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MEDICAL NOTES POWERHOUSE

Medical Notes Powerhouse

The Complete High-Yield Notes for NEET SS & INI SS-ET

Pulmonary, Critical Care, Nephrology & Special Topics



06 VOLUME
of 10 · Volume VI · CH 294–331, 469–...

75	7	10
CHAPTERS	SECTIONS	VOLUME SET

SECTIONS IN THIS VOLUME

- Pulmonary Medicine
- Critical Care
- Nephrology
- Toxicology & Environment
- Genetics & Genomics
- Global Health
- Frontier Medicine

Sources Harrison's Principles of Internal Medicine, 22nd Edition

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CH 294 · Pulmonary Hypertension — PAH, CTEPH & WSPH Classifi...

PH = mPAP >20 mmHg (lowered from ≥25, 2018 WSPH). Master: 5 WSPH groups, hemodynamic types (pre vs post vs combined), BMPR2 hereditary PAH, vasoreactivity test (NO/epoprostenol), three treatment pathways (prostacyclin / endothelin / NO), sotatercept

Definition & Hemodynamic Criteria

- **PH** = pathogenic remodeling of pulmonary vasculature → ↑ PAP + PVR.
- Causes: **left heart disease + primary lung disease most common**; PE → CTEPH; rare hematologic/myeloproliferative/systemic.
- **PAH** = uncommon distinct subtype with obliterative arteriopathy.
- **2018 WSPH redefinition**:
  - **mPAP >20 mmHg** (was ≥25) → earlier diagnosis.
  - **PVR >2.0 WU** (was ≥3.0) for precapillary PH and PAH.
- Untreated → high mortality from **RV failure**.
- Diagnostic delay common (~2 y in PAH).

Hemodynamic Classification (RHC)

Hemodynamic categories at right heart cath

Type	mPAP	PAWP	PVR	Clinical groups
Pre-capillary	>20	**≤15**	**>2.0 WU**	PAH, lung dz, CTEPH, multifactorial
Isolated post-capillary	>20	**>15**	**≤2.0 WU**	Left heart dz (HF, valve, HCM, amyloid)
Combined pre + post	>20	**>15**	**>2.0 WU**	Chronic LHD with vascular remodeling

Fig 294-7 — Hemodynamic + clinical classification flowchart: mPAP >20 → categorize as pre / post / combined → assign clinical group.

WSPH 5-Group Clinical Classification (2018)

Table 294-1 — WSPH groups

Group	Description
1 — PAH	**Idiopathic** (vasoreactive vs non), **heritable** (BMPR2), drug/toxin (meth, anorexigens), CTD (esp. scleroderma), HIV, portal HTN, congenital heart disease, schistosomiasis; PVOD/PCH subtype; persistent PH of newborn
2 — Left heart disease	HFrEF, HFpEF, valvular dz (MS/MR/AS/AR), HCM, amyloid; congenital/acquired post-cap PH
3 — Lung disease / hypoxia	COPD/emphysema, restrictive ILD, mixed obstructive/restrictive, hypoventilation, high altitude, developmental
4 — Pulmonary artery obstruction	**CTEPH**, sarcoma, malignant tumor emboli, hemolytic anemia, MPN, sarcoidosis, NF1
5 — Multifactorial / unclear	Hematologic (sickle, MPN), systemic (sarcoidosis, neurofibromatosis), metabolic, chronic renal failure on HD, pulmonary tumor thrombotic microangiopathy, fibrosing mediastinitis

Pathobiology — PAH

- **Triad**: apoptosis resistance + cell proliferation + dysregulated metabolism + oxidant stress.
- Distal pulmonary arterioles → **hypertrophic + fibrotic + plexogenic remodeling**.
- **Plexiform lesions** = classic PAH histology.
- **In situ thrombosis** common.
- ECM expansion (integrins, collagens, fibronectin) → stiffening.
- Few PAH patients have vasoconstriction-dominant phenotype (CCB-responsive).
- RV dysfunction = ↑ afterload PLUS chronic inflammation/autoimmune sarcomere effects.

Genetic drivers

- **BMPR2 (bone morphogenetic protein receptor-2)** = most common gene in hereditary PAH; **autosomal dominant + variable penetrance (~20%)**.
- Sporadic BMPR2 mutations also reported.
- BMPR2 is in TGF-β superfamily.
- Mechanism: **imbalance pro- vs antiproliferative TGF-β receptor signaling**.
- Other genes:
  - **TBX4** (FGF-10 regulation).
  - **SOX17** (HGF regulation).
  - **EIF2AK4 → pulmonary venoocclusive disease (PVOD)**, autosomal recessive, age 10–60.
- Carriers without disease → ~2.3%/y conversion to clinical PAH.

Pathways targeted by therapy

- **3 classical pathways**:

- **Endothelin** — ↑ ET-1 (vasoconstrictor) → ERAs (bosentan, macitentan, ambrisentan).
- **NO / sGC / cGMP** — ↓ NO → PDE5i (sildenafil, tadalafil) + sGC stimulator (riociguat).
- **Prostacyclin (PGI_2)** — ↓ PGI_2 + ↑ TXA_2 → prostanoids (epoprostenol, treprostinil, iloprost), IP-agonist (selexipag).

- **NEW: Activin signal inhibitor** — sotatercept (rebalances activin / BMPR2 signaling).

Fig 294-2 — BMPR2 / activin signaling in PAH: ↓ BMPR-II-Smad1/5/8 (antiproliferative) + ↑ ActRIIA-Smad2/3 (proproliferative) → vascular remodeling. Sotatercept rebalances this pathway.

Pathophysiology

- ↑ PVR + arterial stiffness → progressive ↑ mPAP.
- RV work ↑ → **RV–PA uncoupling** (myocardial energy depleted → ↓ alveolar perfusion).
- **End-stage**: CO declines → mPAP falls (paradoxical) + RV failure.
- **Systemic manifestations** of right HF:
  - Renal failure (low perfusion + congestion).
  - Hepatic congestion + fibrosis.
  - Iron deficiency.
  - Sarcopenia (type I → type II fiber switch).
  - Cognitive impairment, sleep disturbance.
  - Gut: leaky bowel, malabsorption, cachexia.
  - Thyroid dysfunction.
  - Episcleral vessel abnormalities (BMPR2 hereditary PAH).

