Inhaled Pulmonary Vasodilators

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physiologic effects of inhaled pulmonary vasodilators
Inhaled pulmonary vasodilators yield three physiological advantages:

**#1) reduced pulmonary vascular resistance**
- Pulmonary vasodilation will reduce the resistance of the pulmonary vascular bed. This causes afterload reduction for the right ventricle.
- Reducing pulmonary vascular resistance is beneficial for patients with increased pulmonary vascular resistance (pulmonary hypertension) and/or impaired right ventricle function (e.g., right ventricular myocardial infarction).

**#2) improved ventilation-perfusion (V/Q) matching**

- Inhaled pulmonary vasodilators will tend to be distributed to well-ventilated alveoli, where they cause local vasodilation. This directs blood flow preferentially towards better ventilated areas, improving ventilation-perfusion matching.
- The most well-known consequence of improved ventilation-perfusion matching is improved oxygenation. This partially underlies the utility of pulmonary vasodilators in ARDS.

**#3) reduced blood flow through a right-to-left shunt**
- This is similar to #2 above, but it will occur only in patients who are experiencing shunting of deoxygenated blood into the systemic circulation (which is less common than ventilation-perfusion mismatch).
- The most notable scenario here might be a patient with pulmonary hypertension and a patent foramen ovale (PFO), leading to an intracardiac right-to-left shunt that causes systemic hypoxemia.
- Inhaled pulmonary vasodilators will tend to reduce blood flow through this shunt, for a few reasons:
  - (1) Inhaled pulmonary vasodilators may drop the pressure in the right atrium. In the case of a patent foramen ovale (PFO), this might cause the shunt to close entirely (the PFO will be open only when right-sided pressures exceed left-sided pressures).
  - (2) Inhaled pulmonary vasodilators will reduce the pulmonary vascular resistance, which will tend to cause blood to preferentially pass through the lungs, rather than the shunt. Even if an anatomic shunt remains open, less blood will flow through it.
- In patients with pulmonary hypertension, the presence of an intracardiac right-to-left shunt might be a predictor that inhaled pulmonary vasodilators will improve oxygenation.
  - A right-to-left shunt is easily evaluated at the bedside using echocardiography with a bubble study, as shown below.
  - Identifying patients with intracardiac right-to-left shunting is important, because these patients may respond poorly to recruitment maneuvers (increasing the airway pressure may increase the right-sided pressures, leading to an increase in blood flow through the shunt).
If NO is delivered via nasal prongs, there will be significant dilution of gas en route to the trachea. Consequently, it could be rational to use somewhat higher concentrations of nitric oxide when administering it via nasal prongs (e.g., 50 ppm, which was used in the iNOPE trial). (30633959 [https://pubmed.ncbi.nlm.nih.gov/30633959/])

**mechanism**

Nitroglycerine is metabolized into nitric oxide. Thus, nitroglycerine may be roughly conceptualized as NO in liquid form.

The physiologic mechanism of nitroglycerine is the same as that of nitric oxide (above).

**evidentiary support**

Less experience exists regarding the use of nitroglycerine as a pulmonary vasodilator. However, several studies have shown that it is safe and effective:

- **Yurtseven et al. 2003** (14508317 [https://pubmed.ncbi.nlm.nih.gov/14508317/])
  - Subjects: 20 stable patients with chronic pulmonary hypertension intubated status post mitral valve replacement surgery.
  - Intervention: 2.5 mcg/kg/min nitroglycerine nebulized into the ventilator circuit.
  - Effect: ~20% reduction in pulmonary vascular resistance, no change in systemic vascular resistance.

- **Yurtseven et al. 2006** (17095973 [https://pubmed.ncbi.nlm.nih.gov/17095973/])
  - Subjects: 100 stable patients with chronic pulmonary hypertension intubated status post mitral valve surgery.
  - Intervention: 20 ug/kg nitroglycerine nebulized into the ventilator circuit.
  - Effect: 43% reduction in pulmonary vascular resistance, no change in systemic vascular resistance.

- **Goyal et al. 2006** (16707530 [https://pubmed.ncbi.nlm.nih.gov/16707530/])
  - Subjects: 19 children with ventricular septal defects undergoing elective Swan-Ganz catheterization.
  - Intervention: 25 ug/kg/min nitroglycerine nebulized over 10 minutes.
  - Effect: ~75% reduction in pulmonary vascular resistance, no change in systemic vascular resistance.

