)
 R = resistance
 η = viscosity of blood ("stickiness")
 l = vessel length
 r = vessel radius

Ventilation/perfusion mismatch

Ideally, ventilation (V) is matched to perfusion (Q) per minute (ie, \dot{V}/\dot{Q} ratio = 1) for adequate gas exchange.

Lung zones:

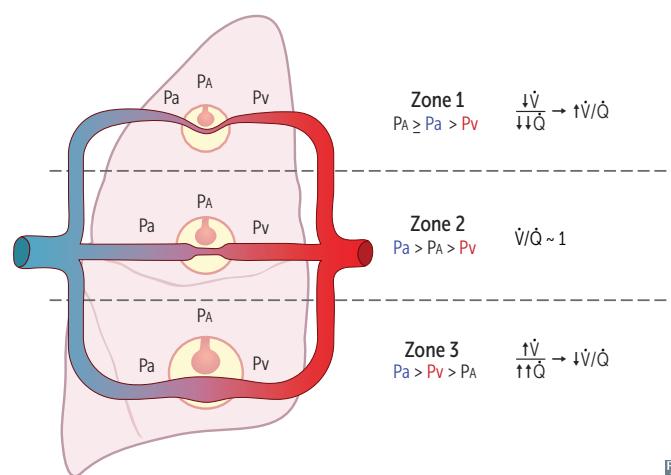
- \dot{V}/\dot{Q} at apex of lung = 3 (wasted ventilation)
- \dot{V}/\dot{Q} at base of lung = 0.6 (wasted perfusion)

Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung.

With exercise (\uparrow cardiac output), there is vasodilation of apical capillaries $\rightarrow \dot{V}/\dot{Q}$ ratio approaches 1. Certain organisms that thrive in high O_2 (eg, TB) flourish in the apex.

$\dot{V}/\dot{Q} = 0$ = “airway” obstruction (shunt). In shunt, 100% O_2 does not improve Pao_2 (eg, foreign body aspiration).

$\dot{V}/\dot{Q} = \infty$ = blood flow obstruction (physiologic dead space). Assuming < 100% dead space, 100% O_2 improves Pao_2 (eg, pulmonary embolus).



Alveolar gas equation

$$\text{PAO}_2 = \text{PIO}_2 - \frac{\text{Paco}_2}{\text{RQ}}$$

$$\approx 150 \text{ mm Hg}^a - \frac{\text{Paco}_2}{0.8}$$

^aAt sea level breathing room air

PAO_2 = alveolar Po_2 (mm Hg)

PIO_2 = Po_2 in inspired air (mm Hg)

Paco_2 = arterial Pco_2 (mm Hg)

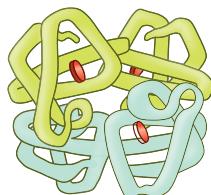
RQ = respiratory quotient = CO_2 produced/
 O_2 consumed

A-a gradient = $\text{PAO}_2 - \text{Pao}_2$. Normal A-a gradient estimated as $(\text{age}/4) + 4$ (eg, for a person < 40 years old, gradient should be < 14).



H

Hemoglobin



Normal adult hemoglobin (Hb) is composed of 4 polypeptide subunits (2 α and 2 β) that each bind one O_2 molecule. Hb is an allosteric protein that exhibits positive cooperativity when binding to O_2 , such that:

- Oxygenated Hb has high affinity for O_2 (300x).
- Deoxygenated Hb has low affinity for O_2 → promotes release/unloading of O_2 .

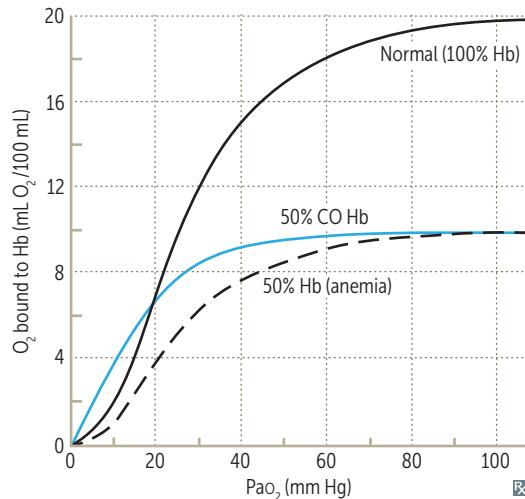
The protein component of hemoglobin acts as buffer for H^+ ions.

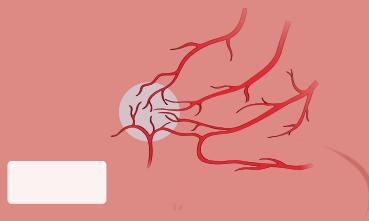
Myoglobin is composed of a single polypeptide chain associated with one heme moiety.
Higher affinity for oxygen than Hb.

Response to high altitude	<p>Constant $\text{F}\text{I}\text{O}_2$ but $\downarrow \text{Pb} \rightarrow \downarrow$ atmospheric oxygen ($\text{P}\text{I}\text{O}_2$) $\rightarrow \downarrow \text{Pao}_2 \rightarrow \uparrow$ ventilation $\rightarrow \downarrow \text{Paco}_2$ \rightarrow respiratory alkalosis \rightarrow altitude sickness (headaches, nausea, fatigue, lightheadedness, sleep disturbance).</p> <p>Chronic \uparrow in ventilation.</p> <p>\uparrow erythropoietin $\rightarrow \uparrow \text{Hct}$ and Hb (due to chronic hypoxia).</p> <p>\uparrow 2,3-BPG (binds to Hb \rightarrow rightward shift of oxyhemoglobin dissociation curve $\rightarrow \uparrow \text{O}_2$ release).</p> <p>Cellular changes (\uparrow mitochondria).</p> <p>\uparrow renal excretion of HCO_3^- to compensate for respiratory alkalosis (can augment with acetazolamide).</p> <p>Chronic hypoxic pulmonary vasoconstriction $\rightarrow \uparrow$ pulmonary vascular resistance \rightarrow pulmonary hypertension, right ventricular hypertrophy (RVH).</p>
Response to exercise	<p>\uparrow HR and \uparrow SV $\rightarrow \uparrow \dot{\text{Q}}$ $\rightarrow \uparrow$ pulmonary blood flow $\rightarrow \uparrow \dot{\text{V}}/\dot{\text{Q}}$ ratio from base to apex (becoming more uniform).</p> <p>\uparrow cellular respiration $\rightarrow \uparrow \text{CO}_2$ production and \downarrow pH at tissues \rightarrow right shift of ODC \rightarrow tissue offloading of more $\text{O}_2 \rightarrow \uparrow \text{O}_2$ consumption. \uparrow RR to meet $\uparrow \text{O}_2$ demand and remove excess $\text{CO}_2 \rightarrow \uparrow$ pulmonary blood flow.</p> <p>Pao_2 and Paco_2 are maintained by homeostatic mechanisms.</p> <p>$\downarrow \text{PvO}_2$ due to $\uparrow \text{O}_2$ consumption.</p> <p>$\uparrow \text{PvCO}_2$ due to $\uparrow \text{CO}_2$ production.</p>
Methemoglobin	<p>Iron in Hb is normally in a reduced state (ferrous Fe^{2+}; “just the 2 of us”). Oxidized form of Hb (ferric, Fe^{3+}) does not bind O_2 as readily as Fe^{2+}, but has \uparrow affinity for cyanide \rightarrow tissue hypoxia from $\downarrow \text{O}_2$ saturation and $\downarrow \text{O}_2$ content.</p> <p>This Fe^{3+} form is called methemoglobinemia. While typical concentrations are 1–2%, methemoglobinemia will occur at higher levels and may present with cyanosis (does not improve with supplemental O_2) and with chocolate-colored blood.</p> <p>Dapsone, local anesthetics (eg, benzocaine), and nitrites (eg, from dietary intake or polluted water sources) cause poisoning by oxidizing Fe^{2+} to Fe^{3+}.</p> <p>Methemoglobinemia can be treated with methylene blue and vitamin C.</p>

