

Pulmonary vasodilation in acute pulmonary embolism – a systematic review

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Abstract

Acute pulmonary embolism is the third most common cause of cardiovascular death. Pulmonary embolism increases right ventricular afterload, which causes right ventricular failure, circulatory collapse and death. Most treatments focus on removal of the mechanical obstruction caused by the embolism, but pulmonary vasoconstriction is a significant contributor to the increased right ventricular afterload and is often left untreated. Pulmonary thromboembolism causes mechanical obstruction of the pulmonary vasculature coupled with a complex interaction between humoral factors from the activated platelets, endothelial effects, reflexes and hypoxia to cause pulmonary vasoconstriction that worsens right ventricular afterload. Vasoconstrictors include serotonin, thromboxane, prostaglandins and endothelins, counterbalanced by vasodilators such as nitric oxide and prostacyclins. Exogenous administration of pulmonary vasodilators in acute pulmonary embolism seems attractive but all come with a risk of systemic vasodilation or worsening of pulmonary ventilation-perfusion mismatch. In animal models of acute pulmonary embolism, modulators of the nitric oxide-cyclic guanosine monophosphate-protein kinase G pathway, endothelin pathway and prostaglandin pathway have been investigated. But only a small number of clinical case reports and prospective clinical trials exist. The aim of this review is to give an overview of the causes of pulmonary embolism-induced pulmonary vasoconstriction and of experimental and human investigations of pulmonary vasodilation in acute pulmonary embolism.

Keywords

right heart failure, pulmonary circulation, animal models, right ventricular afterload

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Introduction

Acute pulmonary embolism (PE) occurs in about 1 in 1000 persons per year and is associated with a high morbidity and mortality,^{1,2} making PE the third most common cause of cardiovascular death in Europe. Cause of death in PE is right ventricular (RV) failure caused by a combination of mechanical obstruction and pulmonary vasoconstriction, which both increases RV afterload.^{3,4}

In PE, the thrombus lodges in the pulmonary arteries and causes immediate mechanical obstruction. The embolism activates the coagulation system, damages the endothelium, stagnate pulmonary blood flow and accordingly initiate secondary pulmonary thrombosis which worsens the mechanical obstruction.^{5,6}

RV dysfunction is related to short-term clinical deterioration⁷ and prognosis.^{4,8–10} Mechanical obstruction alone cannot explain the increased RV afterload and consequent RV dysfunction in PE (Fig. 1). Pulmonary vascular resistance (PVR) does not increase until approximately 50% of the pulmonary vasculature is embolized,⁶ and thrombus mass and percentage of pulmonary vascular obstruction alone correlate poorly to the hemodynamic compromise^{11,12} and prognosis in PE.^{13–15}

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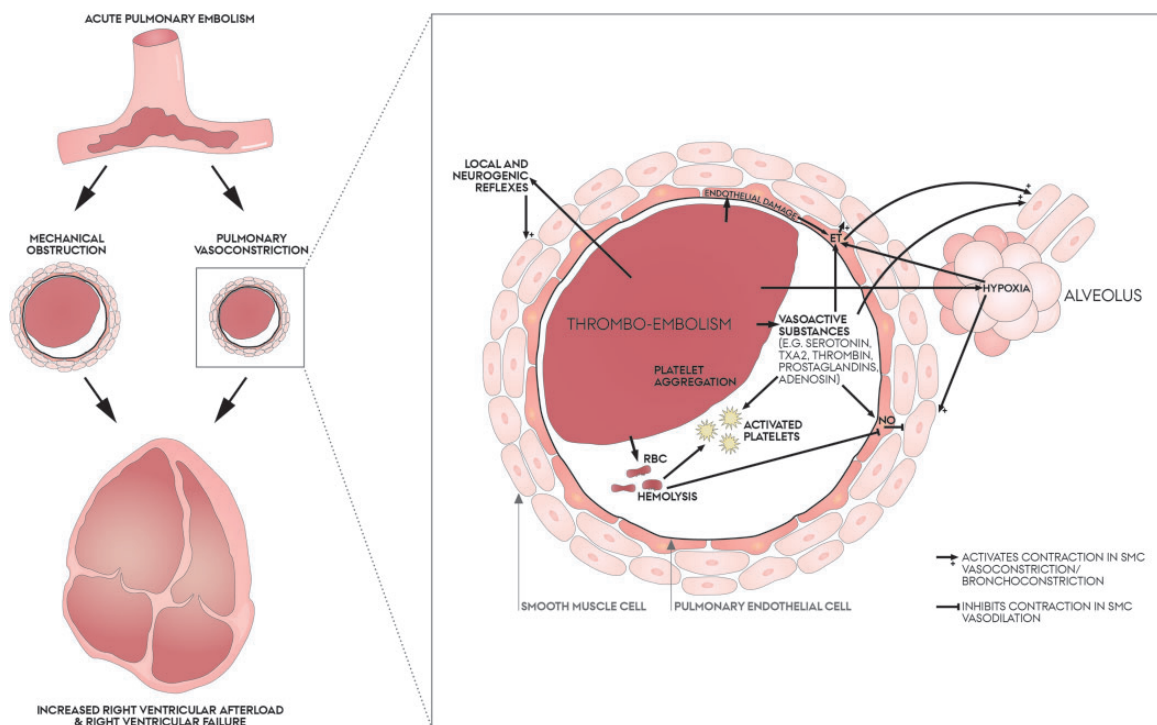