- **Mandal et al. 2010** (20442544 [https://pubmed.ncbi.nlm.nih.gov/20442544/])
  - Subjects: 40 stable patients with chronic pulmonary hypertension intubated following cardiovascular surgery.
  - Intervention: Nebulized nitroglycerine at 2.5 ug/kg/min for 10 minutes.
  - Effect: 40% reduction in the pulmonary vascular resistance, no change in systemic vascular resistance. Effects lasted for 20-30 minutes.

  - Subjects: RCT involving 50 patients with pulmonary hypertension undergoing mitral valve surgery.
  - Intervention: Patients were randomized to receive 5 mg milrinone or 5 mg nitroglycerine nebulized over fifteen minutes following disconnection from cardiopulmonary bypass.
  - Effect: Nitroglycerine was similarly effective compared to milrinone in reducing pulmonary vascular resistance. However, the effect of nitroglycerine was less potent after 75 minutes, suggesting a more transient effect.

**dose & delivery**

Nitroglycerine may be delivered via nebulizer, among either intubated or non-intubated patients. A vibrating mesh nebulizer may be preferable, if available (similar to epoprostenol below).

For a crashing patient (e.g., with PE or pulmonary hypertension), a reasonable dose seems to be ~5 mg nebulized over ~15 minutes.

The duration of action of nebulized nitroglycerine is 20-30 minutes. Therefore, repeated doses or a continuous nebulization therapy may be necessary to maintain efficacy. Nitroglycerine is generally used as a stop-gap measure until another pulmonary vasodilator is available (e.g., nitric oxide or epoprostenol).

**epoprostenol, a.k.a. prostacyclin or prostaglandin I2**

**mechanism**

https://emcrit.org/ibcc/pulmvaso/
overall, these agents are very similar

- Pulmonary vasodilators overall seem to have similar clinical efficacy compared to one another. Studies comparing nitric oxide versus epoprostenol have yielded equivalent results. ([31372630](https://pubmed.ncbi.nlm.nih.gov/31372630/), 29336971)
- These agents have minimal toxicity when used at moderate doses for finite periods of time (extended, high-dose nitric oxide may cause problems, as discussed below).
- Selection of an agent is based largely on logistic grounds:
  - Nitroglycerine or milrinone are often the fastest agents to initiate, so they may be most useful in crashing patients.
  - Nitric oxide or epoprostenol are best suited for prolonged maintenance therapy because they can be precisely titrated.
- Most hospital units will have a preference for one agent (typically either nitric oxide or epoprostenol).
- Many hospitals are transitioning to epoprostenol due to its reduced cost. ([31372630](https://pubmed.ncbi.nlm.nih.gov/31372630/))
- Whatever agent your pharmacists and respiratory therapists prefer should be fine.

mechanism & general properties

- Nitric oxide (NO) is a gas which functions as a cell signaling molecule. Within the lungs, NO stimulates increases in cellular cyclic GMP (cGMP) in vascular smooth muscle, leading to vasodilation.
- NO may also suppress platelet aggregation, but it's dubious whether this effect is clinically significant.
- NO is the prototype pulmonary vasodilator, for which the greatest amount of evidence exists. However, there's no clear evidence that it's superior to other agents.

do, tachyphylaxis, and rebound

- 20 parts per million (ppm) is typically the initial and maximal dose when administered to intubated patients.
- The effectiveness of nitric oxide tends to decrease over a period of days (tachyphylaxis).
- Over several days vasoconstrictive molecules, including endothelins, are up-regulated (to balance out the vasodilatory effect of NO). Rapid discontinuation of nitric oxide may subsequently lead to a rebound increase in pulmonary vascular resistance. ([29349687](https://pubmed.ncbi.nlm.nih.gov/29349687/))

delivery

- NO may be delivered via endotracheal tube, nasal prongs, or high-flow nasal cannula. ([30206010](https://pubmed.ncbi.nlm.nih.gov/30206010/))
- Epoprostenol interacts with the prostaglandin I receptor, leading to increased levels of intracellular cyclic adenosine monophosphate (cAMP). This subsequently leads to relaxation of vascular smooth muscle.
- Aside from vasodilation, epoprostenol may also exert antithrombotic, antifibrotic, and anti-inflammatory effects.