Cyanide vs carbon monoxide poisoning Both inhibit aerobic metabolism via inhibition of complex IV of ETC (cytochrome c oxidase)
→ hypoxia that does not fully correct with supplemental O₂ and ↑ anaerobic metabolism.

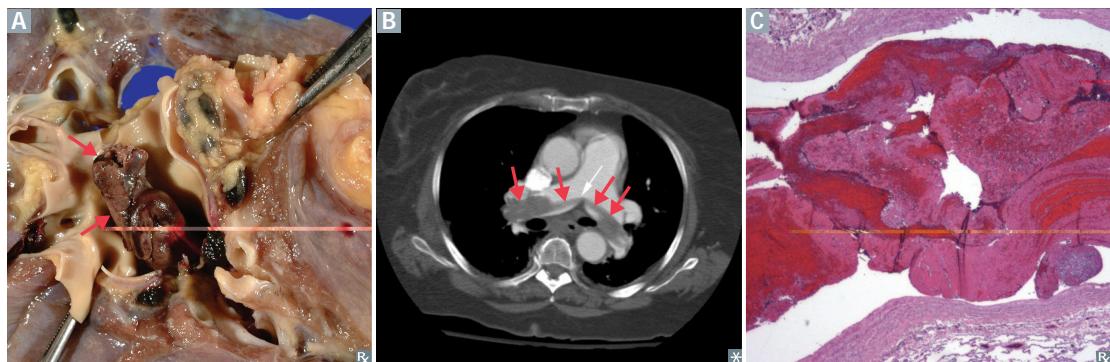
	Cyanide	Carbon monoxide
EXPOSURE	Synthetic product combustion, amygdalin ingestion (found in apricot seeds), cyanide ingestion (eg, in suicide attempts), fire victims.	Motor exhaust, gas heaters, fire victims.
PRESENTATION	Headache, dyspnea, drowsiness, seizure, coma. Skin may appear flushed (“cherry red”). Venules in retina appear bright red. Breath may have bitter almond odor.	Headache, vomiting, confusion, visual disturbances, coma. May have cherry-red skin with bullous skin lesions. Multiple victims may be involved (eg, family due to faulty furnace).
LABS	Normal Pao ₂ . Elevated lactate → anion gap metabolic acidosis.	Normal Pao ₂ . Elevated carboxyhemoglobin on co-oximetry. Classically associated with bilateral globus pallidus lesions on MRI A , although can rarely be seen with cyanide toxicity.
EFFECT ON OXYGEN-HEMOGLOBIN CURVE	Curve normal. Oxygen saturation may appear normal initially. Despite ample O ₂ supply, it cannot be used due to ineffective oxidative phosphorylation.	Left shift in ODC → ↑ affinity for O ₂ → ↓ O ₂ unloading in tissues. Binds competitively to Hb with > 200× greater affinity than O ₂ to form carboxyhemoglobin → ↓ %O ₂ saturation of Hb.
TREATMENT	Decontamination (eg, remove clothing). Hydroxocobalamin (binds cyanide → cyanocobalamin → renal excretion). Nitrites (oxidize Hb → methemoglobin → binds cyanide → cyanomethemoglobin → ↓ toxicity). Sodium thiosulfate (↑ cyanide conversion to thiocyanate → renal excretion).	100% O ₂ . Hyperbaric oxygen if severe.





Pulmonary emboli

Obstruction of the pulmonary artery or its branches by foreign material (usually thrombus) that originated elsewhere. Affected alveoli are ventilated but not perfused (\dot{V}/\dot{Q} mismatch). May present with sudden-onset dyspnea, pleuritic chest pain, tachypnea, tachycardia, hypoxemia, respiratory alkalosis. Large emboli or saddle embolus (red arrows show filling defects in **A**) may cause sudden death due to clot preventing blood from filling LV and increased RV size further compromising LV filling (obstructive shock). CT pulmonary angiography is imaging test of choice for PE (look for filling defects) **B**. ECG may show sinus tachycardia or, less commonly, ST elevation in leads I, aVL, and V₅-V₆ (SIQ3T3 abnormality). Lines of Zahn **C** are interdigitating areas of pink (platelets, fibrin) and red (RBCs) found only in thrombi formed before death; help distinguish pre- and postmortem thrombi. Treatment: anticoagulation (eg, heparin, direct thrombin/factor Xa inhibitors), IVC filter (if anticoagulation is contraindicated). Types: **Fat, Air, Thrombus, Bacteria, Amniotic fluid, Tumor.** An embolus moves like a **FAT BAT**. **Fat emboli**—associated with long bone fractures and liposuction; classic triad of hypoxemia, neurologic abnormalities, petechial rash. **Air emboli**—nitrogen bubbles precipitate in ascending divers (caisson disease/decompression sickness); treat with hyperbaric O₂; or, can be iatrogenic 2° to invasive procedures (eg, central line placement). **Amniotic fluid emboli**—typically occurs during labor or postpartum, but can be due to uterine trauma. Can lead to DIC. Rare, but high mortality.

**Mediastinal pathology**

Normal mediastinum contains heart, thymus, lymph nodes, esophagus, and aorta.

Mediastinal masses

Some pathologies (eg, lymphoma, lung cancer, abscess) can occur in any compartment, but there are common associations:

- Anterior—**4 T's:** thyroid (substernal goiter), thymic neoplasm, teratoma, “terrible” lymphoma.
- Middle—metastases, hiatal hernia, bronchogenic cysts.
- Posterior—esophageal cancer (may present as mass in, or spread to, middle mediastinum), neurogenic tumor (eg, neurofibroma), multiple myeloma.