Fig. 1. On the left, a schematic pathway showing acute pulmonary embolism (PE) to cause both mechanical obstruction of pulmonary arteries and pulmonary vasoconstriction. Both increases right ventricular (RV) afterload causing acute RV dilatation and interventricular septal shift which have been associated specifically with severe, acute PE. The RV may enter a vicious circle of right ventricular failure, circulatory collapse and death. On the right, focus on pulmonary vasoconstriction induced by a pulmonary embolism. Several mechanisms are potential underlying causes: vasoactive substances from the thrombus, hemolysis, activated platelets, endothelial damage, reflexes, and hypoxia. Please see the text for further details.

ET: endothelins; NO: nitric oxide; PEC: pulmonary endothelial cell; RBC: red blood cell; SMC: smooth muscle cell; TXA2: thromboxane A2.

This mismatch between thrombus mass and hemodynamic compromise raises the hypothesis that humoral responses and reflexes activated by the thrombus induce pulmonary vasoconstriction.

Key element in the treatment of PE is reduction of the thrombus mass. But this strategy only targets the mechanical component of the RV afterload increase. According to current guidelines, there are no recommended treatments targeting pulmonary vasoconstriction^{4,16} and its use is not reported in large registries,¹⁷ leaving a significant contributor to the adverse outcome in PE untreated.

Several experimental PE studies have shown a significant reduction in PVR using pulmonary vasodilators that targets a variety of pathways involved in pulmonary vascular tone.¹⁸ Despite evidence from pre-clinical studies, the clinical literature is dominated by case series and few small clinical trials using pulmonary vasodilators in PE.

We aim to provide a clinically relevant introduction to the mechanisms that induce pulmonary vasoconstriction in PE and a comprehensive review of both pre-clinical and clinical studies using pulmonary vasodilators in acute PE.

Methods

We searched MEDLINE via PubMed and Embase for relevant articles with latest update 13 September 2019 (see Appendix 1 for full search strategies).

Articles describing a medical intervention causing pulmonary vasodilation in acute PE using a clinically relevant drug were included. Both human and animal studies were included no matter the year of publication.

Exclusion criteria included especially studies on chronic thromboembolic pulmonary hypertension (CTEPH) and the other causes of pulmonary hypertension (PH) within the World Health Organization classification of PH. Please see Appendix 1 for full list of inclusion and exclusion criteria.

Pulmonary vasoconstriction in acute PE

Pulmonary vasoconstriction is a significant contributor to the increase of PVR in PE. This happens through a number of pathways which are not understood completely. The mechanisms are summarized in Fig. 1.

Hematogenous thromboembolism increases pulmonary arterial pressure (PAP) more effectively than

non-hematogenous material,¹⁹ emphasizing the importance of PE-released vasoconstrictors. Evidence of these humoral or other chemicals was shown more than half a century ago.²⁰ Activated platelets and the thrombus mass^{21–23} secrete thromboxane- A_2 , prostaglandins, adenosine, thrombin, and serotonin^{19,23–27} which induce platelet aggregation and pulmonary vasoconstriction.^{5,19,28} Platelet-activating factor is also increased with acute PE.²⁹ Pulmonary endothelial cells inactivate serotonin and certain prostaglandins³⁰ to maintain homeostasis.

Endothelins (ET) are produced by the pulmonary vascular endothelium when stimulated by thrombin, endothelial injury and hypoxia. ET target the ET_A and ET_B receptors in the smooth muscle cells, and pulmonary vasoconstriction is induced by activation of phospholipase C that increases inositol triphosphate, diacylglycerol and intracellular calcium.^{31,32} ET have been estimated to be in charge of 25% of the PE-induced increase in PVR,³³ but findings are variable.³⁴ ET also induce bronchoconstriction and release of TxA_2 which further potentiate the pulmonary vasoconstrictor effect.³⁵

Prostaglandins cause either smooth muscle contraction or relaxation, depending on the prostaglandin subtype and receptor subtype.¹⁹ Smooth muscle contraction and subsequent vasoconstriction are mediated through receptor coupling with the phospholipase C pathway.³⁶ In acute PE, elevated levels of prostaglandins that induce vasoconstriction have been observed,^{26,37} but prostaglandins may prevent the release of other vasoconstrictors.³⁸ The clinical significance and the net pulmonary vasoconstrictor effect after vasodilation triggered by concomitant prostacyclin release are not known in acute PE.^{39,40}

Histamine release may also play a role in acute pulmonary embolism but have only been sparsely investigated making the clinical significance unknown.^{41,42}

Hemolysis is present in PE causing a release of arginase which converts L-arginine to L-orthinine and urea. Otherwise, L-arginine would have had potential to produce L-citrulline and nitric oxide (NO) catalyzed by nitric oxide synthase. The consequence is reduced availability of NO as vasodilator.⁴³ Additionally, released free heme and hemoglobin (Hb) reacts fast and irreversible with NO and further limits bioavailability of NO.^{44,45} This is normally counteracted by heme oxygenase-1⁴⁵ and by haptoglobin, but haptoglobin is decreased in PE patients.⁴⁶ As NO causes pulmonary vasodilation, hemolysis can be an indirect cause of vasoconstriction.⁴⁷ Hemolysis-released adenosine di-phosphate and free Hb enhance platelet activation⁴⁸ which may cause further obstruction of the pulmonary vessels.

