

PH • Pulmonary Hypertension

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THE STORY IN ONE SENTENCE

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“PH diagnosis needs right heart catheter to measure lung artery pressure directly; type 1 (PAH) gets special medicines and rarely calcium-channel blockers, but only if a vasoreactivity test proves they work; every other type treats the root cause first.”

Normal anatomy — the body's job

Normally, the right side of your heart pumps blood gently through wide, soft arteries in your lungs, where the blood picks up oxygen and drops off carbon dioxide, then returns to the left heart to be pumped out to your body.

BODY'S JOB

The right ventricle (the right heart's main pumping chamber) only has to squeeze against low pressure — about 15–25 mmHg in the pulmonary artery — because the lung vessels are thin-walled, stretchy, and wide open, making it easy for blood to flow through and grab oxygen from the air sacs.

1. Blood returns from your body, low in oxygen and high in carbon dioxide, into the right atrium (the right heart's receiving room).
2. The right atrium squeezes and pushes blood through the tricuspid valve into the right ventricle (the right heart's pumping chamber).
3. The right ventricle squeezes gently and pushes blood through the pulmonary valve into the pulmonary artery, which splits into left and right branches heading to each lung.

4. Inside the lungs, the pulmonary arteries branch into millions of tiny capillaries that wrap around the air sacs (alveoli), where oxygen jumps into the blood and carbon dioxide jumps out into the air you breathe out.
5. Oxygen-rich blood collects in pulmonary veins and flows back to the left atrium, then into the left ventricle, which pumps it out to your whole body through the aorta.

What breaks

In pulmonary high blood pressure (hypertension), pressure inside the lung arteries climbs above 20 mmHg at rest (measured by right heart catheter), forcing the right ventricle to work much harder; the root cause splits into five types.

CLINICAL TERM

PH is defined as mean pulmonary artery pressure (mPAP) ≥ 20 mmHg at rest on right heart catheterization (updated from the old ≥ 25 threshold in 2018 guidelines). The five WHO groups are: Group 1 (pulmonary arterial high blood pressure (hypertension), PAH) from thickening and narrowing of small lung arteries due to cell overgrowth, inflammation, and clot formation inside the vessel walls — causes include with no known cause (idiopathic) PAH, heritable PAH (BMP2 and other gene mutations), drugs (appetite suppressants, methamphetamine), connective-tissue diseases (scleroderma, lupus), congenital heart shunts, portal high blood pressure, HIV, and schistosomiasis. Group 2 (left heart disease) from backup when the left atrium or left ventricle fails or the mitral/aortic valve leaks or narrows, raising pressure backward into the lung veins and then lung arteries. Group 3 (lung disease and low oxygen (hypoxia)) from COPD, interstitial lung disease, sleep pauses in breathing (apnea), or high-altitude living that damages lung tissue and lowers oxygen, causing lung arteries to clamp down (hypoxic vasoconstriction). Group 4 (chronic thromboembolic PH, CTEPH) from old blood clots stuck and scarred into the lung arteries after pulmonary embolism (a clot lodging in a lung artery). Group 5 (multifactorial) from mixed or unclear mechanisms in sarcoidosis, blood disorders, kidney disease on dialysis, thyroid disease, and glycogen storage disease.

How the body compensates

The right ventricle tries to keep up by thickening its muscle wall and squeezing harder, and the kidneys hold onto salt and water to boost blood volume, but these fixes only delay failure — once the right heart dilates and weakens, the spiral accelerates toward shock and death.

1. The right ventricular muscle wall thickens (hypertrophy) to generate more squeeze force against the high lung-artery pressure, keeping stroke volume (blood pumped per beat) near normal for months to years.

2. The kidneys activate the renin-angiotensin-aldosterone system (RAAS) and release antidiuretic hormone (ADH), holding onto sodium and water to expand blood volume and maintain filling pressure — you may gain weight from hidden fluid before swelling appears.
3. Heart rate climbs (tachycardia) to keep total cardiac output (heart rate $\times$ stroke volume) steady when stroke volume starts to drop, but this shortens the time the heart has to fill and rest.
4. Sympathetic nerves release norepinephrine to squeeze blood vessels tighter (vasoconstriction) and make the heart beat harder, but chronic activation wears out receptors and harms the heart muscle over time.
5. As the right ventricle stretches (dilates) from relentless pressure overload, the tricuspid valve ring widens and the valve leaks (tricuspid regurgitation), letting blood slosh backward into the right atrium and body veins instead of forward into the lungs.
6. Compensation tips into decompensation when the right ventricle can no longer keep up: cardiac output falls, blood pressure drops, organs (brain, kidneys, liver) fail from low oxygen and blood flow, and sudden death from arrhythmia or cardiogenic shock becomes likely.