Mediastinitis

Inflammation of mediastinal tissues. Commonly due to postoperative complications of cardiothoracic procedures (≤ 14 days), esophageal perforation, or contiguous spread of odontogenic/retropharyngeal infection.

Chronic mediastinitis—also called fibrosing mediastinitis; due to ↑ proliferation of connective tissue in mediastinum. *Histoplasma capsulatum* is common cause.

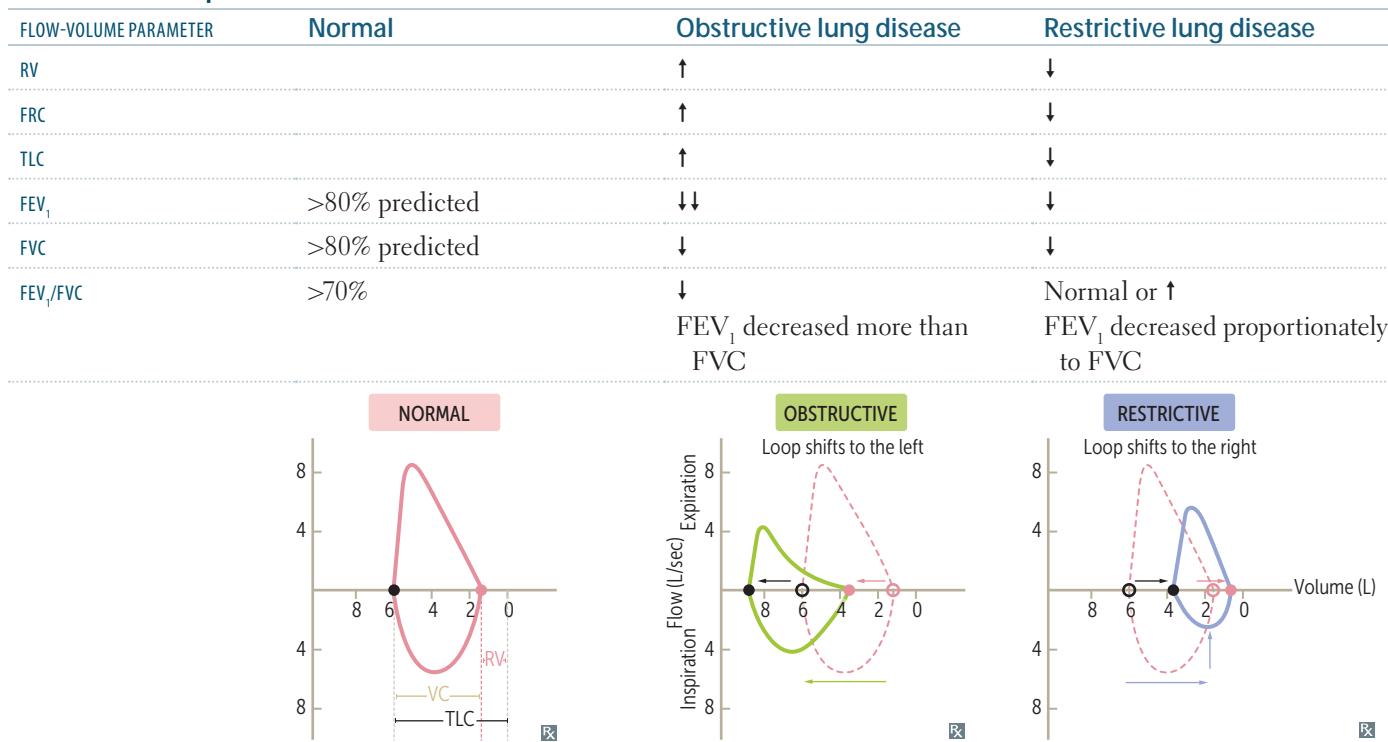
Clinical features: fever, tachycardia, leukocytosis, chest pain, and sternal wound drainage.

Pneumomediastinum

Presence of gas (usually air) in the mediastinum. Can either be spontaneous (due to rupture of pulmonary bleb) or 2° (eg, trauma, iatrogenic, Boerhaave syndrome).

Ruptured alveoli allow tracking of air into the mediastinum via peribronchial and perivascular sheaths.

Clinical features: chest pain, dyspnea, voice change, subcutaneous emphysema, \oplus Hamman sign (crepitus on cardiac auscultation).

Flow-volume loops**Obstructive lung diseases**

Obstruction of air flow (↓↓ FEV₁, ↓ FVC ↓ FEV₁/FVC ratio) → air trapping in lungs (↑ RV, →↑ FRC and ↑ TLC) due to premature airway closure at high lung volumes. Includes COPD (chronic bronchitis and emphysema), asthma, and bronchiectasis.

Chronic obstructive pulmonary disease

Often due to tobacco use (most important risk factor), pollutants, or allergens. Includes chronic bronchitis and emphysema, which often co-exist. Exacerbation: acute worsening of symptoms, often associated with viral or bacterial upper respiratory tract infection.

Chronic bronchitis

DIAGNOSIS Clinical diagnosis. Criteria: productive cough for ≥ 3 months in a year for > 2 consecutive years. May also have dyspnea, wheezes, crackles (due to mucus), cyanosis (hypoxemia due to shunting), 2° polycythemia. Leads to metaplasia of pseudostratified ciliated columnar epithelium into stratified squamous epithelium.

MECHANISMS

Hypertrophy and hyperplasia of mucus-secreting glands in bronchi.

NOTES

↑ Reid index (thickness of mucosal gland layer to thickness of wall between epithelium and cartilage) > 50%.

Emphysema

DIAGNOSIS Radiologic or biopsy diagnosis. CXR: barrel chest, ↑ AP diameter (best seen in lateral **A**), flattened diaphragm, ↑ lung field lucency.