Furthermore, PE-induced vasoconstriction is augmented by local and neurogenic reflexes that might be dependent on localization of the PE.^{19,49,50} Sympathetic activity seems to be increased in both embolized and non-embolized parts of the lung.⁵¹ PE-released substances also cause bronchoconstriction of the small airways,^{23,42,52} leading to hypoxia and

pulmonary vasoconstriction.⁵³ Hypoxia in the lung tissue will inhibit synthesis of vasodilating prostanoids and worsen vasoconstriction.³⁸

For a summary, see Fig. 1. The different mechanisms of pulmonary vasoconstrictors in PE have been reviewed in details previously.^{6,18,19,35,54}

Results

Literature search resulted in 1510 papers and additional five were found by hand search. See Fig. 2 for flow chart on the screening process. A total of 92 papers were included in this review (summarized in Tables 1 to 4).

Here we provide a detailed review of experimental and clinical studies investigating the effects of pulmonary vasodilators in PE. For clarity of presentation, we divided these into four categories based on mechanism of action which will be presented first. The included articles will be presented with the experimental research followed by case reports and clinical studies. Tables 1 to 4 summarize the effects of pulmonary vasodilation in PE according to our review of the literature divided by pathway or mechanism.

NO-sGC-cGMP pathway

The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway exerts its pulmonary vasodilatory effects through paracrine interaction between the pulmonary endothelial cells (PEC) and the underlying smooth muscle cells (SMC). In the PEC, either shear stress or a humoral activator (e.g. serotonin, thrombin) causes increasing cytosolic levels of Ca^{2+} which activates the NO synthase.^{55,56} The active enzyme deaminates L-arginine to L-citrulline and NO. NO diffuses to the SMC where it activates sGC that dephosphorylates guanosine tri-phosphate (GTP) to cGMP which again activates cGMP-dependent protein kinase. Subsequently, sarcoplasmic Ca^{2+} -pumps are activated causing decreased cytosolic Ca^{2+} levels⁵⁷ and decreased activation of calmodulin that otherwise is essential in the activation of myosin light-chain kinase and the myosin-actin cross-bridge cycle.⁵⁸ As this is interrupted, the SMC relaxes and vasodilation occurs.

Nitric oxide. Inhaled NO (iNO) acts as a selective pulmonary agent. It has been suggested to have dual effects, i.e. pulmonary vasodilation through the above-mentioned mechanism in ventilated regions and pulmonary vasoconstriction through inhibition of endogenous NO synthase, most pronounced in hypoxic regions. Therefore, iNO can attenuate ventilation-perfusion mismatch and improve oxygenation.⁵⁷ iNO can dilate the non-constricted pulmonary vasculature and works in combination with inhaled prostacyclin.⁵⁹ NO protects (partly) from PE-induced changes in hemodynamics and both expression of endothelial NO synthase mRNA and the fraction of expiratory NO increases in