Domino effect

1. High pressure in the lung arteries forces the right ventricle to squeeze much harder with every beat. — Whether from thick artery walls (type 1), backup from left heart failure (type 2), oxygen-starved vessel clamping (type 3), clot blockage (type 4), or mixed causes (type 5), the right heart now faces a brick wall instead of an open road, so it has to work like a marathon runner every single minute.
2. The right ventricle muscle thickens at first, then stretches and weakens, causing right heart failure. — Constant overwork makes the muscle bulk up (right ventricular hypertrophy), but eventually the wall thins out, the chamber balloons (dilation), and the pump loses strength — blood can no longer move forward efficiently.
3. Blood backs up into the body's veins, making neck veins bulge, the liver swell and hurt, and legs and belly puff up with fluid. — The failing right heart cannot empty itself, so pressure rises backward through the right atrium into the superior and inferior vena cava (the big veins draining your body); high vein pressure pushes fluid out of blood vessels into tissues (edema) and engorges the liver (hepatomegaly, right-upper-quadrant pain).
4. You feel short of breath, especially when walking or climbing stairs, because your muscles and brain are starved for oxygen. — The weakened right heart pumps less blood through the lungs, so less oxygen gets picked up and delivered to your body; when you exercise, demand spikes but supply cannot keep up, triggering air hunger (dyspnea) and fatigue.

5. You may feel dizzy, lightheaded, or faint (syncope), especially during effort or standing up quickly. — Low cardiac output means less oxygen-rich blood reaches your brain; the brain is extremely sensitive to oxygen drops, so even a brief dip causes dizziness or fainting — this is a red flag for severe PH and high risk of sudden death.
6. Chest discomfort or pressure can occur, mimicking angina, because the thickened right ventricle outgrows its own blood supply. — The right coronary artery feeds the right ventricle, but when the muscle wall thickens dramatically, the existing blood vessels cannot deliver enough oxygen to the deeper layers, causing starved blood flow (ischemia) (oxygen debt) and chest pain, especially during exertion.
7. Without treatment, the right heart fails completely, organs shut down, and sudden death from arrhythmia or shock is common. — End-stage right heart failure means almost no blood moves forward; the brain, kidneys, and liver fail from low oxygen and buildup of waste; the overstretched heart muscle becomes electrically unstable, triggering fatal rhythms like ventricular a fast heart rate (tachycardia) or fibrillation.
8. Every visible sign — loud P2 heart sound, swollen neck veins, enlarged liver, leg swelling (edema), low oxygen on pulse ox — traces back to the same root: high lung artery pressure breaking the right heart. — The loud P2 is the pulmonary valve slamming shut under high pressure; swollen veins and swelling (edema) are backup from right heart failure; low oxygen is poor forward flow through the lungs — none are separate diseases, all are dominoes falling from the same upstream break.

Symptoms · what the patient feels, and why

- Shortness of breath during activity: High pressure in the lung arteries makes it harder for blood to pick up oxygen, so you feel out of breath when your body needs more oxygen—like when walking up stairs or carrying groceries.
- Feeling tired or weak all the time: Your heart has to pump extra hard against the stiff, tight arteries in your lungs, so less oxygen-rich blood reaches your muscles and organs, leaving you feeling drained even after rest.
- Chest discomfort or pressure: The right side of your heart is working much harder than usual to push blood through high-pressure lung vessels, and that extra strain can cause a heavy or tight feeling in your chest.
- Swelling in your ankles, legs, or belly: When the right heart cannot pump blood forward efficiently, blood backs up into the veins; fluid then leaks out into the tissues, causing puffiness (edema) in the legs, ankles, and sometimes the abdomen (ascites).
- Your neck veins bulge or stand out: Blood is backing up from the struggling right heart into the large veins that drain into it, raising the pressure in the jugular veins (the big veins in your neck) so they look swollen or raised.

- **Bluish lips or skin (cyanosis):** When the lungs cannot load enough oxygen into the blood because of the high pressure and poor flow, the blood stays darker and gives a blue tint to lips, fingernails, or skin.
- **Feeling dizzy or fainting (syncope):** During exercise or sudden movement, your heart cannot pump enough oxygen-rich blood to the brain because it is already maxed out fighting the high lung pressure, so your brain briefly runs low on fuel and you feel lightheaded or pass out.
- **A loud second heart sound (P2) when the doctor listens with a stethoscope:** The pulmonary valve (the door between the right heart and lung arteries) slams shut harder and earlier than normal because pressure in the lung arteries is so high, creating a louder 'boom' that the doctor can hear.
- **The right side of your heart gets bigger (right ventricular enlargement):** Pumping against constant high pressure forces the right ventricle (the chamber that sends blood to the lungs) to thicken and stretch over time, like a muscle that gets bulky from overuse.