MECHANISMS

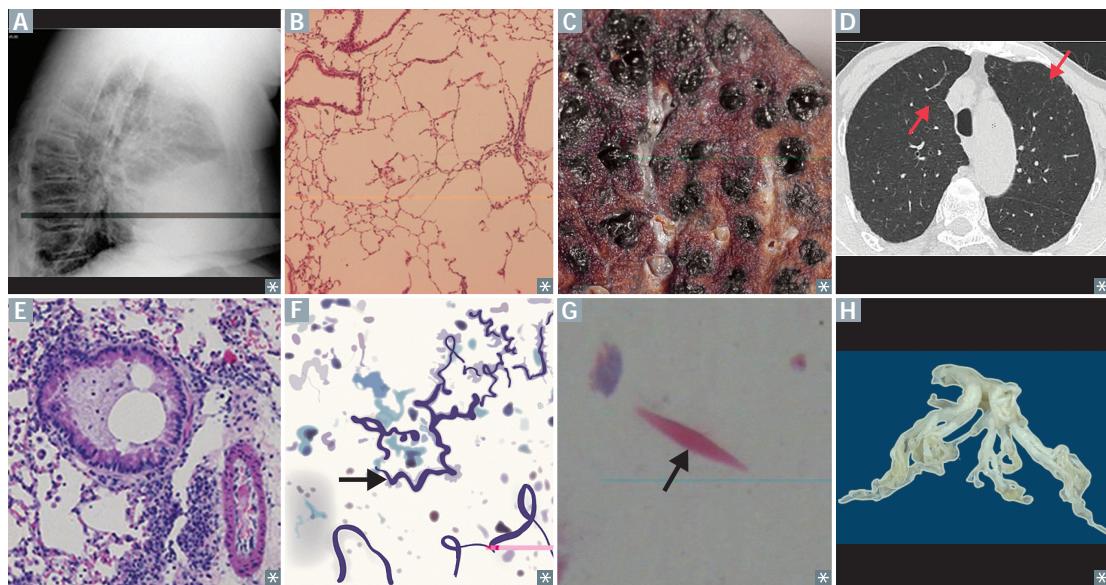
Alveolar wall destruction **B** → ↑ compliance of lung, ↓ recoil, and damage to alveolar capillary membrane → ↓ DLCO; results in ↑ air space.

Centriacinar—spares distal alveoli, frequently in upper lobes. Associated with tobacco smoking **C D**.

Panacinar—affects respiratory bronchioles and alveoli, frequently in lower lobes. Associated with α_1 -antitrypsin deficiency.

Obstructive lung diseases (*continued*)

NOTES	Mediated by oxidative stress, chronic inflammation (CD8+ T cells, neutrophils, and macrophages), and imbalance of proteases and antiproteases (\uparrow elastase activity \rightarrow \uparrow loss of elastic fibers \rightarrow alveolar destruction). Defect/deficiency/absence of α_1 -antitrypsin (antiprotease that inhibits neutrophil elastase) leads to unopposed elastase activity
Asthma	Intermittent obstructive lung disease often triggered by allergens, viral URIs, stress. Associated with atopy. NSAID- or aspirin-exacerbated respiratory disease—asthma, nasal polyps, and COX-inhibitor sensitivity (leukotriene overproduction \rightarrow airway constriction) (Samter's triad).
DIAGNOSIS	Clinical diagnosis. Intermittent episodes of dyspnea, coughing, wheezing, tachypnea. Diagnosis supported by spiroometry (obstructive pattern with bronchodilator response, but may be normal when not in exacerbation) \pm methacholine challenge.
MECHANISMS	Type I hypersensitivity reaction \rightarrow smooth muscle hypertrophy and hyperplasia. Hyperresponsive bronchi \rightarrow reversible bronchoconstriction. Mucus plugging E .
OTHER	Curschmann spirals F —shed epithelium forms whorled mucus plugs. Charcot-Leyden crystals G —eosinophilic, hexagonal, double-pointed crystals formed from breakdown of eosinophils in sputum.
Bronchiectasis	Obstructive lung disease. Most commonly associated with cystic fibrosis.
DIAGNOSIS	Characterized by chronic cough and daily purulent sputum production. Often have recurrent pulmonary infections. Confirmed by imaging demonstrating airway dilation and bronchial thickening. Supported by obstructive PFT pattern.
PATHOPHYSIOLOGY	Initial insult of pulmonary infection combined with obstruction or impaired clearance \rightarrow dysregulated host response \rightarrow bronchial inflammation \rightarrow permanently dilated airways.
NOTES	Many etiologies, including airway obstruction (eg, foreign body aspiration, mass), poor ciliary motility (eg, tobacco smoking, Kartagener syndrome), cystic fibrosis (H shows a coughed up inspissated mucus plug), allergic bronchopulmonary aspergillosis, pulmonary infections (eg, <i>Mycobacterium avium</i>).



Restrictive lung diseases

May lead to ↓ lung volumes (↓ FVC and TLC). PFTs: normal or ↑ FEV₁/FVC ratio. Patient presents with short, shallow breaths.

Types:

- Altered respiratory mechanics (extrapulmonary, normal D_{LCO}, normal A-a gradient):
 - Respiratory muscle weakness—polio, myasthenia gravis, Guillain-Barré syndrome, ALS
 - Chest wall abnormalities—scoliosis, severe obesity
- Diffuse parenchymal lung diseases, also called interstitial lung diseases (pulmonary, ↓ D_{LCO}, ↑ A-a gradient):
 - Pneumoconioses (eg, coal workers' pneumoconiosis, silicosis, asbestosis)
 - Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granulomas; ↑ ACE and Ca²⁺
 - Idiopathic pulmonary fibrosis
 - Granulomatosis with polyangiitis
 - Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
 - Hypersensitivity pneumonitis
 - Drug toxicity (eg, bleomycin, busulfan, amiodarone, methotrexate)
 - Acute respiratory distress syndrome
 - **Radiation-induced lung injury**—associated with proinflammatory cytokine release (eg, TNF-α, IL-1, IL-6). May be asymptomatic but most common symptoms are dry cough and dyspnea +/- low-grade fever. Acute radiation pneumonitis develops within 3–12 weeks (exudative phase); radiation fibrosis may develop after 6–12 months.

Idiopathic pulmonary fibrosis

Progressive fibrotic lung disease of unknown etiology. May involve multiple cycles of lung injury, inflammation, and fibrosis. Associated with tobacco smoking, environmental pollutants, genetic defects.

Findings: progressive dyspnea, fatigue, nonproductive cough, crackles, clubbing. Imaging shows peripheral reticular opacities with traction bronchiectasis +/- “honeycomb” appearance of lung (advanced disease). Histologic pattern: usual interstitial pneumonia. ↓ type 1 pneumocytes, ↑ type 2 pneumocytes, ↑ fibroblasts.

Complications: pulmonary hypertension, right heart failure, arrhythmias, coronary artery disease, respiratory failure, lung cancer.

Hypersensitivity pneumonitis

Mixed type III/IV hypersensitivity reaction to environmental antigens such as thermophilic *Actinomyces* and *Aspergillus*. Often seen in farmers and bird-fanciers. Acutely, causes dyspnea, cough, chest tightness, fever, headache. Often self-limiting if stimulus is removed. Chronically, leads to irreversible fibrosis with noncaseating granuloma, alveolar septal thickening, traction bronchiectasis.

Sarcoidosis

Characterized by immune-mediated, widespread noncaseating granulomas **A**, elevated serum ACE levels, and elevated CD4/CD8 ratio in bronchoalveolar lavage fluid. More common in Black females. Often asymptomatic except for enlarged lymph nodes. CXR shows bilateral adenopathy and coarse reticular opacities **B**; CT of the chest better demonstrates the extensive hilar and mediastinal adenopathy **C**.