Clinical Features

- Most common: **dyspnea on exertion** + fatigue.
- Advanced: **edema**, chest pain, presyncope, **syncope**.
- Early exam often normal.
- **Exam findings of advanced PH**:
  - ↑ JVP, hepatomegaly, ascites, pedal edema.
  - **Accentuated P2**.
  - **RV S_3 or S_4**.
  - **Tricuspid regurgitation murmur**.
  - RV heave/lift.
- **Clues to associated disorders**:
  - Clubbing → chronic lung dz.
  - Sclerodactyly + telangiectasia → **CREST scleroderma**.
  - Crackles + systemic HTN → LHF.
  - Cyanosis at rest → congenital shunt (Eisenmenger).
- Differential: HFpEF, asthma, deconditioning, COPD.

Diagnostic Workup

Initial assessment

- **ECG**: RV hypertrophy, strain (R in V1, ST ↓ V2–V3), RAD, P-pulmonale.
- **CXR**: enlarged main + central PAs, retrosternal space obliterated, peripheral pruning.
- **Echo with agitated saline (bubble study) = most important screening test**:
  - **Estimated PASP >35 mmHg** suggests PH.
  - Notched RVOT continuous-wave Doppler.
  - Hypertrophied/dilated RV.
  - **Septal flattening (D-shape LV)** in pressure overload.
  - Detects shunt, valve dz, LV dysfunction.
- **Normal echo** usually obviates further workup; **echo without TR jet but suspicion remains** → still proceed (1/3 still have PH).

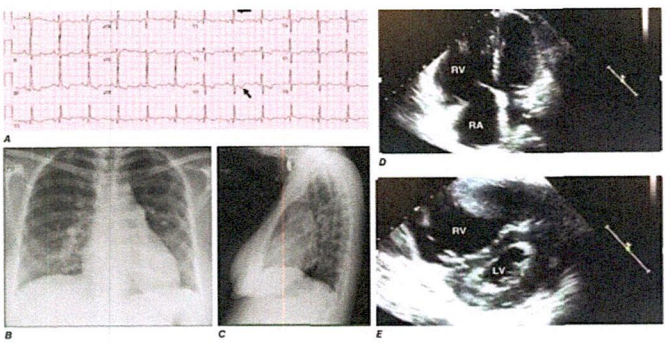


Fig 294-6 — Triad of findings in advanced PAH: (A) ECG with peaked R in V1 + ST ↓ V2–V3 (RVH/strain); (B+C) CXR with enlarged central PAs + obliterated retrosternal space; (D+E) echo apical 4-chamber RV/RA dilation + septal flattening in diastole (pressure overload).

Functional + supportive tests

- **6-MWD**: disease burden + prognosis.
- **CPET**: distinguishes cardiac vs pulmonary; **peak VO_2 <15 mL/kg/min** = poor prognosis.
- **PFTs: isolated ↓ DLCO classic for PAH**.
- **HRCT**: enlarged PA + RV/RA; small vessel pruning; ground-glass + septal thickening → PVOD/PVH.
- **V/Q scan**: primary test to screen for **CTEPH** (mismatched defects).
- **CT-PA** for CTEPH staging; **digital subtraction pulmonary angiography** = definitive for surgical planning.
- **Nocturnal oximetry**: screen all PH (sleep-disordered breathing common).
- **Serology**:
  - HIV.
  - **ANA, RF, anti-Scl-70**.
  - Hepatitis serology + LFTs (portopulmonary HTN).
  - Methamphetamine screen.
  - **BNP / NT-proBNP** — correlates with RV dysfunction, hemodynamics, functional status, treatment response.

Right heart catheterization (RHC) — GOLD STANDARD

- Required for diagnosis + severity assessment + treatment selection.
- **Criteria**:
  - **mPAP >20 mmHg**.
  - PVR >2.0 WU (precapillary) or ≤2.0 (isolated postcapillary).
  - PAWP ≤15 (pre) or >15 (post-capillary).
- Aggressive diuresis pre-RHC can falsely "reveal" precapillary PH in HFpEF — beware.
- **Vasoreactivity test**:
  - Only for **idiopathic or hereditary PAH**.
  - Agent: **inhaled NO or inhaled epoprostenol**.
  - **Positive response: ↓ mPAP ≥10 mmHg to ≤40 mmHg without ↓ CO**.

- **<5% of patients** respond → eligible for **long-term CCB**; **excellent prognosis**.

PAH Subtypes (Group 1)

- **Idiopathic PAH (IPAH)**: : ~3:1; mean age 54–68 y now (was 36 y in 1987 NIH registry); worse hemodynamics + prognosis.
- **Hereditary PAH (BMPR2)**: younger, more severe, worse outcome than IPAH.
- **Other PAH-associated conditions**:
  - **Congenital heart disease**: shunt → **Eisenmenger** (cyanosis + hyperviscosity); surgical repair before PVR >3.0 WU; 4 subgroups.
  - **Connective tissue disease**: **scleroderma (esp. limited/CREST)** most common; very poor prognosis.
  - **Portopulmonary HTN**: 2–10% of portal HTN patients; **distinct from hepatopulmonary syndrome** (intrapulmonary shunting); **mPAP ≥50 → 100% mortality post-LT**; PVR threshold ≥3.0 WU.
  - **HIV-PAH**: no correlation with HIV stage; ePASP >40 → 40% ↑ mortality.
  - **Methamphetamine** use — increasingly recognized.
  - **Schistosomiasis** — common worldwide cause; portal HTN + worm egg pulmonary inflammation.
- **PVOD (pulmonary veno-occlusive disease)**: EIF2AK4 mutation; recessive; presents with PAH-like features but ground-glass on CT.

Treatment — PAH (Group 1)

- **14 FDA-approved therapies**; refer to specialty PH center.
- Goal: **low clinical risk profile** = 1-y mortality <5% (WHO FC I/II, 6-MWD >440 m, CI ≥2.5).
- Risk-factor mods: **low Na diet, diuretics (incl. MRA), O_2, supervised exercise**.
- **1-, 3-, 5-y survival: 82%, 67%, 58%** optimally treated.