Focused exam

- **Loud P2 heart sound (the pulmonary valve part of the second heart sound is louder than normal):** The right side of the heart is pumping against very high pressure in the lung arteries, so the pulmonary valve (the door between the right heart and the lung arteries) slams shut hard and late. This loud snap is your bedside clue that pressure in the lungs is high.
- **Right ventricular heave (a lifting push you can feel along the left edge of the breastbone):** The right ventricle (the lower right chamber of the heart) gets thick and strong trying to push blood through stiff, high-pressure lung vessels. You feel this extra muscle contract against your hand—like pressing on a flexed bicep.
- **Jugular venous distention (neck veins that bulge and get fuller when you press gently on the belly):** Blood backs up into the right atrium (the top right chamber of the heart) because the right ventricle cannot empty it forward. The neck veins fill up like a backed-up drain—this is called hepatojugular reflux and tells you the right heart is failing.
- **Ankle swelling and a liver edge you can feel below the rib cage:** When the right heart fails, blood pools in the body instead of moving forward. Fluid leaks out of blood vessels into the tissues (causing swelling) and the liver gets congested and swells bigger—this is right-sided heart failure.
- **Bluish skin (Cyanosis) (blue color in the lips, tongue, or fingertips):** In severe pulmonary high blood pressure (hypertension) with an Eisenmenger shunt (a hole in the heart that lets blood bypass the lungs), blood does not get enough oxygen. Blue color means oxygen saturation is dangerously low—usually below 88 percent.

- Tricuspid regurgitation murmur (a harsh whooshing sound heard best at the lower left edge of the breastbone, louder when the person breathes in): The right ventricle dilates (stretches out like an overfilled balloon) from fighting high lung pressure, so the tricuspid valve (the door between the top and bottom right chambers) cannot close all the way. Blood leaks backward with every heartbeat.

Diagnostics · every test answers a question

- Transthoracic echocardiogram (ultrasound of the heart) → Is the right ventricle enlarged or thickened, and what is the estimated pulmonary artery systolic pressure?
- Right heart catheterization (a thin tube threaded through a vein into the right heart and pulmonary artery to measure pressures directly) → What is the exact mean pulmonary artery pressure, and is the problem coming from the lungs or from the left heart backing up?
- Six-minute walk test → How far can the person walk in six minutes, and does their oxygen drop?
- Ventilation-blood flow (perfusion) (V/Q) scan (a nuclear medicine scan that shows air flow and blood flow in the lungs) → Are there mismatched areas where air reaches the lung but blood does not, suggesting a clot?
- High-resolution chest CT with contrast (a detailed X-ray scan of the lungs) → Are the lung arteries enlarged, are there clots or webs inside them, and is there underlying lung disease?
- Pulmonary function tests (spirometry and diffusing capacity for carbon monoxide, DLCO) → Is there airway obstruction, restriction, or poor gas exchange that could cause or worsen pulmonary high blood pressure (hypertension)?
- BNP or NT-proBNP (blood test for heart strain) → Is the right ventricle under stress and starting to fail?
- Connective tissue disease antibody panel (ANA, anti-Scl-70, anti-centromere, anti-U1-RNP) → Is there an autoimmune disease (especially scleroderma) causing the pulmonary high blood pressure (hypertension)?

Treatment logic

- Right heart catheterization to confirm the diagnosis and measure exact pressures → Gives you the real mean pulmonary artery pressure (mPAP) and pulmonary artery wedge pressure (PAWP) so you know which of the five groups the patient has and how severe it is. This number decides whether the patient gets pulmonary vasodilators (drugs that open lung blood vessels) or needs a different treatment.