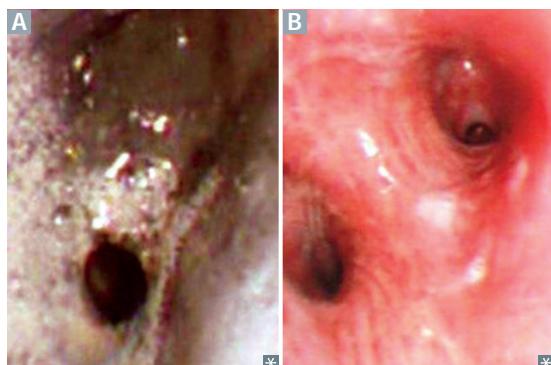
Associated with Bell palsy, parotid enlargement, granulomas (noncaseating epithelioid, containing microscopic Schaumann and Asteroid bodies), Rheumatoid arthritis-like arthropathy, ↑ Calcium, Ocular uveitis, Interstitial fibrosis, vitamin D activation (due to ↑ 1 α -hydroxylase in macrophages), Skin changes (eg, lupus pernio, erythema nodosum) (**SARCOIDS**).

Treatment: glucocorticoids (if symptomatic).

**Inhalation injury and sequelae**

Complication of inhalation of noxious stimuli (eg, smoke). Caused by heat, particulates (< 1 μm diameter), or irritants (eg, NH_3) → chemical tracheobronchitis, edema, pneumonia, ARDS. Many patients present 2° to burns, CO inhalation, cyanide poisoning, or arsenic poisoning. Singed nasal hairs or soot in oropharynx common on exam.

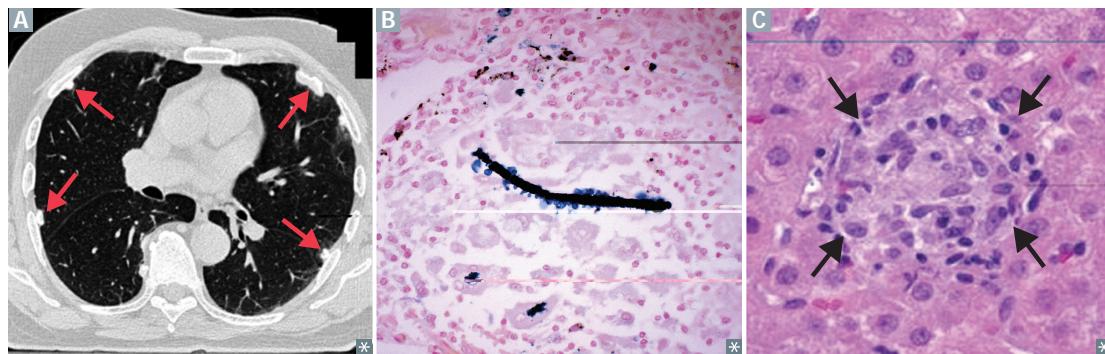
Bronchoscopy shows severe edema, congestion of bronchus, and soot deposition (**A**, 18 hours after inhalation injury; **B**, resolution at 11 days after injury).

**Mesothelioma**

Malignancy of the pleura associated with asbestos. May result in hemorrhagic pleural effusion (exudative), pleural thickening.

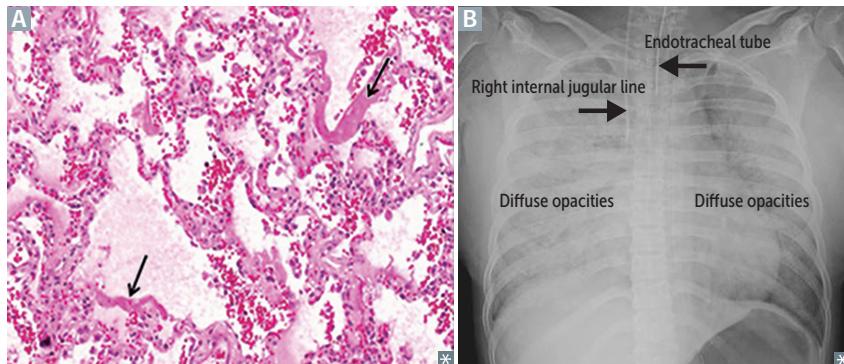
Histology may show psammoma bodies. EM may show polygonal tumor cells with microvilli, desmosomes, tonofilaments. Calretinin and cytokeratin 5/6 \oplus in almost all mesotheliomas, \ominus in most carcinomas. Tobacco smoking is not a risk factor.

Pneumoconioses	Asbestos is from the roof (was common in insulation), but affects the base (lower lobes). Silica, coal, and berries are from the base (earth), but affect the roof (upper lobes).	
Asbestos-related disease	Asbestos causes asbestosis (pulmonary fibrosis), pleural disease, malignancies. Associated with shipbuilding, roofing, plumbing. “Ivory white,” calcified, supradiaphragmatic and pleural A plaques are pathognomonic. Risk of bronchogenic carcinoma > risk of mesothelioma. ↑ risk of Caplan syndrome (rheumatoid arthritis and pneumoconioses with intrapulmonary nodules).	Affects lower lobes. Asbestos (ferruginous) bodies are golden-brown fusiform rods resembling dumbbells, found in alveolar sputum sample, visualized using Prussian blue stain B , often obtained by bronchoalveolar lavage. ↑ risk of pleural effusions.
Berylliosis	Associated with exposure to beryllium in aerospace and manufacturing industries. Granulomatous (noncaseating) C on histology and therefore occasionally responsive to glucocorticoids. ↑ risk of cancer and cor pulmonale.	Affects upper lobes.
Coal workers' pneumoconiosis	Prolonged coal dust exposure → macrophages laden with carbon → inflammation and fibrosis. Also called black lung disease. ↑ risk of Caplan syndrome .	Affects upper lobes. Small, rounded nodular opacities seen on imaging. Anthracosis —asymptomatic condition found in many urban dwellers exposed to sooty air.
Silicosis	Associated with sandblasting , foundries , mines . Macrophages respond to silica and release fibrogenic factors, leading to fibrosis. It is thought that silica may disrupt phagolysosomes and impair macrophages, increasing susceptibility to TB. ↑ risk of cancer, cor pulmonale, and Caplan syndrome.	Affects upper lobes. “ Eggshell ” calcification of hilar lymph nodes on CXR. The silly egg sandwich I found is mine!