Three classical drug classes

Table 294-2 — FDA-approved PAH therapies

Class / Pathway	Drugs	Notes
Prostanoids (PGI_2)	**Epoprostenol** IV continuous (1st available; t½ 6 min; survival benefit); **treprostinil** SC/IV/inhaled/oral (t½ 4 h); **iloprost** inhaled	Vasodilator + antiproliferative + antiplatelet
IP receptor agonist	**Selexipag** oral BID	↓ disease progression + hospitalization 43% (GRIPHON trial); long half-life metabolite
Endothelin receptor antagonists (ERA)	**Bosentan (non-selective ETA/B)**, **macitentan (non-selective, optimized)**, **ambrisentan (selective ETA)**	Hepatotoxicity (bosentan), teratogenic; SERAPHIN trial (macitentan)
PDE5 inhibitors	**Sildenafil**, **tadalafil** oral	Prevent cGMP breakdown → ↑ NO vasodilation
sGC stimulator	**Riociguat**	Stabilizes NO-sGC binding + direct sGC stimulation; **only approved drug for inoperable CTEPH**
Activin signal inhibitor (NEW)	**Sotatercept**	Fc-ActRII fusion protein; ligand trap → rebalances activin/BMPR2; +40 m 6-MWD (STELLAR trial); telangiectasia in 10%

Initial treatment by risk profile

- **Vasoreactive (positive vasoreactivity test) without high-risk features → oral CCB** (high-dose nifedipine, amlodipine, diltiazem).
- **Non-vasoreactive WITHOUT high-risk features → initial dual oral therapy**: ambrisentan + tadalafil (AMBITION trial) or macitentan + tadalafil.
- **Non-vasoreactive WITH high-risk features → upfront triple therapy**: IV/SC prostacyclin (treprostinil/epoprostenol) + ambrisentan + tadalafil.
- **High-risk features**:
  - WHO FC IV.
  - Chest pain or syncope.
  - **pVO_2 <11 mL/kg/min**.
  - **NT-proBNP >1100 ng/mL**.
  - Moderate pericardial effusion.
  - **CI <2.0 L/min/m²**.
  - **PVR ≥12 WU**.

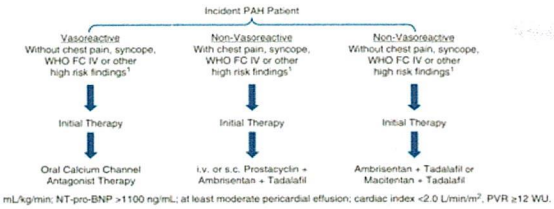


Fig 294-11 — Initial PAH treatment: vasoreactive → CCB; non-vasoreactive moderate-risk → dual oral; high-risk → IV/SC prostacyclin + ERA + PDE5i.

Other group treatments

- **Group 2 (LHD-PH)**: treat underlying — optimize HF (SGLT2i, MRA, diuretic), valve surgery if MS/MR; **no PAH-specific drugs** (may harm).
- **Group 3 (lung disease)**: O_2; treat underlying lung dz; **inhaled treprostinil** approved for ILD-PH (INCREASE trial); avoid PDE5i routinely in COPD-PH.
- **Group 4 (CTEPH)**: lifelong anticoagulation (warfarin preferred); operable → **pulmonary endarterectomy = potentially CURATIVE**; inoperable → **riociguat ± balloon pulmonary angioplasty**.
- **Group 5**: treat underlying; supportive care.

Fig 294-9 — CTEPH imaging + surgical specimen: (A) contrast CT showing obstructive vascular pattern in segmental PAs; (B) angiogram showing stricture + webbing + dearborization; (C) fibrotic chronic clot resected at pulmonary endarterectomy (curative in most CTEPH).

Fig 294-12 — CTEPH algorithm: multidisciplinary team → endarterectomy if operable; non-operable → riociguat ± BPA; lifelong anticoag.

♥ NEET SS HIGHLIGHTS

♥ **2018 WSPH**: mPAP >20 (was ≥25); PVR >2.0 WU (was ≥3.0).
♥ **BMPR2** = most common gene in hereditary PAH; AD, penetrance ~20%.
♥ **EIF2AK4** = pulmonary veno-occlusive disease (autosomal recessive).
♥ **Vasoreactivity test**: inhaled NO or epoprostenol; positive = ↓ mPAP ≥10 mmHg to ≤40 without ↓ CO; <5% positive; CCB-responsive.
♥ **Selective ETA** antagonist = ambrisentan; **non-selective** = bosentan, macitentan.
♥ **Bosentan = hepatotoxic**; all ERAs teratogenic.
♥ **Epoprostenol** = first prostanoid; survival benefit; IV continuous; t½ 6 min.
♥ **Selexipag** = oral selective IP-receptor agonist (non-prostanoid).
♥ **Riociguat** = sGC stimulator; ONLY approved drug for inoperable CTEPH (do NOT combine with PDE5i).
♥ **Sotatercept** (STELLAR) = new activin signal inhibitor; rebalances TGF-β/BMPR2.
♥ **AMBITION trial**: upfront combination ambrisentan + tadalafil > monotherapy.
♥ **SERAPHIN**: macitentan ↓ events 45%.
♥ **GRIPHON**: selexipag ↓ events 43%.
♥ **CTEPH**: V/Q scan to screen (mismatched defects); pulmonary endarterectomy = potentially curative.
♥ **Eisenmenger**: progressive PVR ↑ from large L→R shunt → reverses to R→L → cyanosis.
♥ **Limited scleroderma (CREST)** → PAH commonly; **diffuse scleroderma** → ILD + PH commonly.
♥ **Portopulmonary HTN**: 2–10% of portal HTN; mPAP ≥50 → 100% mortality post-LT.
♥ **Hepatopulmonary syndrome**: intrapulmonary shunt, NOT same as portopulmonary.
♥ Echo: **PASP >35 mmHg** = suggests PH; **septal flattening (D-shape)** = pressure overload.
♥ **Isolated ↓ DLCO** in PFT classic for PAH.
♥ **6-MWD >440 m** = good prognosis; **pVO_2 <15** = poor.
♥ **Schistosomiasis** = most common PAH cause worldwide (5% develop PAH).

❦ CLINICAL PEARLS

❦ **Hereditary PAH**: screen family with echo annually + risk counsel; offer BMPR2 testing.
❦ **Aggressive pre-RHC diuresis** in HFpEF patients can hide elevated PAWP → falsely look pre-capillary.
❦ **D-shaped LV** on echo + RV dilation = think PH.
❦ Acute pulmonary vasoreactivity is RARE — only 5% of IPAH; CCBs CONTRAINDICATED in non-responders (worsens hemodynamics).
❦ **Riociguat + PDE5i = severe hypotension** (combined cGMP elevation).
❦ **Riociguat + nitrates** = contraindicated.
❦ Sildenafil in HFpEF — RELAX trial NEGATIVE; don't use.
❦ **Avoid PAH drugs in Group 2 (LHF)** — pulmonary edema risk from increased preload.
❦ **Sotatercept**: telangiectasia, epistaxis common SE.
❦ **Iron deficiency** very common in PAH — repletion improves outcomes.
❦ Pregnancy in PAH = HIGH mortality (30–50%); contraception essential.