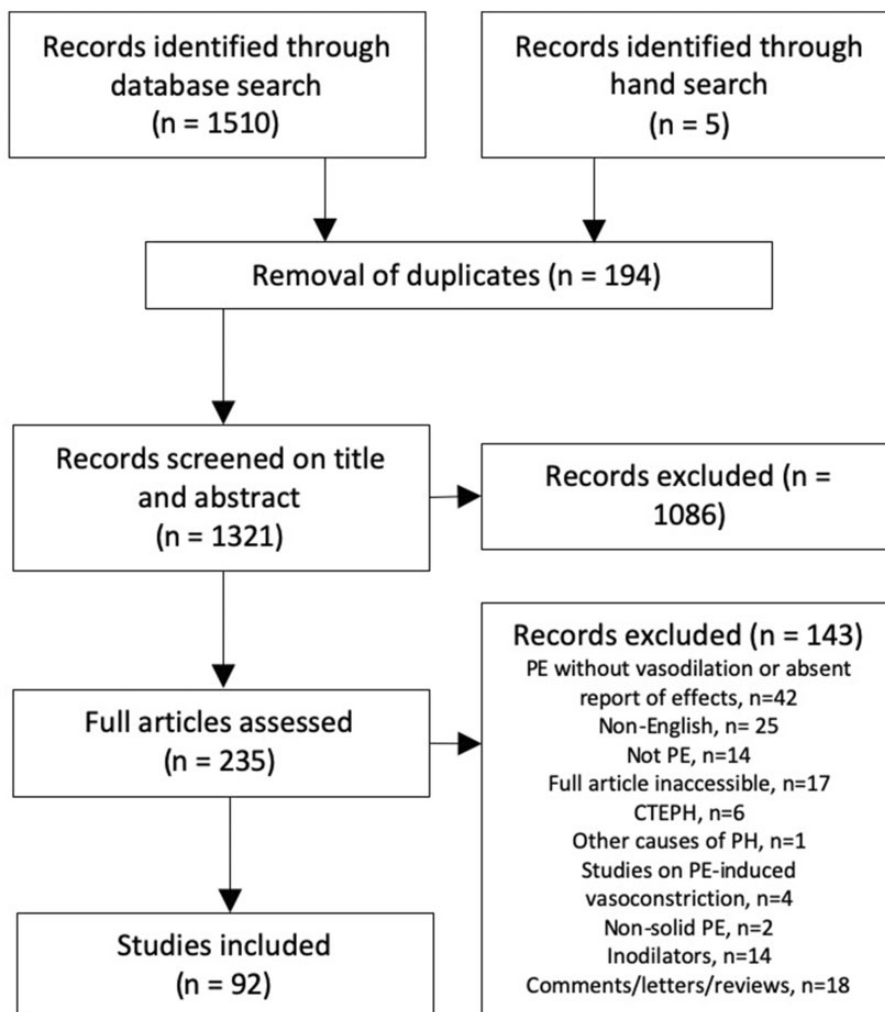


Fig. 2. Flow diagram of the review selection process.
CTEPH: chronic thromboembolic pulmonary hypertension; PE: pulmonary embolism.

PE.^{60–62} NO consumption increases in both animals and humans with PE,⁶³ and the endogenous NO production seems lifesaving in PE as antagonism of NO synthase causes death in PE-animals.^{62,64} Accordingly, iNO has a potential therapeutic role in PE.

In general, iNO lowered PAP and PVR in animal models^{65–76} and increased cardiac output (CO) in some studies.^{70,72} The effect is possibly caused by reduced pulmonary vascular tone in the periphery of the pulmonary artery tree, especially regions with distally localized emboli.⁷³ The reduced RV afterload might explain less myocardial damage evident by lowered cardiac troponins.^{65,76,77} One study using fat-emboli in a canine model did, however, not detect any effects on pulmonary or cardiac function.⁷⁸ Due to the rationale of inhaled administration, only one study noticed effect on the systemic vasculature with decreased mean arterial pressure (MAP).⁶⁸ Some studies investigated dose–response relationship without consistent results,^{67,68} suggesting low-dose treatment to be favorable. iNO can be useful in combination with other treatment

strategies where the agents showed additive effects on PAP, PVR or vessel diameter.^{59,72} The effects of iNO seem to be without prolonged effects.⁶⁹

Other NO-donors have also been tested in animal models of PE. Both nitroglycerin, nitrite and nitroprusside lower mean PAP^{51,79–81} and PVR^{80,82–86} but not always.⁸⁷ One must be aware that systemic administration of NO-donors increases the risk of systemic side effects with decrease in MAP, systemic vascular resistance (SVR) or stroke volume,^{79,82,83,85,88} but not consistently.^{51,81,84,87} Combination of NO-donor and other vasodilators may be even more efficient but increases the risk of side effects.⁸⁶ NO-donor lowered sympathetic activity in the lungs, lowered ET-1 levels and increased NO levels.⁵¹

NO has additional non-hemodynamic effects. iNO lowers von Willebrand factor and glycoprotein IIb/IIIa as central parts in endothelial function and thrombosis.⁷⁶ NO affects apoptotic pneumocytes,⁷⁴ and both endogenous and exogenous NO inhibits platelet aggregation in animals and humans^{67,89–91} which might be relevant in PE.

Table 1. Vasodilation through the NO-sGC-cGMP pathway in acute pulmonary embolism.

Treatment	Experimental glass beads/air PE	microsphere/	Experimental autologous (blood, fat, muscle, collagen) PE	Case reports	Clinical trials	Guideline recommendation
Nitric oxide	Lowers PVR, mPAP but not MAP. ^{66,68-71,73,80,84-86} No effect on mPAP but increase in CO. ⁸⁷	Lowers PVR, mPAP, increases CO. ^{51,65,67,72,74-76,79,81-83} Lowers cardiac damage. ^{65,76,77} No hemodynamic effects. ⁷⁸ Decreased stroke volume ⁸⁸ or MAP/SVR ^{79,83}	Lowers PVR, mPAP, increases CO. ^{92-94,96,108} Five cases in combination with thrombolysis, thrombectomy or embolectomy ^{97,99-102} Five cases of post-operative PE ^{98,107} Two PE cases in patients with PFO or VSD ^{106,109} One post-partum patient with PE ⁹⁵ Four pediatric cases ¹⁰³⁻¹⁰⁵ One case of autoimmune hemolytic anaemia ⁴⁷ One PE case with deterioration on iNO ¹¹⁰	Eight patients, single arm. Safe. Trend towards improvement. ¹¹² iNOPE trial, double-blinded, 78 patients with intermediate-high-risk PE randomized to iNO + O ₂ or placebo. Neutral on both endpoints ¹¹¹	Either no recommendations ¹⁶ or "Inhalation of nitric oxide may improve the hemodynamic status (. . .) no evidence for its clinical efficacy or safety." ⁴	
sCG stimulators/activators	Lowers mPAP and PVR. Risk of decreased MAP. ^{84,118-120}	Lowers PVR and mPAP and increases CO ⁷⁵	None	None	No recommendations ^{4,16}	
PDE-5 inhibitors	Lowers mPAP and PVR, no effect on MAP. ^{84,86,126-131}	Lowers mPAP and PVR ^{75,124,125}	Three PE cases ^{136,138,139} One case of acute-on-chronic PE ¹³⁷ One case with congenital VSD ¹⁰⁹ Two cases of post-operative PE ^{98,135} One child with non-thrombotic PE ¹⁴⁰	None	No recommendations ^{4,16}	