Acute respiratory distress syndrome

PATHOPHYSIOLOGY	Alveolar insult → release of pro-inflammatory cytokines → neutrophil recruitment, activation, and release of toxic mediators (eg, reactive oxygen species, proteases, etc) → capillary endothelial damage and ↑ vessel permeability → leakage of protein-rich fluid into alveoli → formation of intra-alveolar hyaline membranes (arrows in A) and noncardiogenic pulmonary edema (normal PCWP) → ↓ compliance and \dot{V}/\dot{Q} mismatch → hypoxic vasoconstriction → ↑ pulmonary vascular resistance. Loss of surfactant also contributes to alveolar collapse (eg, preterm infants, drowning).
CAUSES	Sepsis (most common), aspiration pneumonia, burns, trauma, pancreatitis, drowning injuries.
DIAGNOSIS	Diagnosis of exclusion with the following criteria (ARDS): <ul style="list-style-type: none"> ▪ Abnormal chest X-ray (bilateral lung opacities) B ▪ Respiratory failure within 1 week of alveolar insult ▪ Decreased $\text{PaO}_2/\text{FiO}_2$ (ratio < 300, hypoxemia due to ↑ intrapulmonary shunting and diffusion abnormalities) ▪ Symptoms of respiratory failure are not due to HF/fluid overload
CONSEQUENCES	Impaired gas exchange, ↓ lung compliance; pulmonary hypertension.
MANAGEMENT	Treat the underlying cause. Mechanical ventilation: ↓ tidal volume, ↑ PEEP (keeps alveoli open during expiration).



Sleep apnea	Repeated cessation of breathing > 10 seconds during sleep → disrupted sleep → daytime somnolence. Diagnosis confirmed by sleep study. Nocturnal hypoxia → systemic and pulmonary hypertension, arrhythmias (atrial fibrillation/flutter), sudden death. Hypoxia → ↑ EPO release → ↑ erythropoiesis.
Obstructive sleep apnea	Respiratory effort against airway obstruction. PaO_2 is usually normal during the day. Associated with obesity, loud snoring, daytime sleepiness. Usually caused by excess parapharyngeal/oropharyngeal tissue in adults, adenotonsillar hypertrophy in children. Treatment: weight loss, CPAP, dental devices, hypoglossal nerve stimulation, upper airway surgery.
Central sleep apnea	Impaired respiratory effort due to CNS injury/toxicity, Congestive HF , opioids. May be associated with Cheyne-Stokes respirations (oscillations between apnea and hyperpnea). Treatment: positive airway pressure.
Obesity hypoventilation syndrome	Also called Pickwickian syndrome. Obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) → hypoventilation → ↑ Paco_2 during waking hours (retention); ↓ PaO_2 and ↑ Paco_2 during sleep. Treatment: weight loss, positive airway pressure.

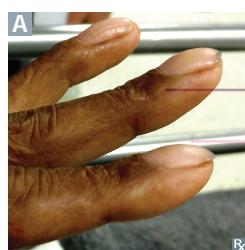
Pulmonary hypertension Elevated mean pulmonary artery pressure (> 20 mm Hg) at rest. Results in arteriosclerosis, medial hypertrophy, intimal fibrosis of pulmonary arteries, plexiform lesions. \uparrow pulmonary vascular resistance $\rightarrow \uparrow$ RV pressure \rightarrow RVH (parasternal heave on examination), RV failure.

ETIOLOGIES

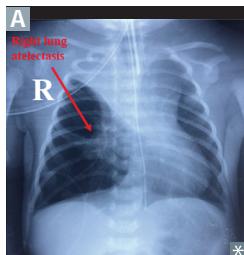
Pulmonary arterial hypertension (group 1)	Often idiopathic. Females $>$ males. Heritable PAH can be due to an inactivating mutation in <i>BMPR2</i> gene (normally inhibits vascular smooth muscle proliferation); poor prognosis. Pulmonary vasculature endothelial dysfunction results in \uparrow vasoconstrictors (eg, endothelin) and \downarrow vasodilators (eg, NO and prostacyclins). Other causes include drugs (eg, amphetamines, cocaine), connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis.
Left heart disease (group 2)	Causes include systolic/diastolic dysfunction and valvular disease.
Lung diseases or hypoxia (group 3)	Destruction of lung parenchyma (eg, COPD), lung inflammation/fibrosis (eg, interstitial lung diseases), hypoxic vasoconstriction (eg, obstructive sleep apnea, living in high altitude).
Chronic thromboembolic (group 4)	Recurrent microthrombi $\rightarrow \downarrow$ cross-sectional area of pulmonary vascular bed.
Multifactorial (group 5)	Causes include hematologic, systemic, and metabolic disorders, along with compression of the pulmonary vasculature by a tumor.

Physical findings in select lung diseases

ABNORMALITY	BREATH SOUNDS	PERCUSSION	FRÉMITS	TRACHEAL DEVIATION
Pleural effusion	\downarrow	Dull	\downarrow	None if small Away from side of lesion if large
Atelectasis	\downarrow	Dull	\downarrow	Toward side of lesion
Simple pneumothorax	\downarrow	Hyperresonant	\downarrow	None
Tension pneumothorax	\downarrow	Hyperresonant	\downarrow	Away from side of lesion
Consolidation (lobar pneumonia, pulmonary edema)	Bronchial breath sounds; late inspiratory crackles, egophony, whispered pectoriloquy	Dull	\uparrow	None

Digital clubbing

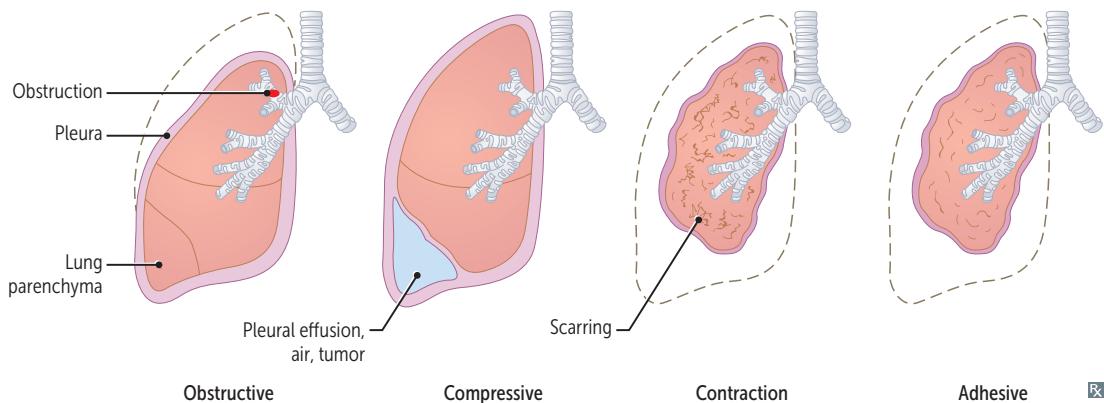
Increased angle between nail bed and nail plate ($> 180^\circ$) **A**. Pathophysiology not well understood; in patients with intrapulmonary shunt, platelets and megakaryocytes become lodged in digital vasculature \rightarrow local release of PDGF and VEGF. Can be hereditary or acquired. Causes include respiratory diseases (eg, idiopathic pulmonary fibrosis, cystic fibrosis, bronchiectasis, lung cancer), cardiovascular diseases (eg, cyanotic congenital heart disease), infections (eg, lung abscess, TB), and others (eg, IBD). Not typically associated with COPD or asthma.