- PDE5 inhibitor (sildenafil 20 mg three times daily or tadalafil 40 mg once daily) or endothelin receptor antagonist (ambrisentan 5–10 mg daily, bosentan 125 mg twice daily, or macitentan 10 mg daily) for Group 1 pulmonary arterial high blood pressure (hypertension) → Relaxes and opens the thick, stiff blood vessels in the lungs by blocking signals that make them squeeze tight (endothelin) or by boosting signals that make them relax (nitric oxide and cGMP). This lowers pulmonary artery pressure and lets the right heart pump more easily.
- Treat the upstream cause: diuretics and GDMT for left heart failure (Group 2), oxygen and inhalers for COPD or interstitial lung disease (Group 3), anticoagulation and surgery for chronic clots (Group 4) → Stops blood from backing up into the lungs (Group 2 left heart failure), restores oxygen and opens airways (Group 3 lung disease), or removes the clot dam blocking blood flow (Group 4 CTEPH). Fixing the root cause lowers pulmonary pressure naturally.
- Loop diuretic (furosemide 20–80 mg daily, titrated to symptoms) for fluid overload and right heart failure → Removes extra fluid that backs up when the right heart fails, so the patient can breathe easier, neck veins go down, and swelling improves. This takes load off the right heart.
- Supplemental oxygen (target oxygen saturation 90 percent or higher) for patients with low oxygen in the blood (hypoxemia) → Low oxygen makes pulmonary blood vessels squeeze tight (hypoxic vasoconstriction). Giving oxygen relaxes them a little and lowers pulmonary pressure. This helps the right heart work less hard.
- Pulmonary thromboendarterectomy (PTE surgery to cut out organized clots from the pulmonary arteries) for chronic thromboembolic pulmonary high blood pressure (hypertension) (Group 4 CTEPH) → Physically removes the clot dam blocking blood flow in the lungs. This can cure the patient if the clots are accessible and the surgery is done at an expert center. Mean pulmonary artery pressure drops immediately, and the right heart can recover.
- Riociguat (a soluble guanylate cyclase stimulator, 0.5–2.5 mg three times daily) for inoperable or persistent CTEPH, or for Group 1 PAH → Boosts the nitric oxide pathway even when nitric oxide levels are low, which relaxes pulmonary blood vessels and lowers pressure. This is the only drug proven to help patients with CTEPH who cannot have surgery.

Medications

Sildenafil (Revatio) · PDE5 inhibitor (phosphodiesterase-5 blocker)

Sildenafil blocks an enzyme (PDE5) that breaks down a helpful molecule called cGMP. When cGMP stays around longer, the smooth muscle inside the lung arteries relaxes and the vessels

open wider. That lowers the pressure and makes it easier for the heart to push blood through the lungs.

1. Your body makes a signal molecule called nitric oxide in the lung artery wall.
2. Nitric oxide tells the muscle cell to make cGMP, which relaxes the muscle.
3. Normally, an enzyme called PDE5 chews up cGMP quickly, so the relaxation does not last long.
4. Sildenafil blocks PDE5, so cGMP sticks around longer.
5. The muscle stays relaxed, the artery stays wider, and pressure drops.

SAFETY WATCH

Do NOT take sildenafil if you use nitrate medicines (nitroglycerin, isosorbide) for chest pain—the combination can make your blood pressure crash dangerously low. · Watch for headache, flushing (warm red face), upset stomach, or stuffy nose—common and usually mild. · Rare but serious: sudden vision loss or sudden hearing loss. Stop the medicine and call your doctor right away. · Can cause an erection that will not go away (priapism) in men—go to the ER if it lasts more than 4 hours. · Your doctor will check your liver and may adjust the dose if your liver is not working well.

Tadalafil (Adcirca) · PDE5 inhibitor (phosphodiesterase-5 blocker)

Tadalafil blocks the same enzyme (PDE5) that sildenafil does, but it lasts longer in your body—about 24 hours instead of 4 to 6. It keeps cGMP levels up so the lung arteries stay relaxed and open all day. That lowers the pressure the right side of your heart has to push against.

1. Nitric oxide in the artery wall triggers the cell to make cGMP.
2. cGMP tells the muscle to relax and the artery to widen.
3. PDE5 breaks down cGMP, ending the relaxation.
4. Tadalafil blocks PDE5, so cGMP stays active longer.
5. The artery stays open, pressure stays lower, and you take the pill once a day instead of three times.

SAFETY WATCH

Never combine with nitrate drugs (nitroglycerin, isosorbide)—blood pressure can drop to dangerous levels. · Common side effects: headache, muscle aches, back pain, indigestion, flushing, stuffy nose. · Rare but serious: sudden loss of vision in one or both eyes, sudden hearing loss. Stop and call your doctor immediately. · Priapism (painful erection lasting over 4 hours) is a medical emergency. · Tell your doctor about liver or kidney problems—dose may need to be lower.

Bosentan (Tracleer) · Endothelin receptor antagonist (ERA)

Bosentan blocks receptors for endothelin, a powerful chemical that tightens lung arteries and makes their walls thicker. By blocking both endothelin receptors (ET-A and ET-B), bosentan stops that squeezing and thickening, so the arteries stay more open and the pressure drops.

1. In pulmonary arterial high blood pressure (hypertension), the lungs make too much endothelin.
2. Endothelin locks onto ET-A receptors and tells the muscle to squeeze and grow thicker.
3. It also locks onto ET-B receptors, which can help clear endothelin but also cause some squeezing.
4. Bosentan sits on both receptor types so endothelin cannot attach.
5. Without endothelin's signal, the muscle relaxes and the vessel wall stops thickening.