**pharmacokinetics**

- Epoprostenol itself has a half-life of roughly 2-5 minutes. After discontinuing epoprostenol, oxygenation will return to baseline in under 30 minutes.
- A rebound phenomenon might occur following prolonged use, similar to that of NO (although there seems to be little evidence regarding this).

![Figure 1. Set up for iEPO delivery via HFNC. iEPO, inhaled epoprostenol; HFNC, high-flow nasal cannula.](https://emcrit.org/ibcc/pulmvaso/attachment/hfncepo/)

**dose**

- ARDS:
  - Dose range is 0-50 ng/kg/min.
  - Epoprostenol is typically started at maximal dose (50 ng/kg/min) and subsequently weaned down once the patient is stabilizing.
- Pulmonary hypertension or right ventricular failure:
  - Dose range is 0-50 ng/kg/min.
  - For a crashing patient, the maximal dose may be started and weaned down. Alternatively, for a more stable patient it may be rational to start at the lower dose range and up-titrated.
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Traditionally, epoprostenol has been delivered via nebulizer into a ventilator circuit of an intubated patient.

High-flow nasal cannula (HFNC) may be used to deliver epoprostenol. This is more effective when using a mesh vibrating nebulizer (published studies have used the Aerogen Solo [https://www.aerogen.com/aerogen-solo-3/](https://www.aerogen.com/aerogen-solo-3/)). The concept behind a vibrating mesh nebulizer is explained in the video below 🔗.

Use of very high flow rates will dilute the epoprostenol and reduce lung deposition. However, use of very low flow rates will lead to entrainment of room air, which is also undesirable. The optimal flow rate might be about half of the patient’s own inspiratory flow rate. Consequently, an intermediate flow rate (e.g., ~10-40 liters/minute) might be desirable. The best approach is probably empiric titration of flow rate (with 10-15 minutes spent at various flow rates to determine maximal efficacy).

A BiPAP circuit may also be used in combination with a nebulizer (figure above).

This appears to work, although there is less evidence to support it.

Figure 1. A. Inhaled epoprostenol setup and administration through noninvasive positive pressure ventilation. B. Inhaled epoprostenol setup and administration through high-flow oxygen therapy through nasal cannula.

Vibrating Mesh Technology Aerogen
Milrinone may be used as a pulmonary vasodilator in a fashion similar to nitroglycerine (immediate administration as a stop-gap measure, while setting up nitric oxide or epoprostenol).

Nebulized milrinone appears to have similar potency compared to nitroglycerine, but a longer duration of action. This could potentially allow for intermittent nebulized therapies to be used as maintenance therapy (e.g., 4 mg milrinone nebulized Q4 hours). (https://pubmed.ncbi.nlm.nih.gov/30216198)

For an intubated patient in peri-arrest, 2.5 mg milrinone may be given as a bolus via an endotracheal tube.

Oxygen is the original gangster of inhaled pulmonary vasodilators. Vasodilation in response to higher levels of oxygen is an evolutionary strategy designed to maximize ventilation-perfusion matching. If the lungs are exposed to higher concentrations of oxygen, this may cause diffuse vasodilation with a reduction in pulmonary vascular resistance. In patients with decompensated right ventricular failure, higher concentrations of oxygen than are necessary might be useful to reduce the pulmonary vascular resistance and thereby off-load the right ventricle (if other pulmonary vasodilators aren't immediately available).

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Contraindications & adverse effects

Overall, inhaled pulmonary vasodilators are extremely safe. The primary concern regarding the use of inhaled pulmonary vasodilators is often resource utilization rather than toxicity, as these agents tend to be expensive. However, some potential issues warrant consideration.

The main concern: worsening cardiogenic pulmonary edema

- Improved blood flow through the right heart due to pulmonary vasodilators will increase the preload of the left ventricle. This is generally beneficial (as it will improve the cardiac output). However, in patients with severe left ventricular failure, increasing the left ventricular preload may exacerbate cardiogenic pulmonary edema.
  - Pulmonary vasodilators are most useful in isolated right ventricular failure (e.g., dilated and dysfunctional right ventricle, with a compressed and hyperkinetic left ventricle).
  - Pulmonary vasodilators may be unhelpful in patients with bi-ventricular heart failure and active cardiogenic pulmonary edema.
  - Pulmonary vasodilators may also exacerbate pulmonary edema in the context of pulmonary veno-occlusive disease (an exceedingly rare cause of chronic pulmonary hypertension which may be associated with CREST syndrome and scleroderma).