Atelectasis

Alveolar collapse (right upper lobe collapse against mediastinum in A). Multiple causes:

- Obstructive—airway obstruction prevents new air from reaching distal airways, old air is resorbed (eg, foreign body, mucous plug, tumor)
- Compressive—external compression on lung decreases lung volumes (eg, space-occupying lesion, pleural effusion)
- Contraction (cicatrization)—scarring of lung parenchyma that distorts alveoli (eg, sarcoidosis)
- Adhesive—due to lack of surfactant (eg, NRDS in premature infants)

Decreased via incentive spirometry or ↑ PEEP during mechanical ventilation.

**Pleural effusions**

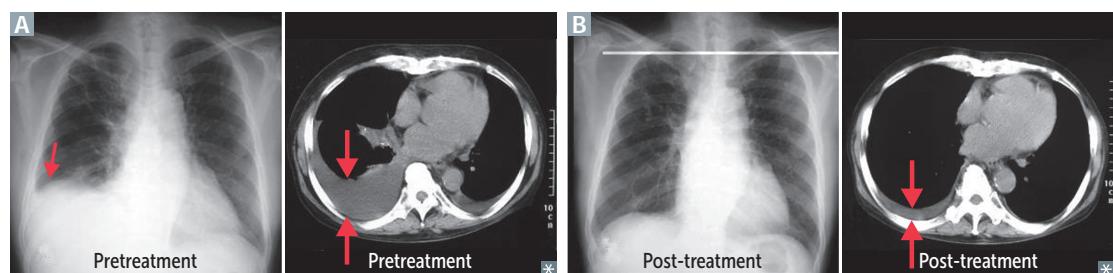
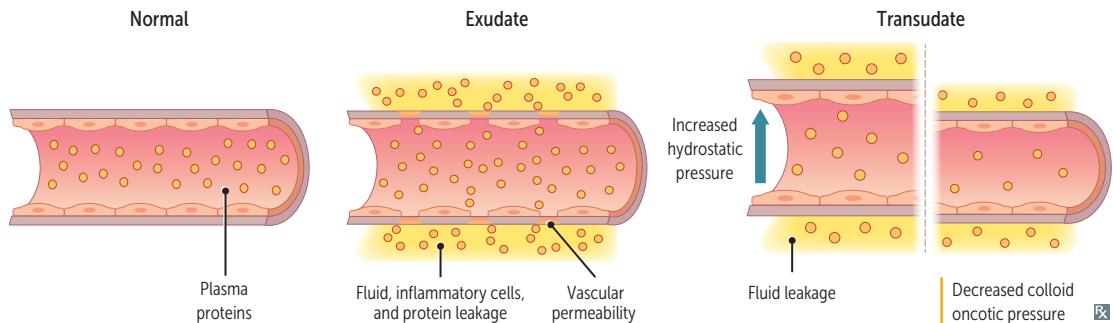
Excess accumulation of fluid A between pleural layers → restricted lung expansion during inspiration. Can be treated with thoracentesis to remove/reduce fluid B. Based on the Light's criteria, fluid is consistent with an exudate if pleural fluid protein/serum protein > 0.5, pleural fluid LDH/serum LDH > 0.6, or pleural fluid LDH > 2/3 upper limit of normal serum LDH.

Exudate

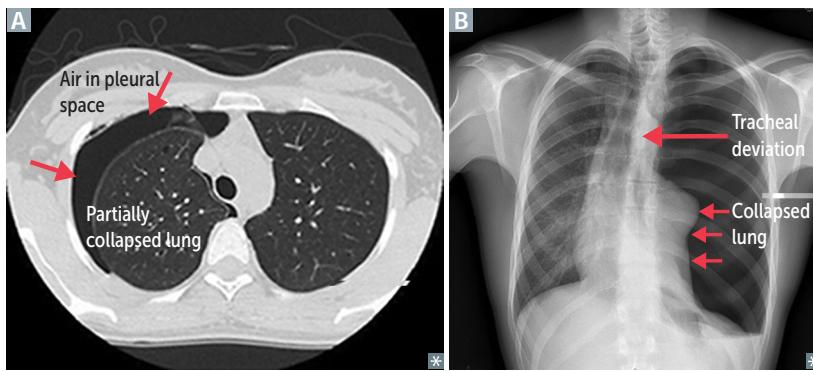
Cloudy fluid (cellular). Due to infection (eg, pneumonia, tuberculosis), malignancy, connective tissue disease, lymphatic (chylothorax), trauma. Often requires drainage due to ↑ risk of infection.

Transudate

Clear fluid (hypocellular). Due to ↑ hydrostatic pressure (eg, HF, Na⁺ retention) and/or ↓ oncotic pressure (eg, nephrotic syndrome, cirrhosis).



Pneumothorax	Accumulation of air in pleural space A . Dyspnea, uneven chest expansion. Chest pain, ↓ tactile fremitus, hyperresonance, and diminished breath sounds, all on the affected side.
Primary spontaneous pneumothorax	Due to rupture of apical subpleural bleb or cysts. Occurs most frequently in tall, thin, young males. Associated with tobacco smoking.
Secondary spontaneous pneumothorax	Due to diseased lung (eg, bullae in emphysema, Marfan syndrome, infections), mechanical ventilation with use of high pressures → barotrauma.
Traumatic pneumothorax	Caused by blunt (eg, rib fracture), penetrating (eg, gunshot), or iatrogenic (eg, central line placement, lung biopsy, barotrauma due to mechanical ventilation) trauma.
Tension pneumothorax	Can be from any of the above. Air enters pleural space but cannot exit. Increasing trapped air → tension pneumothorax. Trachea deviates away from affected lung B . May lead to increased intrathoracic pressure → mediastinal displacement → kinking of IVC → ↓ venous return → ↓ cardiac output, obstructive shock (hypotension, tachycardia), jugular venous distention. Needs immediate needle decompression and chest tube placement.