SAFETY WATCH

Bosentan can harm your liver. You **MUST** get blood tests for liver enzymes every month while you take it. · It causes birth defects—women must use two forms of reliable birth control and get a pregnancy test every month. Do **NOT** take bosentan if you are pregnant or might become pregnant. · Can lower your red blood cell count (anemia)—your doctor will check blood counts regularly. · Can interact with hormonal birth control pills and make them less effective—use a barrier method as backup. · Watch for swelling in your legs, yellow skin or eyes, dark urine, or severe tiredness and report them right away.

Ambrisentan (Letairis) · Endothelin receptor antagonist (ERA)

Ambrisentan blocks only the ET-A receptor, the one that squeezes lung arteries and tells the wall to thicken. It leaves the ET-B receptor alone, which may help your body clear extra endothelin. By stopping the squeeze signal, ambrisentan lowers lung artery pressure.

1. High endothelin levels tell lung arteries to tighten and grow thick.
2. Endothelin uses the ET-A receptor to send most of that message.
3. Ambrisentan covers the ET-A receptor so endothelin cannot attach.
4. The muscle stops squeezing and the wall stops thickening.
5. Pressure in the lung arteries goes down, and the right heart does not have to work as hard.

SAFETY WATCH

Can harm the liver—you need monthly blood tests to check liver enzymes. · Causes birth defects—women **MUST** use reliable birth control and get monthly pregnancy tests. Never take if you are pregnant. · Can cause fluid retention and swelling (edema), especially in the legs. · Watch for sudden weight gain, trouble breathing, or swelling—call your doctor. · Can lower red blood cell count (anemia)—your doctor will monitor blood counts. · Available only through a restricted program (REMS) because of the pregnancy risk.

Macitentan (Opsumit) · Endothelin receptor antagonist (ERA)

Macitentan blocks both ET-A and ET-B receptors for endothelin, stopping the signal that makes lung arteries squeeze and thicken. It binds very tightly to the receptors and gets into the tissue well, so it keeps working even as your body tries to make more endothelin.

1. Pulmonary arterial high blood pressure (hypertension) causes high endothelin levels.
2. Endothelin tells lung arteries to tighten and the walls to grow thick.
3. Macitentan covers both the ET-A and ET-B receptors.
4. Endothelin cannot deliver its squeezing message.
5. The arteries relax, pressure drops, and the walls stop getting thicker.

SAFETY WATCH

Can damage the liver—monthly blood tests for liver enzymes are required. · Causes severe birth defects—women must use two reliable forms of birth control and have monthly pregnancy tests. Do **NOT** take if pregnant. · Can lower red blood cell count (anemia) and your hemoglobin—your doctor will check blood counts regularly. · Watch for swelling, sudden weight gain, trouble breathing, or yellow skin and eyes. · Available only through a restricted REMS program because of the pregnancy risk.

Epoprostenol (Flolan, Veletri) · Prostacyclin (prostaglandin I₂ analogue)

Epoprostenol is a man-made version of prostacyclin, a natural chemical your body makes to open blood vessels and stop platelets from clumping. In PAH, your lungs do not make enough prostacyclin. Epoprostenol replaces it, relaxing the lung arteries and lowering pressure. It also stops the vessel walls from getting thicker.

1. Epoprostenol locks onto prostacyclin receptors in the lung artery wall.
2. That signal raises a molecule called cAMP inside the muscle cell.
3. High cAMP tells the muscle to relax and the artery to open.
4. Epoprostenol also tells platelets not to stick together, which helps prevent tiny clots.
5. Over time, it slows the thickening and scarring of the artery walls.

SAFETY WATCH

Requires a permanent central IV catheter, which carries a risk of serious infection (sepsis) and blood clots. · Must be kept cold and mixed fresh every day—cannot be interrupted even for minutes, or your pressure can spike dangerously. · Common side effects: jaw pain (especially when eating), flushing, headache, diarrhea, nausea, muscle and bone pain. · Can cause low blood pressure—watch for dizziness or fainting. · You and your caregivers need special training to mix and manage the pump safely. · Never stop or lower the dose suddenly without your doctor—rebound high pressure can be fatal.

Treprostinil (Remodulin, Tyvaso, Orenitram) · Prostacyclin (prostaglandin I₂ analogue)

Treprostinil works just like epoprostenol—it mimics prostacyclin to relax lung arteries, lower pressure, and stop platelets from clumping. It lasts longer in the body, so you can give it under the skin (subcutaneous), through an IV, by breathing it in (inhaled), or as a pill, depending on the form.

1. Treprostinil attaches to prostacyclin receptors.
2. The cell makes more cAMP.
3. cAMP relaxes the muscle and opens the artery.
4. Platelets get the signal not to stick together.
5. The artery wall gets a signal to stop thickening.