Anti-platelet effects (nitric oxide & epoprostenol, rare)

- Both nitric oxide and epoprostenol are felt to exert some anti-platelet effects.
- The magnitude of these effects and their clinical impact are unclear and somewhat dubious. It might be wise to avoid these agents in patients with active hemorrhage (especially intracranial), but otherwise this doesn't seem to be very relevent clinically.

Methemoglobinemia (nitric oxide, rare)

- Methemoglobinemia may occur when nitric oxide is given for prolonged time periods at high doses (usually >20 ppm). (24734313)
- Some guidelines recommend routine measurement of methemoglobin (e.g., daily). However, it’s unclear whether this is necessary if NO is provided at doses of 0-20 ppm. (30172035)
- The IBCC chapter on methemoglobinemia is here.

Renal dysfunction (nitric oxide, rare)

- Meta-analysis suggests that NO can increase the risk of acute kidney injury. However, this effect seems limited to its use at higher doses (e.g., >20 ppm) for prolonged periods of time (e.g., >7 days). (25887847)
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**Deposition on ventilator circuit** *(epoprostenol in glycine diluent, rare)*

- Epoprostenol, when reconstituted in glycine, may lead to deposition of glycine diluent on components of the respiratory circuit (e.g., exhalation valves). ([28323647](https://pubmed.ncbi.nlm.nih.gov/28323647/)) This doesn't seem to be a major problem. However, some attention to the ventilator circuit may be prudent, so that components can be replaced if they become dysfunctional.
- This problem might be limited to brands of epoprostenol which are reconstituted in glycine (e.g., FLOLAN).

Pulmonary vasodilators function as a bridge

Pulmonary vasodilators may cause a host of physiologic improvements (e.g., improved oxygenation, improved ventilation, and improved right ventricular function). Unfortunately, these improvements are short-lived. In the case of nitric oxide, the drug itself becomes less effective over a period of days. Epoprostenol may remain effective for a bit longer, but inhaled epoprostenol therapy can't be continued forever.

Therefore, inhaled pulmonary vasodilators must inevitably function as temporary bridges to stabilize the patient, until transition to another treatment. Some examples include:

- Bridge to another therapy (e.g., ECMO or thrombolysis).
- Bridge to pulmonary or myocardial recovery (e.g. right ventricular myocardial infarction will often recover within a few days following revascularization).
- Bridge to a chronic intravenous systemic pulmonary vasodilator (very rarely, in patients with chronic pulmonary hypertension).

A bridge is effective only if there is somewhere to go at the end of the bridge. Thus, pulmonary vasodilators cannot directly save lives – they merely sustain some patients in the hopes that another therapy will save the patient. This leads to considerable confusion, because pulmonary vasodilators may function perfectly well, yet fail to produce clinical benefit if there is no destination to bridge the patient towards.

Pulmonary vasodilators in ARDS

**Concept**

- Potential mechanisms of benefit:
  - (1) Improvement in oxygenation
  - (2) Reduction of pulmonary hypertension and acute RV dysfunction (which is a common problem among intubated ARDS patients)
- An optimal candidate for pulmonary vasodilator therapy in ARDS might be a patient with refractory hypoxemia plus right ventricular dysfunction. In particular, the subset of ARDS patients who experience right-to-left shunting through a patent foramen ovale who might be ideal candidates for inhaled pulmonary vasodilators.

**Evidence**

[https://emcrit.org/ibcc/pulmvaso/](https://emcrit.org/ibcc/pulmvaso/)
Inhaled pulmonary vasodilators have been shown to improve oxygenation and to reduce pulmonary pressures. Inhaled pulmonary vasodilators have not been shown to improve mortality. Although this might seem disappointing, it's actually fairly predictable. There are several reasons that inhaled pulmonary vasodilators wouldn't be expected to affect mortality in heterogeneous groups of ARDS patients:

- (1) Most ARDS patients die from multi-organ failure, not hypoxemia. Therefore, a therapy which improves oxygenation won't affect the most common cause of death.
- (2) Studies are generally underpowered to detect small differences in mortality.
- (3) Pulmonary vasodilators function only as transient bridges to other treatments. They don't treat the underlying pathophysiology of ARDS.