✦ MNEMONIC

PH GROUPS *WSPH 5 categories*

1 — PAH (idiopathic, hereditary, CTD, HIV, portal, congenital, schisto, drug)
2 — LHD (HFpEF, HFrEF, valve, HCM, amyloid)
3 — Lung disease (COPD, ILD, hypoxia, OSA)
4 — Pulmonary artery obstruction (CTEPH)
5 — Unclear / multifactorial (MPN, sarcoid, CKD, fibrosing mediastinitis)

Group 1 + 4 commonly use PAH-specific drugs; groups 2/3 mostly don't.

PAH DRUGS *Pathways targeted*

P — Prostacyclin pathway — epoprostenol, treprostinil, iloprost, selexipag
E — Endothelin antagonists — bosentan, macitentan, ambrisentan
N — NO / cGMP — sildenafil, tadalafil (PDE5i); riociguat (sGC stimulator)
S — Sotatercept — new activin trap (BMPR2 rebalance)

Triple combo for severe disease: prostacyclin IV + ERA + PDE5i.

✎ MCQ CORNER

Q1. A 36 y/o woman has progressive exertional dyspnea. Echo: estimated PASP 65 mmHg, septal flattening, RV dilation. RHC: mPAP 42 mmHg, PAWP 9 mmHg, PVR 8 WU. Inhaled NO causes mPAP to drop to 35 mmHg with no change in CO. Next step?

A. Start macitentan + tadalafil
✓ **B. Start oral CCB at high dose**
C. Start IV epoprostenol
D. Refer for lung transplant

► *Positive vasoreactivity test (↓ mPAP ≥10 mmHg to ≤40 without ↓ CO) — patient is vasoreactive. Less than 5% of IPAH patients respond. CCBs (nifedipine, amlodipine, diltiazem) are standard, with excellent prognosis. CCBs are CONTRAINDICATED in non-responders.*

Q2. Which gene is most commonly associated with HEREDITARY pulmonary arterial hypertension?

✓ **A. BMPR2**
B. EIF2AK4
C. SOX17
D. TBX4

► *BMPR2 (bone morphogenetic protein receptor 2) = most common cause of hereditary PAH, autosomal dominant with variable penetrance ~20%. EIF2AK4 causes PVOD (recessive). SOX17 and TBX4 also implicated.*

Q3. A 50 y/o with chronic dyspnea has CT showing webbing and abrupt narrowing of segmental pulmonary arteries. V/Q scan: multiple mismatched defects. Prior PE 3 years ago. mPAP 38 mmHg, PAWP 8, PVR 7 WU. Best treatment?

A. Lifelong anticoagulation + observation
✓ **B. Lifelong anticoagulation + assess for pulmonary endarterectomy**
C. Sildenafil + ambrisentan
D. Selexipag monotherapy

► *CTEPH (Group 4). All patients need lifelong anticoagulation (warfarin preferred). Refer to expert center for pulmonary endarterectomy — potentially CURATIVE. If inoperable, use riociguat (sGC stimulator) ± balloon pulmonary angioplasty.*

Q4. A patient with PAH on tadalafil + ambrisentan is started on riociguat for refractory symptoms. Within hours, BP drops to 70/40. Most likely mechanism?

A. Anaphylaxis
✓ **B. Combined cGMP elevation (PDE5i + sGC stimulator)**
C. Cardiogenic shock from RV failure
D. Sepsis

► *PDE5 inhibitors (tadalafil) and sGC stimulators (riociguat) both elevate cGMP — combined use causes severe hypotension. This combination is contraindicated. Same risk with nitrates + riociguat.*

Q5. Per the 2018 WSPH definition, what is the mPAP threshold for diagnosing pulmonary hypertension?

A. ≥25 mmHg
✓ **B. >20 mmHg**
C. ≥15 mmHg
D. >30 mmHg

► *2018 6th WSPH lowered mPAP threshold from ≥25 to >20 mmHg to facilitate earlier diagnosis. Also: PVR threshold for precapillary PH lowered to >2.0 WU.*

Q6. Which drug is approved for inoperable CTEPH?

A. Macitentan
✓ **B. Riociguat**
C. Bosentan
D. Selexipag

► *Riociguat is the only approved drug for inoperable CTEPH. Balloon pulmonary angioplasty is increasingly used as adjunct. Pulmonary endarterectomy remains curative in operable CTEPH.*

LAST MINUTE REVISION

► **2018 WSPH**: mPAP >20; PVR >2.0 WU for precapillary.
► **5 WSPH groups**: PAH / LHD / lung dz / CTEPH / multifactorial.
► Most common PH causes: **LHD + lung disease**.
► **PAH = group 1**: idiopathic, hereditary, drug/toxin, CTD, HIV, portal, CHD, schisto.
► **BMPR2** = #1 hereditary PAH gene; AD; penetrance ~20%.
► **EIF2AK4** = PVOD (AR).
► **TBX4, SOX17** = other PAH risk genes.
► **Schistosomiasis** = #1 cause of PAH worldwide.
► **Hemodynamic classification**: precap (PAWP ≤15), isolated postcap (PAWP >15, PVR ≤2), combined.
► **Echo**: PASP >35; D-shape LV; TR jet; agitated saline for shunt.
► **RHC = gold standard**; required for diagnosis.
► **Vasoreactivity test**: inhaled NO/epoprostenol; positive = ↓ mPAP ≥10 to ≤40 without ↓CO; <5% positive; CCB candidates.
► Isolated ↓ DLCO classic for PAH.
► **6-MWD >440 m** = good prognosis; pVO_2 <15 mL/kg/min = poor.
► BNP/NT-proBNP for severity + response.
► **3 classical pathways**: PGI_2 + ET + NO/cGMP.
► **Prostanoids**: epoprostenol (IV), treprostinil (SC/IV/inhaled/oral), iloprost (inhaled).
► **Selexipag** = oral IP-receptor agonist.
► **ERAs**: bosentan, macitentan (non-sel), ambrisentan (selective ETA).
► Bosentan = **hepatotoxic**; all ERAs teratogenic.
► **PDE5i**: sildenafil, tadalafil; **sGC stimulator**: riociguat.
► **Riociguat + PDE5i / nitrates = CI** (severe hypotension).
► **Sotatercept** (STELLAR) = new activin signal inhibitor; +40 m 6-MWD.
► **AMBITION**: upfront dual (ambrisentan + tadalafil) > monotherapy.
► Triple upfront for high-risk (FC IV, pVO_2 <11, CI <2.0, NT-proBNP >1100, PVR ≥12 WU).
► Goal: 1-y mortality <5% (low-risk profile).
► 1-, 3-, 5-y survival: 82, 67, 58%.
► **Group 2 (LHF-PH)**: optimize HF; **no PAH drugs** (may worsen).
► **Group 3 (lung-PH)**: O_2, treat lung dz; inhaled treprostinil for ILD-PH (INCREASE).
► **CTEPH**: V/Q for screen; mismatched defects; **lifelong warfarin**; **endarterectomy = curative** if operable; **riociguat ± BPA** if not.
► **Eisenmenger**: PVR >3 WU → R→L shunt reverses, cyanosis.
► **Limited scleroderma** → PAH; **diffuse** → ILD + PH.
► **Portopulmonary HTN** ≠ hepatopulmonary syndrome.
► Pregnancy + PAH = 30–50% mortality → contraception.
► Iron deficiency common; repletion improves outcome.