SAFETY WATCH

Subcutaneous form (Remodulin): injection-site pain is very common and can be severe; some patients cannot tolerate it. · IV form: requires a central line, with infection and clot risk. · Inhaled form (Tyvaso): can cause cough, throat irritation, or headache; you need a special nebulizer four times a day. · Oral form (Orenitram): can cause headache, diarrhea, nausea, flushing, and jaw pain. · All forms can lower blood pressure—watch for dizziness. · Do NOT stop or skip doses suddenly—rebound pulmonary high blood pressure (hypertension) can be life-threatening.

Iloprost (Ventavis) · Prostacyclin (prostaglandin I₂ analogue)

Iloprost is a prostacyclin mimic that you breathe in as a mist six to nine times a day. It goes straight to the lung arteries, relaxes the muscle, and opens the vessels. By delivering the medicine directly to the lungs, it lowers pressure there with less effect on the rest of the body.

1. You breathe in iloprost mist through a nebulizer.
2. The drug lands on the lung artery walls.

3. It locks onto prostacyclin receptors and raises cAMP inside the cells.
4. The muscle relaxes, the artery opens, and pressure drops.
5. The effect lasts about 30 to 90 minutes, so you need to inhale it many times a day.

SAFETY WATCH

Common: cough, headache, flushing, jaw pain, flu-like aches. · Can cause low blood pressure or fainting—sit down during and after treatments. · Can trigger wheezing or trouble breathing if you have asthma or COPD—your doctor may give a bronchodilator first. · Each treatment takes about 10 minutes; you need a special nebulizer (I-neb or BreeLib) and must carry it everywhere. · Do NOT skip or stop treatments suddenly—pressure can spike.

Selexipag (Uptravi) · Prostacyclin receptor agonist (non-prostanoid)

Selexipag is a pill that you take twice a day. It is NOT a prostacyclin itself, but it turns into a molecule that locks onto prostacyclin receptors and mimics what prostacyclin does—relax lung arteries and lower pressure. Because it is not an actual prostacyclin, it lasts longer and is more stable.

1. You swallow the pill; your liver turns it into the active form.
2. The active form attaches to prostacyclin receptors.
3. The cell makes more cAMP, which relaxes the muscle.
4. The lung arteries open wider and pressure drops.
5. The effect lasts longer than inhaled prostacyclins, so you take it twice daily.

SAFETY WATCH

Very common: headache, diarrhea, nausea, vomiting, jaw pain, muscle pain, flushing, joint pain. · Side effects are often worst when you first start or raise the dose—many patients need weeks to adjust. · Can cause low blood pressure. · Take with food to reduce stomach upset. · Do NOT stop suddenly—talk to your doctor first.

Riociguat (Adempas) · Soluble guanylate cyclase (sGC) stimulator

Riociguat boosts an enzyme called soluble guanylate cyclase, which makes cGMP—the same relaxing molecule that PDE5 inhibitors protect. Riociguat works in two ways: it makes the enzyme more sensitive to nitric oxide AND it directly turns on the enzyme even when nitric oxide is low. That raises cGMP, relaxes lung arteries, and lowers pressure.

1. Normally, nitric oxide turns on sGC to make cGMP, which relaxes the muscle.

2. In pulmonary high blood pressure (hypertension), nitric oxide is often low, so cGMP is low and arteries stay tight.
3. Riociguat makes sGC more sensitive to whatever nitric oxide is there.
4. It also flips the sGC switch directly, even without nitric oxide.
5. More cGMP is made, the muscle relaxes, and pressure drops.

SAFETY WATCH

Never take riociguat with PDE5 inhibitors (sildenafil, tadalafil) or nitrates—blood pressure can fall to dangerous levels. · Causes severe birth defects—women must use reliable birth control and get monthly pregnancy tests. Do NOT take if pregnant. · Common side effects: headache, dizziness, indigestion, nausea, diarrhea, swelling in legs. · Can cause bleeding (nosebleeds, coughing up blood, heavy periods)—tell your doctor if this happens. · Available only through a restricted REMS program because of pregnancy risk. · Check blood pressure regularly; watch for fainting or light-headedness.

Calcium-channel blockers (CCBs): Nifedipine, Diltiazem, Amlodipine · Calcium-channel blocker

CCBs block calcium from entering the muscle cells in artery walls. Without calcium, the muscle cannot squeeze. That keeps the lung arteries relaxed and open. CCBs work ONLY in a small group of PAH patients whose arteries open up during a vasodilator test (acute vasoreactivity test) at heart catheterization. For those few, CCBs can lower pressure safely and long-term.