Note: Summary of review of the NO-sGC-cGMP pathway to induce pulmonary vasodilation in acute pulmonary embolism. Divided by treatment option, animal or clinical data and guideline recommendation. Please see text for further details.
 CO: cardiac output; iNO: inhaled nitric oxide; MAP: mean arterial pressure; mPAP: mean pulmonary arterial pressure; NO: nitric oxide; PAP: pulmonary artery pressure; PE: pulmonary embolism; PFO: persistent foramen ovale; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; VSD: ventricular septal defect.

Table 2. Prostaglandin-induced pulmonary vasodilation in acute pulmonary embolism.

Treatment	Experimental microspheres/glass beads/air-PE	Experimental autologous (blood, fat, muscle, collagen) PE	Case reports	Clinical trials	Guideline recommendation
Prostaglandins	Positive effects on PAP, PVR and lung function. ^{80,143,156-158} No effects compared to NO. ⁶⁶ Risk of side effects ¹⁵³	Lowers mPAP and PVR. ^{25,146,151,154,155} Risk of side effects or no pulmonary effects. ^{79,88,152,153}	Eight PE cases ¹⁶⁰⁻¹⁶² One case with CO ₂ -embolism ¹⁵⁹ One newborn with no effect ¹⁰⁵	14 Patients randomized to intravenous epoprostenol or placebo, no effect ¹⁶³	No recommendations ^{4,16}

Note: Summary of review of the different prostaglandins causing pulmonary vasodilation in acute pulmonary embolism. Divided by animal or clinical data and guideline recommendation. Please see text for further details.

mPAP: mean pulmonary arterial pressure; NO: nitric oxide; PAP: pulmonary artery pressure; PE: pulmonary embolism; PVR: pulmonary vascular resistance.

NO has been used clinically in acute PE inspired by the experimental results and by the experience from using NO as a pulmonary vasodilator in acute respiratory distress syndrome and pulmonary hypertension.

A large variety of case reports have been published on the use of iNO, ranging from iNO administered to patients with RV failure (including PE-induced) as primary indication; as bridge to embolectomy or thrombolysis; with acute-on-chronic PE; during PE-induced cardiac arrest; on extra-corporal membrane oxygenation (ECMO) support or in case of contraindication to thrombolysis.⁹²⁻⁹⁸ Some cases describe the use of iNO to treat increased PAP after embolectomy of acute PE⁹⁹⁻¹⁰¹ though not all with impressive hemodynamic responses.¹⁰² iNO has been used in children and even infants with PE without success.¹⁰³⁻¹⁰⁵ The influence of hemolysis on pulmonary vasoconstriction was evident in a case of autoimmune hemolytic anaemia, where PAP was significantly elevated despite only small clot burden, and iNO had impressive effect.⁴⁷ One case described how iNO closed a persistent foramen ovale in a patient with PE and multiple cerebral infarcts.¹⁰⁶

A number of case reports describe significant or even dramatic positive hemodynamic effects of iNO, and the effects seem to be present shortly after beginning of treatment^{47,93-95,99,107-109} and at low doses.^{97-99,108} Whether these temporal improvements represent the direct effect of iNO remain uncertain.

iNO might also have negative effects. Case report data suggest that iNO-induced pulmonary vasodilation might worsen ventilation-perfusion mismatch and decrease oxygenation. Bhorade et al.⁹² only saw two of four PE patients with RV failure to respond to iNO. Tulleken et al.¹¹⁰ reported a case with a patient in cardiogenic shock due to PE and even low-dose iNO rapidly worsened PaO₂ and saturation. The side effects disappeared when iNO was withdrawn. This patient may have had undiagnosed CTEPH, but the risk must be taken into consideration. Conversely, three of four patients reported by Capellier et al.⁹⁴ presented with acute PE and a history of PE, and iNO showed positive effects in all cases.