Further exploration of why medications predictably fail to improve mortality in critical care RCTs is here and here.

**bottom line?**

- Inhaled pulmonary vasodilators should **not** be used routinely in ARDS patients.
- Inhaled pulmonary vasodilators may be used to transiently stabilize ARDS patients who are failing to respond to other treatments, as a bridge to more definitive therapy.
  - For example, ARDS patients commonly deteriorate immediately following intubation (e.g., with hypotension and hypoxemia). Patients will often respond to positive pressure ventilation with recruitment, but this is a gradual process which may take several hours. Inhaled pulmonary vasodilators may be useful as an initial therapy to stabilize patients in the post-intubation period, acting as a bridge to other treatments (e.g. proning, APRV ventilation, or ECMO).
- The best candidates for inhaled pulmonary vasodilators might be patients with two or more of the following clinical features:
  - Hypoxemia refractory to conventional therapy.
  - Right-to-left intra-cardiac shunt through a patent foramen ovale.
  - Right ventricular dysfunction (e.g. due to acute or chronic pulmonary hypertension).

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**pulmonary vasodilators in acute pulmonary embolism**

**concept**

- Patients with massive PE don't die from hypoxemia; they die from cardiovascular collapse due to acute pulmonary hypertension. Thus, any intervention to reduce the pulmonary hypertension could be valuable.
- Much of the hemodynamic deterioration due to PE isn't due to the clot itself, but rather to pulmonary vasoconstrictors which are released in response to the clot. To make matters even worse, severe PE appears to cause depletion of normal nitric oxide levels! Exogenous pulmonary vasodilators are a rational approach to counteract this.
- Compared to systemic vasoconstrictors (e.g., norepinephrine), inhaled pulmonary vasodilators offer the ability to improve cardiac output without increasing right ventricular workload.

**evidence**

- Case series describe the successful use of nitric oxide to stabilize patients with massive PE. ([22005573](https://pubmed.ncbi.nlm.nih.gov/22005573/), [16598645](https://pubmed.ncbi.nlm.nih.gov/16598645/)).
- The INOPE trial randomized 76 patients with submassive PE to placebo vs. inhaled nitric oxide at 50 ppm for 24 hours. ([30633959](https://pubmed.ncbi.nlm.nih.gov/30633959/)).
  - The primary endpoint was a composite of having both a normal right ventricle on echocardiography and a high-sensitivity troponin <14 pg/mL. Patients treated with NO had a nonsignificant improvement in meeting this endpoint. Since this is a composite, binary endpoint, it may have lacked the sensitivity to detect improvement in this relatively small patient population.
  - Post-hoc analysis did suggest that NO improved right ventricular function after 24 hours.
  - Nitric oxide appeared to be safe.

**bottom line?**

- Pulmonary vasodilators shouldn't be used routinely for PE patients (especially for patients with low-risk submassive PE who are hemodynamically stable).

https://emcrit.org/ibcc/pulmvaso/
Pulmonary vasodilators appear useful to temporarily stabilize patients with massive PE or high-risk submassive PE, as a bridge to more definitive therapy (e.g., systemic thrombolysis or mechanical clot extraction). This may be especially true of inhaled nitroglycerine, which is generally available at the bedside within minutes (faster than most other potential therapies).

### Pulmonary vasodilators in decompensated pulmonary hypertension

- Inhaled pulmonary vasodilators may reduce pulmonary pressures and thereby facilitate forward blood flow through the right heart. This may be useful in decompensated chronic pulmonary hypertension. Similarly, pulmonary vasodilators may be useful to prevent decompensation for these patients undergoing surgery (both intraoperatively and postoperatively).
- Pulmonary vasodilators may be especially useful immediately following intubation, when patients with pulmonary hypertension have a tendency to experience cardiac arrest. It's possible that immediate initiation of an inhaled pulmonary vasodilator could help stabilize these patients in the peri-intubation period, until they have had some time to accommodate to mechanical ventilation.
- For patients with chronic pulmonary hypertension and acute volume overload leading to congestive organ failure (e.g. congestive nephropathy), inhaled pulmonary vasodilators could facilitate temporary decongestion and improved organ function. This could serve as a bridge to diuresis. ([30216198](https://pubmed.ncbi.nlm.nih.gov/30216198/))