1. Normally, calcium flows into muscle cells and triggers squeezing.
2. CCBs plug the calcium channels so calcium cannot get in.
3. Without calcium, the muscle stays relaxed.
4. The lung arteries stay open and pressure drops.
5. This works ONLY if your arteries can still relax—most PAH patients have stiff, remodeled vessels that will not respond.

SAFETY WATCH

Only use CCBs if you tested positive on acute vasoreactivity testing during right-heart catheterization. Most PAH patients do NOT qualify. · High doses are needed (nifedipine 120–240 mg/day, diltiazem 240–720 mg/day)—much higher than for regular high blood pressure. · Can cause low blood pressure, dizziness, fainting, swelling in legs, headache, flushing. · Diltiazem and verapamil can slow your heart rate—not safe if you already have a slow heart or heart block. · Your doctor will recheck you with repeat right-heart catheterization after a few months to make sure the CCB is still working. · If pressure goes back up or you get worse, CCBs must be stopped and other PAH drugs started.

Oxygen (supplemental O₂) · Medical gas / supportive therapy

Oxygen is NOT a drug, but breathing extra oxygen helps when your blood oxygen level is low (hypoxemia). Low oxygen makes lung arteries squeeze tight (hypoxic vasoconstriction), which raises pressure even more. By keeping oxygen levels normal, you prevent that extra squeezing and take some load off the right heart. Oxygen is especially important in Group 3 pulmonary high blood pressure (hypertension) (lung disease) and at high altitude.

1. When oxygen in the air sacs (alveoli) is low, nearby lung arteries sense it and squeeze tight to redirect blood to better-ventilated areas.
2. If oxygen is low everywhere (like in COPD or sleep pauses in breathing (apnea)), all the lung arteries squeeze, and pressure goes up.
3. Breathing extra oxygen raises the oxygen level in the air sacs.
4. The arteries sense normal oxygen and relax.
5. Pressure drops and the right heart does not have to push as hard.

SAFETY WATCH

You need a prescription and regular checks of your oxygen level (pulse oximetry or arterial blood gas). · Use only the flow rate your doctor prescribes—too much oxygen can be harmful in some lung diseases (like COPD with high CO₂). · Oxygen is flammable—keep away from open flames, cigarettes, stoves, and candles. · Nasal cannulas and tubing can cause skin irritation or nosebleeds; use water-based lubricant if needed. · Portable oxygen concentrators and tanks are heavy and can limit mobility—work with your team to find the best setup. · Long-term oxygen does NOT mean you are dying; it means your body needs help keeping oxygen levels safe.

Diuretics (water pills): Furosemide (Lasix), Bumetanide, Torsemide, Spironolactone · Loop diuretic or aldosterone antagonist

Diuretics help your kidneys dump extra salt and water into the urine. In pulmonary high blood pressure (hypertension), the right heart can get weak and blood backs up, causing fluid to leak into the lungs, belly, and legs (edema, fluid buildup in the belly (ascites)). Diuretics pull that extra fluid out, which makes breathing easier and takes pressure off the heart. They do NOT lower pulmonary artery pressure directly.

1. When the right heart is weak or overloaded, blood backs up into the veins.
2. Fluid leaks out of the blood vessels into the tissues (swelling) and body cavities (fluid in lungs or belly).
3. Diuretics tell the kidneys to hold onto less salt and water.
4. More salt and water leave the body as urine.

5. Total fluid volume drops, swelling goes down, and the heart has less volume to pump.

SAFETY WATCH

Can cause low potassium (hypokalemia) with loop diuretics or high potassium (hyperkalemia) with spironolactone—your doctor will check blood tests regularly. · Can cause dehydration, dizziness, fainting, or kidney injury if the dose is too high. · Watch your weight every day—sudden weight loss or gain tells your doctor whether the dose is right. · Can make you urinate frequently, especially in the first few hours after taking the pill—plan bathroom access. · Spironolactone can cause breast tenderness or enlargement (gynecomastia) in men. · Tell your doctor if you feel weak, have muscle cramps, or notice a very slow or fast heartbeat—these can be signs of electrolyte problems.

Anticoagulation (blood thinners): Warfarin, Apixaban, Rivaroxaban · Anticoagulant (vitamin K antagonist or direct oral anticoagulant)

Blood thinners do NOT dissolve clots, but they stop new clots from forming. In CTEPH (Group 4), clots are stuck in the lung arteries. In PAH (Group 1), slow blood flow and thick vessel walls raise clot risk. Anticoagulants keep the blood from clotting as easily, which may prevent more clots from piling on and making things worse. Warfarin has been used traditionally; newer agents (apixaban, rivaroxaban) are being studied.