Clinicians must remember that iNO does carry a risk of toxicity and adverse effects. NO can result in formation of methemoglobin or the oxidants NO₂ or ONOO⁻ causing oxidant damage to lung tissue.⁵⁷ However, in 38 patients receiving 50 ppm iNO by nasal cannula for 24 h, methemoglobin never increased¹¹¹ showing that side effects are avoidable by use of low dose iNO and close clinical surveillance. Withdrawal of iNO can result in rebound pulmonary hypertension which is why cessation must be preceded by gradual down titration of the dose.⁵⁷

The experimental studies and case reports led to a more systematic testing of a protocol to administer iNO in eight patients with acute PE. The protocol was deemed safe and there was a trend toward improvement in Borg dyspnea score.¹¹² This single arm, phase I study was followed by the phase II, iNOPE trial:¹¹³ a double-blinded, randomized,

Table 3. Antagonism of endothelin in acute pulmonary embolism.

Treatment	Experimental microsphere/glass beads/air PE	Experimental autologous (blood, fat, muscle, collagen) PE	Case reports	Clinical trials	Guideline recommendation
Endothelin antagonism	Lowers mPAP and PVR ^{85,173,174,176,177}	Lowers mPAP and PVR, increases CO ^{33,72,171,172,175}	None	None	No recommendations ^{4,16}

Note: Summary of review of the endothelin antagonists to cause pulmonary vasodilation in acute pulmonary embolism. Divided by animal or clinical data and guideline recommendation. Please see text for further details.

CO: cardiac output; mPAP: mean pulmonary arterial pressure; PE: pulmonary embolism; PVR: pulmonary vascular resistance.

Table 4. Hydralazine-induced pulmonary vasodilation in acute pulmonary embolism.

Treatment	Experimental microsphere/glass beads/air PE	Experimental autologous (blood, fat, muscle, collagen) PE	Case reports	Clinical trials	Guideline recommendation
Hydralazine	Divergent effects on PVR. ^{80,185} May improve CO ⁸⁰	Lowers PAP and PVR, improves CI. ^{79,82,88,184} May lower MAP ⁷⁹	Six PE cases with limited effect ¹⁸⁷ One case with postoperative PE with positive effect ¹⁸⁶	None	No recommendations ^{4,16}

Note: Summary of review of the hydralazine-induced pulmonary vasodilation in acute pulmonary embolism. Divided by animal or clinical data and guideline recommendation. Please see text for further details.

CI: cardiac index; CO: cardiac output; MAP: mean arterial pressure; PAP: pulmonary artery pressure; PE: pulmonary embolism; PVR: pulmonary vascular resistance.

multicenter trial where 76 patients with intermediate-high risk PE were randomized 1:1 to iNO (up to 50 ppm, delivered by nasal cannula) plus oxygen or nitrogen placebo at 50 ppm.¹¹¹ The composite endpoint was complete normalization of troponins and RV function on echocardiogram after 24 h. The study was neutral on its primary and secondary endpoints but did show positive effects on RV hypokinesis and dilatation.¹¹¹

For summary, please see Table 1.

Soluble guanylate cyclase. The dimeric enzyme, soluble guanylate cyclase (sGC) is activated by NO and catalyzes the second messenger cGMP from GTP.¹¹⁴ From a pharmacological perspective, the sGC enzyme has two oxidative states that determine its ability to produce cGMP. The constitutive, non-oxidized sGC enzyme contains a prosthetic heme moiety that binds NO and allows cGMP production, and can also increase cGMP production in the presence of specifically designed organic molecules known as “sGC stimulators”. For example, the sGC stimulator Riociguat is approved for the treatment of CTEPH but not acute PE. However, when exposed to oxidant stress, the sGC enzyme discharges the NO-binding the heme moiety and therefore cannot bind NO, but can be activated by an exosite with specifically designed organic molecules known as “sGC activators”.¹¹⁵ One commercially available activator is cinaciguat, which has been tested in humans with heart failure, but not in humans with PE. An important hypothetical consideration is that acute PE appears to produce an oxidative state in circulating platelets¹¹⁶ suggesting the possibility of

pulmonary arterial endothelial sGC oxidation, which may impair effectiveness of iNO. PE-induced platelet hyperactivity (evident by increased cytosolic concentration of Ca²⁺) was not affected by iNO, but the Ca²⁺ concentration was suppressed by activation, but not stimulation, of sGC (unpublished data).

Regardless of its effect on sGC in the pulmonary vascular endothelial cells, stimulation of sGC also inactivates platelets and prolongs bleeding time¹¹⁷ which might be salutary in patients with PE.

A few animal studies have investigated the hemodynamic effects of sGC in PE, mostly in models of non-autologous PE material. The sGC stimulator BAY 41-8543 abolished the PE-induced hemodynamic changes, lowered blood lactate and PVR and increased CO.^{118,119} The stimulator BAY 41-2272 lowered PAP and PVR^{84,120} and even showed a dose–response relationship. However, the highest dose decreased MAP and SVR, too.¹²⁰ In a porcine model of autologous PE, Riociguat lowered PVR in a dose-dependent manner and increased CO at high doses.⁷⁵ See Table 1 for summary.

Our review did not find any clinical reports on the use of sGC-stimulation in PE in humans.