UPDATES

◉ **2018 6th WSPH** — Lowered mPAP cutoff to >20 and PVR to >2.0 WU; 5-group classification refined.
◉ **STELLAR (Hoeper 2023)** — Sotatercept (activin inhibitor) improved 6-MWD by 40 m on background triple therapy.
◉ **INCREASE trial** — Inhaled treprostinil ↑ 6-MWD in ILD-PH (group 3).
◉ **2022 ESC/ERS PH Guideline** — Adopts WSPH definitions, emphasizes early referral + combination therapy.
◉ **Balloon pulmonary angioplasty** evolving for inoperable CTEPH; multiple sessions usually needed.
◉ **RELAX trial** negative — Sildenafil does NOT help HFpEF-PH.
◉ **Activin trap + BMPR2 axis** emerging as a new therapeutic frontier in PAH.

CH 295 · Approach to Respiratory Disease — History, Examinat...

Bedside framework for respiratory complaints — symptoms, focused exam signs, categories of disease, stepwise diagnostic algorithm. NEET SS / INI SS-ET high yield.

Disease Categories — The 3-Bucket Framework

- Most respiratory disease → **cough and/or dyspnea**.
- **3 major categories:** (1) Obstructive, (2) Restrictive, (3) Vascular.
- Obstructive = MCC (most common).
- Infection + malignancy can mimic all 3 patterns.
- Alternative grouping = gas-exchange (**hypoxemia, hypercarbia, mixed**) — but many disorders have normal gases.

Table 295.1 — Categories of respiratory disease (high-yield)

Category	Mechanism	Classic examples
Obstructive	Airway disease	**Asthma, COPD**, bronchiectasis, bronchiolitis
Restrictive — parenchymal	Lung tissue	**IPF, asbestosis**, DIP, sarcoidosis
Restrictive — neuromuscular	Pump failure	**ALS, GBS, MG**
Restrictive — chest wall/pleural	External	**Kyphoscoliosis**, AS, chronic effusion
Vascular	Pulm vessels	**PE, PAH**, venoocclusive dz, vasculitis
Malignancy	Tumor	Bronchogenic CA (NSCLC, SCLC), mets
Infectious	Microbe	Pneumonia, bronchitis, tracheitis

History — Symptom Decoding

Dyspnea descriptors

- **"Chest tightness" / "can't get a deep breath"** → obstructive lung disease.
- **"Air hunger" / "suffocation"** → CHF.
- Acute onset → laryngeal edema, bronchospasm, mucus plug, PE, pulm edema, pneumonia, **pneumothorax**.
- Slowly progressive + exacerbations → **COPD, IPF**.
- Episodic with triggers (URI, allergen) → **asthma**.
- Dyspnea on exertion = early lung/heart disease — quantify by degree of activity tolerated.

Cough

- Acute + purulent sputum → infection (sinusitis, tracheitis, bronchitis, bronchiectasis, pneumonia).
- Note sputum quantity, quality, **blood**.
- **Chronic cough = >8 weeks** → asthma, COPD, bronchiectasis, GERD, postnasal drip, IPF.
- **Hemoptysis = urgent eval** (Chap 41).
- Non-respiratory cough: cardiac, GI, psychogenic — broad DDx.

Other symptoms

- **Wheezing** = airway disease (asthma classic).
- **Hemoptysis** = infection, bronchogenic CA, PE.
- Chest pain in respiratory dz → **parietal pleura** (pneumothorax) or pulmonary vascular (PAH). Lung parenchyma has no pain fibers.
- Cor pulmonale → abdominal bloating, pedal edema.

Social / exposure history — must-ask

- Cigarettes (pack-years) → **COPD, lung CA, DIP, Langerhans cell histiocytosis**.
- **E-cig / vaping → EVALI** (acute or subacute lung injury).
- Secondhand smoke from household.
- Occupational/home inhalation: **asbestos, silica, wood smoke, bird excrement**.
- Travel → TB.
- Geographic fungal exposure: **Histoplasma**.
- Fever/chills → infection.
- Joint pain, rash, dry eyes/mouth → autoimmune/rheumatologic ILD.
- Prior irradiation, drugs (amiodarone, MTX, bleomycin) → drug/radiation lung injury.

Physical Examination

Vitals & general

- RR — tachypnea or hypopnea.
- **SpO_2 at rest + on exertion** (some hypoxia only with exertion).
- **Inability to complete sentence** = severe impairment → expedite eval.
- Accessory muscle use, severe kyphoscoliosis (restrictive).

Percussion

- Diaphragm excursion + lung size.
- **Dull** → pleural effusion. **Hyperresonant** → pneumothorax.

Palpation

- Limited role.
- **Subcutaneous emphysema** in barotrauma.
- ↑ **tactile fremitus** = consolidation. ↓ **fremitus** = pleural effusion.
- Symmetry of chest expansion → detect unilateral disease.