1. Blood clotting is a chain reaction involving many proteins (clotting factors).
2. Warfarin blocks vitamin K, so your liver cannot make some of those factors.
3. DOACs (apixaban, rivaroxaban) directly block one factor in the clotting chain (factor Xa).
4. Without enough clotting factors, the blood takes longer to clot.
5. That lowers the chance of new clots forming in the slow-moving blood in lung arteries.

SAFETY WATCH

Bleeding is the main risk—can be minor (nosebleeds, bruising, bleeding gums) or life-threatening (brain bleed, stomach bleed). · Warfarin requires frequent blood tests (INR) and dose adjustments; many foods and drugs change how it works. · DOACs do NOT require routine blood tests, but there is no easy way to reverse them quickly if serious bleeding happens (though reversal agents exist for some). · Avoid contact sports and activities with high fall or injury risk. · Tell every doctor and dentist you see that you take a blood thinner. · Call your doctor right away if you have black or bloody stools, vomit that looks like coffee grounds, severe headache, or any fall or injury to your head. · Warfarin causes birth defects—do NOT take if you are pregnant or planning pregnancy; use effective birth control.

Red flags

- Sudden fainting or near-fainting during exercise—this can mean your heart is at its limit and cannot send enough blood to your brain.
- New or worsening leg swelling, bulging neck veins, or a swollen belly—these are signs that the right heart is failing and blood is backing up into your body.
- Blue lips, fingernails, or skin—this means your blood oxygen is dangerously low.
- Chest pain that feels like pressure or squeezing, especially with activity—the struggling right heart may not be getting enough oxygen itself.
- Coughing up blood (hemoptysis)—high lung pressure can burst small blood vessels in the airways.

Nursing priorities

1. Monitor oxygen saturation continuously and keep SpO₂ above 90 percent with supplemental oxygen as ordered — Low oxygen (hypoxemia) makes pulmonary arteries squeeze tighter (hypoxic vasoconstriction), which raises pressure in the lungs and forces the already-weak right heart to work even harder.
2. Watch for signs of right heart failure: measure jugular venous distension (how high neck veins sit), check for new or worsening leg swelling, listen for extra heart sounds, and report immediately if patient becomes confused or blood pressure drops — Right ventricular failure happens when the right heart cannot pump against high lung pressures anymore; blood backs up into the body causing organ damage, and forward flow drops causing shock and death.
3. Give diuretics (water pills like furosemide) exactly on schedule and track daily weights, intake and output, and electrolytes (sodium, potassium) — Fluid overload from a failing right heart causes dangerous swelling in the liver, belly, and legs; diuretics pull off extra fluid but can cause low potassium (hypokalemia) and kidney injury if we give too much.
4. Avoid giving too much intravenous fluid; give fluid boluses only when ordered and monitor closely for worsening shortness of breath or dropping oxygen levels — The failing right ventricle is very sensitive to preload (how much blood fills it); too much IV fluid overstretches the right heart, drops its squeeze strength, and can tip the patient into cardiogenic shock.
5. Teach the patient to pace activities, rest between tasks, and call for help instead of straining (like during bowel movements), and give stool softeners as ordered — Valsalva maneuvers (bearing down, straining) and sudden exertion cause big pressure swings that the stiff, sick right heart cannot handle, triggering fainting (syncope), arrhythmias (irregular heartbeats), or cardiac arrest.

6. Administer pulmonary vasodilator medications (sildenafil, tadalafil, bosentan, ambrisentan, macitentan, epoprostenol) on time and through the correct route, and never stop them suddenly — These drugs open up tight lung blood vessels (vasodilation) and lower the pressure the right heart pumps against; missing doses or stopping suddenly causes rebound pulmonary vasoconstriction and can cause rapid right heart failure and death.
7. Monitor blood pressure closely, especially after giving vasodilator medications, and report systolic BP below 90 or symptoms of dizziness and lightheadedness — Pulmonary vasodilators also relax body arteries (systemic vasodilation), which can drop blood pressure too low; low blood pressure (hypotension) reduces blood flow to the brain, kidneys, and the heart muscle itself, worsening organ failure.
8. Coordinate care so the patient gets an echocardiogram (heart ultrasound), right heart catheterization if not done yet, and specialty referral to a pulmonary high blood pressure (hypertension) expert center — Pulmonary high blood pressure (hypertension) has five different types with completely different treatments; wrong treatment (like giving PAH drugs for Type 2 or Type 3) harms patients, and accurate diagnosis requires specific tests and expert interpretation.

Sources

- ESC/ERS Guidelines for Pulmonary Hypertension 2022
- AHA/ACC Pulmonary Hypertension Scientific Statement
- Chest (Journal of the American College of Chest Physicians)
- World Health Organization Pulmonary Hypertension Classification

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