Pneumonia

TYPE	TYPICAL ORGANISMS	CHARACTERISTICS
Lobar pneumonia	<i>S pneumoniae</i> (most common), <i>Legionella</i> , <i>Klebsiella</i>	Intra-alveolar exudate → consolidation A ; may involve entire lobe or the whole lung.
Bronchopneumonia	<i>S pneumoniae</i> , <i>S aureus</i> , <i>H influenzae</i> , <i>Klebsiella</i>	Acute inflammatory infiltrates from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobe.
Interstitial (atypical) pneumonia	<i>Mycoplasma</i> , <i>Chlamydophila pneumoniae</i> , <i>Chlamydophila psittaci</i> , <i>Legionella</i> , <i>Coxiella burnetii</i> , viruses (RSV, CMV, influenza, adenovirus)	Diffuse patchy inflammation localized to interstitial areas at alveolar walls; CXR shows bilateral multifocal opacities B . Generally follows a more indolent course (“walking” pneumonia).
Cryptogenic organizing pneumonia	Etiology unknown. ⊖ sputum and blood cultures, often responds to glucocorticoids but not to antibiotics.	Formerly called bronchiolitis obliterans organizing pneumonia (BOOP). Noninfectious pneumonia characterized by inflammation of bronchioles and surrounding structure.
Aspiration pneumonia	Aspiration of oropharyngeal or gastric contents → pulmonary infection. Risk factors: altered mental status (↓ cough reflex or glottic closure), dysphagia, neurologic disorders (eg, stroke), invasive tubes (eg, nasogastric tube).	Presents days after aspiration event in dependent lung segment. More common in RLL if sitting up and RUL if lying down due to bronchial anatomy. Can progress to abscess. Aspiration (chemical) pneumonitis —presents hours after aspiration event. Due to gastric acid-mediated inflammation. Presents with infiltrates in lower lobe(s) and resolves with supportive treatment.



Lung cancer

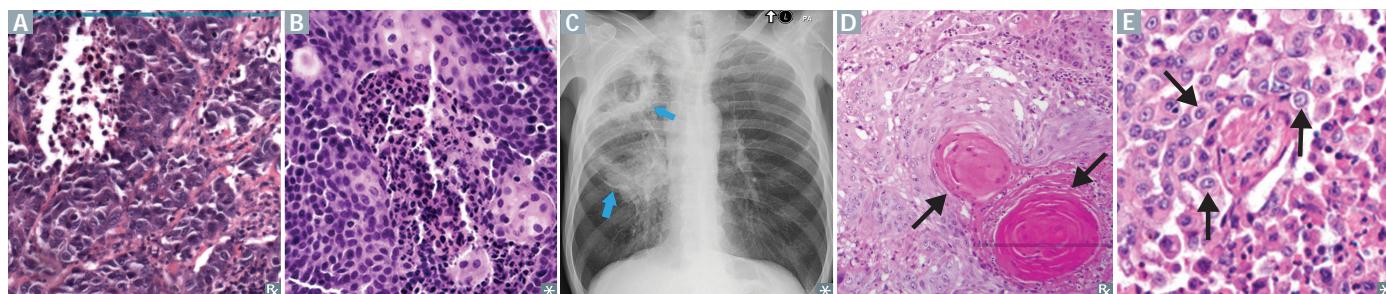
Leading cause of cancer death.
Presentation: cough, hemoptysis, bronchial obstruction, wheezing, pneumonic “coin” lesion on CXR or noncalcified nodule on CT.
Sites of metastases from lung cancer: **liver** (jaundice, hepatomegaly), **adrenals**, **bone** (pathologic fracture), **brain**; “Lung ‘mets’ Love affective **boneheads** and **brainiacs**.
In the lung, metastases (usually multiple lesions) are more common than 1° neoplasms. Most often from breast, colon, prostate, and bladder cancer.

SPHERE of complications: Superior vena cava/thoracic outlet syndromes, **Pancoast tumor**, Horner syndrome, **Endocrine** (paraneoplastic), **Recurrent laryngeal nerve compression** (hoarseness), **Effusions** (pleural or pericardial).

Risk factors include tobacco smoking, secondhand smoke, radiation, environmental exposures (eg, radon, asbestos), pulmonary fibrosis, family history.

Squamous and **small cell** carcinomas are **sentral** (central) and often caused by tobacco **smoking**.
Hamartomas are found incidentally on imaging, appearing as well-circumscribed mass.

TYPE	LOCATION	CHARACTERISTICS	HISTOLOGY
Small cell			
Small cell (oat cell) carcinoma	Central	Undifferentiated → very aggressive. May cause neurologic paraneoplastic syndromes (eg, Lambert-Eaton myasthenic syndrome, paraneoplastic myelitis, encephalitis, subacute cerebellar degeneration) and endocrine paraneoplastic syndromes (Cushing syndrome, SIADH). Amplification of <i>myc</i> oncogenes common. Managed with chemotherapy +/- radiation.	Neoplasm of neuroendocrine Kulchitsky cells → small dark blue cells A . Chromogranin A \oplus , neuron-specific enolase \oplus , synaptophysin \oplus .
Non–small cell			
Adenocarcinoma	Peripheral	Most common 1° lung cancer. Most common subtype in people who do not smoke. More common in females than males. Activating mutations include <i>KRAS</i> , <i>EGFR</i> , and <i>ALK</i> . Associated with hypertrophic osteoarthropathy (clubbing). Bronchioloalveolar subtype (adenocarcinoma <i>in situ</i>): CXR often shows hazy infiltrates similar to pneumonia; better prognosis.	Glandular pattern, often stains mucin \oplus B . Bronchioloalveolar subtype: grows along alveolar septa → apparent “thickening” of alveolar walls. Tall, columnar cells containing mucus.
Squamous cell carcinoma	Central	Hilar mass C arising from bronchus; cavitation; cigarettes; hypercalcemia (produces PTHrP).	Keratin pearls D and intercellular bridges (desmosomes).
Large cell carcinoma	Peripheral	Highly anaplastic undifferentiated tumor. Strong association with tobacco smoking. May produce hCG → gynecomastia (enlarged breasts). Less responsive to chemotherapy; removed surgically. Poor prognosis.	Pleomorphic giant cells E .
Bronchial carcinoid tumor	Central or peripheral	Excellent prognosis; metastasis rare. Symptoms due to mass effect (wheezing) or carcinoid syndrome (flushing, diarrhea).	Nests of neuroendocrine cells; chromogranin A \oplus .



Pseudoephedrine, phenylephrine

MECHANISM	Activation of α -adrenergic receptors in nasal mucosa → local vasoconstriction.
CLINICAL USE	Reduce hyperemia, edema (used as nasal decongestants); open obstructed eustachian tubes.
ADVERSE EFFECTS	Hypertension. Rebound congestion (rhinitis medicamentosa) if used more than 4–6 days. Associated with tachyphylaxis. Can also cause CNS stimulation/anxiety (pseudoephedrine).

Pulmonary hypertension drugs

DRUG	MECHANISM	CLINICAL NOTES
Endothelin receptor antagonists	Competitively antagonizes endothelin-1 receptors → ↓ pulmonary vascular resistance.	Hepatotoxic (monitor LFTs). Example: bosentan.
PDE-5 inhibitors	Inhibits PDE-5 → ↑ cGMP → prolonged vasodilatory effect of NO.	Also used to treat erectile dysfunction. Contraindicated when taking nitroglycerin or other nitrates (due to risk of severe hypotension). Example: sildenafil.
Prostacyclin analogs	PGI ₂ (prostacyclin) with direct vasodilatory effects on pulmonary and systemic arterial vascular beds. Inhibits platelet aggregation.	Adverse effects: flushing, jaw pain. Examples: epoprostenol, iloprost.