Phosphodiesterase-5 inhibitors. Cyclic guanosine monophosphate (cGMP) is the active second messenger in relaxation of SMC and pulmonary vasodilation. cGMP is inactivated by phosphodiesterase-5 (PDE-5).¹²¹ Inhibiting PDE-5 (e.g. with sildenafil) will increase the level of cGMP and cause pulmonary vasodilation. Inhibition of PDE-5 prevents

hemodynamic changes in fat-embolism,¹²² suggesting the pathway also to be part of PE-pathophysiology. Non-specific PDE inhibition does reduce PAP and PVR without effects on MAP in PE.¹²³

In models of autologous PE, sildenafil improved hemodynamics in PE, though with a risk of decreased SVR.^{75,124,125} Sildenafil seems to prevent oxidative stress, nitric oxide consumption and pulmonary arterial endothelial apoptosis; effects that were enhanced by antioxidative N-acetylcysteine.¹²⁵

In a number of animal studies with microspheres, sildenafil has shown to lower mean PAP (mPAP) and PVR index.^{84,86,126–131} There was, in general, no additional effect on hemodynamics when another pulmonary vasodilator was added to the sildenafil treatment which suggests the vasodilation from sildenafil to be sufficient. When added effect was noted, the combination of more vasodilators came with a risk of systemic vasodilation.⁸⁶

The risk of increasing ventilation-perfusion mismatch in PE by vasodilation may also apply to sildenafil. In healthy pigs, sildenafil increases intrapulmonary shunt flow and lowers PaO₂,¹³² and in pigs with single lung ventilation-induced pulmonary hypertension, sildenafil dose-dependently enhanced desaturation.¹³³ This effect may be species dependent, as sildenafil actually improves oxygenation in patients with pulmonary arterial hypertension.¹³⁴

Sildenafil has been used in PE in a few published case reports. Sildenafil showed promising effects in both acute post-operative PE and acute-in-chronic PE.^{98,135–137} In a patient with congenital heart disease and acute-in-chronic PE, sildenafil dramatically improved oxygenation.¹⁰⁹ The use of sildenafil made withdrawal of inotropes possible shortly after treatment,^{135,138} whereas another case report measures the effects of sildenafil on the following day.¹³⁹ This was, however, a severely ill patient with five-day history of saddle PE and in cardiogenic shock. The treatment may also be efficient in children.¹⁴⁰

Findings are summarized in Table 1.

Prostanoid pathway

Prostaglandins are products from arachidonic acid, catalyzed by cyclooxygenase (COX). They are mostly produced in endothelial cells and act at different receptors on the SMC with different downstream effects. Some receptors activate adenylate cyclase which dephosphorylates adenosine triphosphate to cyclic adenosine monophosphate that lowers cytosolic Ca²⁺ levels and causes pulmonary vasodilation. Other receptors inhibit the adenylate cyclase or activate phospholipase C, both to increase calcium levels and cause vasoconstriction^{30,36} which is why the net effect of increased prostanoid release in PE is complex.

Administration of the drugs can dilate pulmonary vasculature with both normal and constricted tone.^{59,141} Different prostanoids are secreted in acute PE.^{26,37,142,143} Inhibition of the COX enzyme seems to improve

hemodynamics,^{37,41,144–146} suggesting prostaglandin synthesis to be central in the pathology of PE. PE may even cause release of negative inotropic agents, which is synthesized through the COX-pathway¹⁴⁷ and might represent prostanoids. In one small randomized trial, administration of diclofenac was associated with a trend toward improved right ventricular function on echocardiography in humans with PE.¹⁴⁸

Besides hemodynamic effects, prostacyclin is one of the most potent endogenous inhibitors of platelet aggregation^{25,149,150} and may even enhance the effects of thrombolysis.^{151,152} Other prostanoids also prevent platelet aggregation,³⁸ but platelets in acute thromboembolism may respond differently to prostanoids than normally.¹⁵⁰ For example, on thromboelastography, platelets from patients with PE had a decreased response to adenosine diphosphate stimulation compared with platelets from healthy patients.¹¹⁶

Preclinical studies have shown divergent hemodynamic effects with both prostacyclin (PGI₂) and prostaglandin E₁ (PGE₁) with either no relevant response in dogs in both synthetic and autologous emboli material^{66,79,88,153} or a reduction in PVR or PAP.^{146,151,154–156}

More consistently, in porcine models of non-autologous PE, both PGE₁- and PGI₂-administration reduce PVR and mPAP and even better than NO-donors, hydralazine and calcium channel blockers.^{80,157} In mice, both a PGI and PGE₁ even reduced PE-related mortality,²⁵ maybe through protective effects on the pulmonary vasculature in PE.^{143,156,158} The effects of PGI₂ seem to have rapid onset, but duration of effects after cessation is more uncertain^{146,151} (see Table 2).