Auscultation — sound → diagnosis

Table 295.2 — Lung sounds & their meaning

Sound	Mechanism	Classic association
Wheeze	Airway narrowing	Asthma; also CHF (cardiac wheeze), bronchogenic CA (monophonic)
Polyphonic wheeze	Multiple airway sizes	Asthma
Monophonic wheeze	Single airway	**Bronchogenic CA**
Rhonchi	Mid-size airway secretions	Bronchitis (acute) / bronchiectasis, COPD (chronic)
Stridor	Upper airway obstruction	Inspiratory, focal, heard over neck
Crackles (rales)	Alveolar fluid OR fibrosis	Pulmonary edema (basal), pneumonia, **IPF (Velcro)**
↓ breath sounds	Air trapping or absent transmission	**Emphysema** (diffuse quiet), PTX / effusion (focal)

Egophony / pectoriloquy

- **Egophony** = "EEE → AH" over consolidated parenchyma.
- Present in **pneumonia**; **absent in IPF** — helps distinguish alveolar fluid from interstitial fibrosis.
- Whispered pectoriloquy + bronchial breath sounds also indicate alveolar filling.

Other-system signs

- **Symmetric pedal edema** → cor pulmonale.
- **Asymmetric pedal edema** → DVT/PE.
- JVD → right heart failure / volume overload.
- **Pulsus paradoxus** in obstructive lung dz → impending respiratory failure (severe asthma exacerbation).
- **Clubbing** → CF, IPF, lung CA, bronchiectasis.
- **Cyanosis** when **>5 g/dL deoxy-Hb**.
- Joint/skin exam — rheumatologic lung disease.

NEET SS HIGHLIGHTS

- **Obstruction** = ↓ FEV_1/FVC <70%. **Restriction** = TLC <80% predicted.
- **Restriction + ↓ DLCO** = parenchymal disease (IPF).
- **Restriction + normal DLCO** = neuromuscular or chest wall.
- Plateau of inspiratory loop = **extrathoracic** large-airway obstruction; expiratory plateau = **intrathoracic**.
- Velcro crackles = **IPF**. Cardiac wheeze = CHF.
- Pulsus paradoxus + asthma → severe attack.
- Cyanosis appears at >5 g/dL deoxy-Hb (not $\%SpO_2$).

Diagnostic Evaluation

Strategy

- **Acute** → parallel testing for life threats (PE, multilobar pneumonia).
- **Chronic** → stepwise.

Pulmonary function testing (PFT)

- **Spirometry** = first test. Effort-dependent.
- **FEV_1/FVC <70%** → airflow obstruction (asthma, COPD, bronchiectasis).
- **Flow-volume loop** less effort-dependent — shape localizes large-airway obstruction:
  - Loop plateau locations:
    - **Inspiratory plateau** → variable **extrathoracic** obstruction (e.g., vocal cord paralysis).
    - **Expiratory plateau** → variable **intrathoracic** obstruction (e.g., tracheomalacia).
    - **Both plateaus (fixed)** → fixed lesion (tracheal stenosis, goiter).
- Symmetric ↓ FEV_1 + FVC → measure **lung volumes** (plethysmography or He-dilution) + **DLCO**.
- TLC <80% predicted = restriction.
- Restriction + ↓ DLCO = parenchymal (IPF, sarcoid).
- Restriction + normal DLCO + ↓ MIP/MEP = neuromuscular weakness.
- Normal spirometry + ↓ DLCO → consider **pulmonary vascular disease** (PAH, PE).

Imaging

- **CXR** = first imaging — screens parenchymal, pleural, cardiac silhouette, mediastinum.
- **HRCT** = study of choice for ILD, bronchiectasis, emphysema characterization.
- **CT-PA** = first-line for PE in stable patient.
- **V/Q scan** = preferred if renal failure, contrast allergy, pregnancy.

Blood, sputum & serology

- ABG → gas exchange, A-a gradient.
- CBC: eosinophilia → ABPA, eosinophilic pneumonia, EGPA.
- Sputum: Gram stain, culture, AFB (TB), cytology.
- Serology: ANCA (GPA), anti-GBM (Goodpasture), ANA (CTD-ILD), ACE (sarcoid limited utility).

Bronchoscopy & invasive

- **Flexible bronchoscopy** — BAL, TBLB, endobronchial biopsy, EBUS-TBNA for mediastinal nodes.
- **Surgical lung biopsy / VATS** when ILD histology unclear.
- Thoracentesis for pleural effusion (Light's criteria).

CLINICAL PEARLS

- Lung parenchyma has **no pain fibers** — chest pain comes from parietal pleura or pulm vasculature.
- **EVALI** = E-cigarette / vaping use-associated lung injury — important new exposure.
- Monophonic wheeze in older smoker → think **endobronchial tumor** until proven otherwise.
- Symmetric vs asymmetric pedal edema = cor pulmonale vs DVT/PE — decisive bedside distinction.
- **Beck Triad** (JVD, ↓ BP, muffled heart sounds) for tamponade; pulsus paradoxus shared with severe asthma.

✦ MNEMONIC

STOPED *Smoking-related lung disease*

S — Smoker's airway disease (COPD)
T — Tumor — bronchogenic carcinoma
O — Oral cancer / aerodigestive tract
P — Pulmonary Langerhans cell histiocytosis
E — Emphysema; EVALI (e-cig variant)
D — Desquamative interstitial pneumonitis (DIP)

All STRONGLY associated with cigarette / e-cig exposure.

✎ MCQ CORNER

Q1. 55 y/o smoker, 6 months DOE, chronic cough, exam = quiet chest, ↓ breath sounds throughout. PFT most likely shows?

✓ **A. ↓ FEV_1/FVC, ↑ TLC, ↓ DLCO**
B. Normal FEV_1/FVC, ↓ TLC, ↓ DLCO
C. ↓ FEV_1/FVC, normal TLC, normal DLCO
D. Normal PFT

► *Emphysema → obstructive pattern (↓ FEV_1/FVC) + hyperinflation (↑ TLC) + alveolar destruction (↓ DLCO).*

Q2. Patient with bilateral basal Velcro crackles, dry cough, clubbing. Best imaging?