### Pulmonary vasodilators in right ventricular myocardial infarction

#### Concept
- Right ventricular myocardial infarction is somewhat unique compared to other disease states discussed above, in that it involves right ventricular pump failure (without elevated pulmonary vascular resistance). Nonetheless, the same fundamental problem exists – mismatch between the right ventricular contractility versus the pulmonary vascular resistance (the right ventricular after-load).
- Inhaled pulmonary vasodilators will reduce the right ventricular afterload, thereby decongesting the right ventricle and promoting forward blood flow. This is analogous to the use of systemic afterload reduction for patients with left ventricular infarction (i.e., inhaled nitroglycerine instead of intravenous nitroglycerine). Pulmonary vasodilators have an advantage compared to systemic administration of inotropes (e.g., dobutamine), since pulmonary vasodilators can improve perfusion while simultaneously reducing myocardial workload – and thereby reduce myocardial ischemia.
- Inhaled pulmonary vasodilators could represent a relatively simple and safe alternative to percutaneous insertion of a right ventricular assist device (RVAD).

#### Evidence
- RCT-level evidence doesn't exist for RV myocardial infarction, since such a rare condition is difficult to study with RCTs. For example, RCT-level evidence doesn't exist to support the placement of a percutaneous right ventricular assist device (RVAD) either.
- One RCT did evaluate the use of nitric oxide within a broader population of patients with STEMI. Nitric oxide was found to be safe, with some trends towards improved outcomes. This study supports the safety of using nitric oxide in patients with myocardial infarction. ([29800130](https://pubmed.ncbi.nlm.nih.gov/29800130/))
- Inhaled nitric oxide has been shown to increase cardiac output among patients with RVMI, without causing hypotension (figure below). ([15312861](https://pubmed.ncbi.nlm.nih.gov/15312861/))
- Case reports describe patients with refractory cardiogenic shock who have responded to inhaled pulmonary vasodilators, including both nitric oxide and epoprostenol. ([28298620](https://pubmed.ncbi.nlm.nih.gov/28298620/), [20674235](https://pubmed.ncbi.nlm.nih.gov/20674235/)).
summary

The Internet Book of Critical Care Summary

Quick-start guide to pulmonary dilators

Who is a good candidate?

- ARDS with refractory hypoxemia
- Decompensated chronic pulmonary hypertension
- Crashing pulmonary embolism patient
- Shocked patient with right ventricular MI

Contraindications / Adverse effects

- Can worsen cardiogenic pulmonary edema 2/2 LV failure.
- Epoprostenol or NO may impair platelet function, avoid in hemorrhage

Which agent to use?

- All agents have similar efficacy, use whatever you have.
- Nitroglycerine or milrinone are useful in crashing patients, because they can be obtained immediately and given through nebulizers (no special setup required). Nitric oxide or Epoprostenol are usually used for ongoing maintenance therapy.

Dosing of different agents

Nitroglycerine

- 5 mg nebulized over 1.5 minutes, repeat PRN (lasts ~30 min).
- A continuous nebul using 200-400 mcg/ml solution may be reasonable until nitric oxide or Epoprostenol is available (this utilizes the nitroglycerine solution for IV administration that is pre-mixed in large glass bottles).

Milrinone

- Same dose as nitroglycerine (5 mg nebulized).
- May give 2.5 mg via ETT as a bolus in a peri-arrest patient.
- Lasts longer than nitroglycerine, may be repeated q3-4 hr.

Nitric Oxide (NO)

- Intubated or via high-flow cannula: Start at 20 parts per million.
- Administered via nasal prongs: Start at 20-50 parts per million.
- May wean down gradually as patient improves.

Epoprostenol

- Start at 50 ng/kg/min (max dose).
- May wean down gradually as patient improves.
Confusion between inhaled versus intravenous routes for pulmonary vasodilators. For optimal clinical benefit (especially regarding oxygenation), these agents must be given via an inhaled route.

The misconception that inhaled pulmonary vasodilators can only be used among intubated patients.

Under-utilization of pulmonary vasodilators among patients with right ventricular failure (e.g. leading to the requirement for a right ventricular assist device).

**Going further:**


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