A. CXR alone
✓ **B. HRCT chest**
C. CT-PA
D. V/Q scan

► *Classic IPF presentation → HRCT shows subpleural reticulation + honeycombing (UIP pattern).*

Q3. Inspiratory plateau on flow-volume loop with normal expiratory limb suggests:

A. Fixed tracheal stenosis
B. Variable intrathoracic obstruction
✓ **C. Variable extrathoracic obstruction**
D. Asthma

► *Inspiratory plateau alone = variable extrathoracic obstruction (e.g., vocal cord dysfunction, paralysis).*

Q4. Egophony (E → A) on auscultation indicates:

A. Pneumothorax
✓ **B. Lobar consolidation / pneumonia**
C. Pleural effusion
D. Emphysema

► *Egophony = abnormal sound transmission through consolidated alveoli. Absent in IPF — distinguishes alveolar filling from fibrosis.*

Q5. Cyanosis becomes clinically detectable when deoxygenated Hb exceeds:

A. 2 g/dL
✓ **B. 5 g/dL**
C. 8 g/dL
D. 10 g/dL

► *>5 g/dL deoxy-Hb. Anemic patients may not show cyanosis despite severe hypoxemia; polycythemics show it earlier.*

◷ LAST MINUTE REVISION

► 3 categories: obstructive, restrictive (parenchymal / NM / chest-wall), vascular.
► MCC respiratory dz pattern = obstructive.
► FEV_1/FVC <70% = obstruction; TLC <80% pred = restriction.
► Restriction + ↓ DLCO = parenchymal; + normal DLCO = NM/chest wall.
► Normal spirometry + isolated ↓ DLCO → think **vascular** (PAH).
► Loop: insp plateau = extrathoracic; exp plateau = intrathoracic; both = fixed.
► Chronic cough = >8 wks; top causes: asthma, GERD, postnasal drip, ACEI.
► Hemoptysis → urgent eval; bronchogenic CA, TB, bronchiectasis, PE.
► EVALI = e-cig lung injury (new entity).
► DIP + pulm Langerhans = smoking-related ILD.
► Velcro crackles = IPF; egophony = pneumonia (consolidation).
► Quiet chest + ↓ breath sounds = emphysema; absent BS = PTX or effusion.
► Monophonic wheeze = endobronchial tumor.
► Pulsus paradoxus + asthma = severe attack.
► Clubbing: CF, IPF, lung CA, bronchiectasis (NOT COPD alone).
► Cyanosis at >5 g/dL deoxy-Hb.
► Symmetric pedal edema = cor pulmonale; asymmetric = DVT.
► Lung parenchyma = no pain fibers.

CH 296 · Disturbances of Respiratory Function — Mechanics, G...

Respiratory physiology essentials — lung mechanics, ventilation, gas exchange, V/Q, and 5 classic PFT patterns. Massive NEET SS / INI SS-ET yield.

Respiratory System — Three Components

- **3 mechanical components:** (1) Lung + airways, (2) Neuromuscular system (NMS), (3) Chest wall (incl. abdomen, heart, respiratory muscle mass).
- Alveolar surface area ≈ **70 m²**; thoracic volume ≈ **7 L**.
- Function = oxygenate blood + eliminate CO_2.
- Inadequate V/Q matching = MCC of impaired gas exchange.

Volume Mechanics — Statics

Elastic recoil

- **Lung** → tendency to **collapse** (surface tension + tissue elastin).
- **Chest wall** → tendency to **expand outward**.
- **FRC = passive equilibrium** where outward chest recoil = inward lung recoil.
- Transpulmonary pressure = Palv − Ppleural; keeps alveoli inflated.
- At **high lung volumes** → lung stiff (low compliance).
- At **low lung volumes** → chest wall stiff; small airways close → gas trapping.
- Aging + obstructive disease ↑ closing volume → gas trapping at higher volumes.

Lung volumes — definitions

Table 296.1 — Lung volumes & capacities

Term	Definition
TLC	Total lung capacity — maximal inflation
FRC	Functional residual capacity — passive equilibrium
RV	Residual volume — minimal inflation (after max exhalation)
VC	Vital capacity = TLC − RV
FVC	Forced VC — VC done forcefully
FEV_1	Forced expiratory volume in 1 sec
TV	Tidal volume — quiet breathing
ERV	Expiratory reserve volume = FRC − RV
IRV	Inspiratory reserve = TLC − (FRC + TV)

- **RV cannot be measured by spirometry alone** — needs body plethysmography or He-dilution.
- He-dilution **underestimates** RV/TLC in obstruction (poorly-ventilated regions don't equilibrate).
- Plethysmography measures **total intrathoracic gas** — accurate even with bullae.

Flow Mechanics — Dynamics

Airway resistance

- Normal **Raw < 2 $cmH_2O/L/s$**.
- Airway tree branches → total cross-section ↑ **peripherally** → flow velocity ↓ **peripherally**.
- Resistance highest in **medium-sized bronchi**, not the smallest.

Dynamic airflow limitation (Bernoulli)

- Forced exhalation → high velocity in central airways → ↓ intraluminal pressure → airway collapse → **flow limit**.
- More force ≠ more flow — flow plateaus.
- Determinants of max expiratory flow: gas density, airway diameter/distensibility, **lung elastic recoil**, frictional loss.
- **Fibrosis** → ↑ recoil → max flows **elevated** for any given volume.
- **Emphysema** → ↓ recoil → max flows **decreased**.
- **Asthma / bronchitis** → narrowed lumen → ↓ flow at any pressure.

Dynamic hyperinflation

- Severe obstruction → expiration incomplete → operating FRC **creeps up** toward TLC.
- Stiffer at high volume → ↑ elastic work of breathing.
- Patient feels **"cannot inhale"** despite root cause being **expiratory obstruction**.
- Equivalent to **auto-PEEP** in ventilated patients.

Ventilation

Dead space & alveolar ventilation

- **Anatomic dead space (V_D)** ≈ 150 mL (conducting airways).
- **Physiologic dead space** = anatomic + alveolar (ventilated but not perfused).
- **Alveolar ventilation $V_A = (V_T - V_D) \times RR$.**
- Tidal volume < V_D → NO fresh gas reaches alveoli.
- PE distal lung = added physiologic dead space.

CO_2 & ventilatory adequacy

- **$PaCO_2 \approx VCO_2 / V_A$** — inversely proportional to alveolar ventilation.
- Target **$PaCO_2$ ≈ 40 mmHg**.
- ↓ **$PaCO_2$** → alveolar hyperventilation.
- ↑ **$PaCO_2$** → alveolar hypoventilation.
- **$EtCO_2$ capnography** = non-invasive estimate.

Alveolar gas equation

- **$PAO_2 = FiO_2 \times (P_{bar} - P_{H_2O}) - PaCO_2 / R$**
- R = respiratory quotient ≈ 0.85 (typical diet).
- P_{H_2O} = 47 mmHg at 37°C.
- Sea-level air: $PAO_2 \approx 0.21 \times (760 - 47) - 40/0.8 \approx$ **100 mmHg**.
- **(A − a) gradient = $PAO_2 - PaO_2$**; normal <15 (young) or < age/4 + 4.

Gas Exchange

Diffusion

- Hb fully saturates by **⅓ length of alveolar capillary**.
- O_2 uptake = **perfusion-limited**, not diffusion-limited (normally).
- Diffusion limitation only in: **thickened ILD walls + exercise + high altitude + elite athletes**.
- CO_2 also equilibrates rapidly.

5 causes of hypoxemia

Table 296.2 — Hypoxemia causes & response to O_2

Cause	A-a gradient	Responds to O_2?
↓ FiO_2 (high altitude)	Normal	Yes
Hypoventilation	Normal	Yes
V/Q mismatch (MCC)	↑	Yes
Shunt (R→L, ARDS, ASD)	↑ ↑	**NO (refractory)**
Diffusion limit (ILD)	↑	Yes

V/Q heterogeneity vs shunt

- **V/Q heterogeneity** = most common — partial reoxygenation of mixed blood; **responds to O_2.**
- **Shunt** = perfusion of unventilated alveoli — venous blood passes unchanged.
- Shunt hypoxemia **refractory to O_2** because Hb in ventilated regions is already saturated and dissolved O_2 contributes minimally.
- Nonlinear O_2-Hb curve magnifies shunt effect on mixed PaO_2.

NEET SS HIGHLIGHTS

- **5 hypoxemia causes:** ↓ FiO_2, hypoventilation, V/Q, shunt, diffusion.
- Only first 2 → **normal** A-a gradient.
- **Shunt = O_2-refractory** (other 4 respond).
- **FEV_1/FVC < 70% = obstruction; TLC < 80% pred = restriction.**
- He-dilution underestimates lung volumes in obstruction; **plethysmography** = accurate.
- Dynamic hyperinflation = **auto-PEEP** ≡ feels like inability to inhale.
- DLCO: ↓ in **emphysema, ILD, PAH, anemia**; ↑ in **asthma, polycythemia, alveolar hemorrhage, L→R shunt.**

Five Classic PFT Patterns

Table 296.3 — Disease vs PFT signature (% predicted)

Pattern	TLC	FRC	RV	FVC	FEV_1/FVC	Raw	DLCO
Normal	100	100	100	100	>0.7	<2	100
Restriction — ↑ recoil (IPF)	60	60	60	60	0.75	1.0	60 ↓
Restriction — chest wall (obesity)	95	65	100	92	0.92	1.0	95
Restriction — NM (MG)	75	100	120	60	0.60	1.0	80
Obstruction — asthma	100	104	120	90	0.35→0.75 post-BD	2.5	120 ↑
Obstruction — emphysema	130	220	310	60	0.35 (no BD response)	1.5	40 ↓

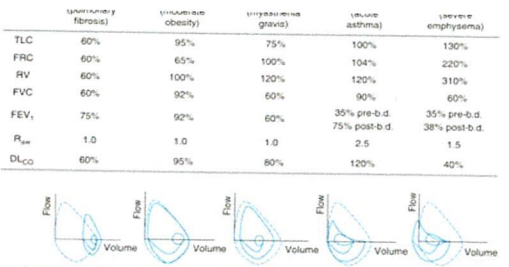


FIGURE 296-6 Common abnormalities of pulmonary function (see text). Pulmonary function values are expressed as a percentage of normal predicted values, except for R_{aw}, which is expressed as cmH$_2$O/L/s (normal, <2 cmH$_2$O/L/s). The figures at the bottom of each column show the typical configuration of flow-volume loops in each condition, including the flow-volume relationship during tidal breathing. b.d., bronchodilator; D_{LCO}, diffusion capacity of lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; R_{aw}, airways resistance; RV, residual volume; TLC, total lung capacity.

normal, as both lung recoil and passive chest wall recoil are normal. However, TLC is low and RV is elevated because respiratory muscle strength is insufficient to push the passive respiratory system fully toward either volume extreme. Caught between the low TLC and the elevated RV, FVC and forced expiratory volume in 1 s (FEV_1) are reduced as "innocent bystanders." As airway size and lung vasculature are unaffected, both R_{aw} and Dt_{CO} are normal. Oxygenation is normal unless weakness becomes so severe that the patient has insufficient strength to reopen collapsed alveoli during sighs, with resulting atelectasis.

Airflow Obstruction due to Decreased Airway Diameter—Example: Acute Asthma During an episode of acute asthma, luminal narrowing due to smooth muscle constriction as well as reached before the patient must inhale again. Both FVC and FEV_1 are markedly decreased, the former because of the severe elevation of RV and the latter because loss of lung elastic recoil reduces the pressure driving maximal expiratory flow and also reduces tethering open of small intrapulmonary airways. The flow-volume loop demonstrates marked scooping, with an initial transient spike of flow attributable largely to expulsion of air from collapsing central airways at the onset of forced exhalation. Otherwise, the central airways remain relatively unaffected, so R_{aw} is normal in "pure" emphysema. Loss of alveolar surface and capillaries in the alveolar walls reduces Dt_{CO}; however, because poorly ventilated emphysematous acini are also poorly perfused (due to loss of their capillaries), arterial hypoxemia usually is not seen at rest until emphysema becomes very severe. However, during

Fig 296.6 — The 5 classic PFT patterns with corresponding flow-volume loops. IPF/NM/obesity = restriction; asthma/emphysema = obstruction with characteristic scooping.

Restrictive ILD (IPF) — ↑ recoil

- All volumes ↓ (TLC, FRC, RV, FVC).
- Max flows **increased relative to volume** (stiff lung pulls open airways).
- ↓ **DLCO** (capillary destruction).
- Flow-volume loop = miniaturized normal, shifted left.

Chest wall — moderate obesity

- ↓ **FRC** only initially; TLC + RV preserved.
- Mild hypoxemia from basal V/Q (closure of dependent airways).
- DLCO normal unless OSA + PAH coexist.

Neuromuscular weakness (MG)

- Lung mechanics normal → **FRC normal.**
- Weak muscles → can't reach TLC (↓) or push to RV (↑).
- FVC + FEV_1 ↓ as 'innocent bystanders'.
- Raw + DLCO normal.
- ↓ **MIP / MEP** diagnostic.