Risk of side effects must of course be kept in mind and should not exceed the benefits of treatment. Alpert et al. showed reduction in PAP in macro-embolism but not in micro-embolism when treated with PGE₁, but in both situations noted a significant decrease in SVR and MAP.¹⁵³ Similar reductions in MAP is noted both by PGE₁ and PGI₂.^{79,146,151,152}

Clinical case reports on the use of prostaglandins have been published. One case with CO₂ gas emboli showed normalization of PAP only minutes after administration of inhaled epoprostenol.¹⁵⁹ A total of seven cases with submassive PE showed positive effects of inhaled prostacyclin with a follow-up over weeks,^{160,161} whereas Webb et al.¹⁶² reported positive but transient effects on PAP without effects on MAP. This was in a PE patient that presented in shock and hence in a more critical condition. In one case of a newborn PE patient, epoprostenol showed no effect.¹⁰⁵

One clinical randomized, single-blinded trial has investigated the effects of prostaglandin treatment in acute PE. Kooter et al.¹⁶³ randomized 14 PE patients to receive intravenous epoprostenol or placebo on top of standard treatment. Endpoints were echocardiographic and biochemical parameters. They did not find any significant effects of

epoprostenol compared to placebo.¹⁶³ The patients included by Kooter et al. had preserved tricuspid annular plane systolic excursion (TAPSE) and low right ventricular to left ventricular ratio at baseline and were perhaps not affected severely enough by their acute PE for epoprostenol to show an effect. The chosen prostaglandin or the route of administration may be another explanation to the lack of positive results as inhaled and intravenous prostaglandins have shown convincing effect in both CTEPH and primary pulmonary hypertension.^{164–166}

Endothelin pathway

ET (mostly ET-1) are produced in the lungs, especially the endothelium. Their synthesis is upregulated by shear stress, stretch, thrombin, hypoxia and pH but inhibited by NO and prostacyclin. ET exert paracrine effect on the SMC, bind to G-protein coupled ET_A and ET_B receptors which increases intracellular inositol triphosphate and calcium¹⁶⁷ acting as potent vasoconstrictors and bronchoconstrictors.^{35,168} The effects of ET on the pulmonary vasculature might be complex, as it depends on the concentration of ET, the site of the receptor, the ongoing pathology and the tone of the pulmonary vasculature.^{85,168} ET also affect the release of NO and prostacyclin and play a role in the regulation of hypoxic pulmonary vasoconstriction^{35,167} which adds to the complexity. Whether or not ET concentrations are elevated in acute PE remains controversial.^{34,35}

Besides hemodynamic effects, ET stimulates platelet aggregation, cell adhesion and thrombosis,¹⁶⁷ and plasma levels of ET are increased in both humans and in animal models during acute PE.^{169,170}

Antagonizing the ET receptors in acute PE has been investigated in a few animal studies (see Table 3). In dogs with autologous PE, ET-A antagonism lowered PAP and PVR and increased CO, also in combination with iNO.^{72,171,172} Han et al.¹⁷¹ even showed additive effects of combined ET-A antagonism and urokinase treatment. In air-embolism models, both non-selective ET-antagonism and ET-A antagonism lowered PAP and PVR,^{173,174} suggesting that the ET-A receptor to be responsible for most of ETs vasoconstrictive properties.⁸⁵ In piglets, ET antagonism decreased PAP but lowered MAP and showed no effect on oxygenation or ventilation-perfusion mismatch.^{33,175} Conversely, in rodents with air-embolism, ET antagonism improved oxygenation and lowered RV systolic pressure.^{176,177}

Clinically, ET antagonism is widely used in CTEPH patients,¹⁷⁸ but our review did not find any reports on the clinical use of ET antagonism in acute PE.

Hydralazine

Hydralazine dilates blood vessels, lowers blood pressure and is used in hypertension and congestive heart failure. Hydralazine opens Ca²⁺-dependent potassium channels,¹⁷⁹

causing hyperpolarization and closure of voltage-dependent Ca²⁺ channels which lowers cytosolic Ca²⁺ levels and causes relaxation. Mechanisms may also involve the inositol triphosphate pathway and the prostacyclin pathway.^{180,181} It appears that hydralazine can lower PVR in both normal and pathological conditions in animals and humans.^{182,183}

Hydralazine has been tested in experimental PE; please see Table 4 for a summary. In dogs with autologous PE, hydralazine lowered PVR and PAP and increased cardiac output,^{79,82,88,184} but a reduction in MAP was also noticed.⁷⁹ One study did not see a reduction in PAP but positive effect on the output pressure.¹⁸⁵ In a porcine model of glass bead-induced PE, hydralazine lowered MAP but was unable to lower mPAP and had the smallest reduction in PVR compared to PGE-1 and NO-donors. Hydralazine was, however, the only drug to increase cardiac output.⁸⁰

Besides the hemodynamic effects, hydralazine enhanced the effect of thrombolysis.¹⁸⁴

There are only few examples of the use of hydralazine in acute PE in humans. Bates et al. reported a case on a post-operative PE patient in shock. Hydralazine lowered PVR and PAP significantly over 24 h and increased cardiac index. After withdrawal of hydralazine, the hemodynamics deteriorated, and the treatment was repeated successfully.¹⁸⁶

McGoon et al.¹⁸⁷ reported 26 patients with pulmonary hypertension, of which 6 had PE as the underlying cause. In the PE-subgroup, hydralazine did not affect PVR nor PAP but increased pulmonary blood flow and arteriovenous oxygen difference and lowered SVR. The time frame of treatment was not reported relative to symptom onset (see Table 4).

We did not find any prospective, clinical study on the use of hydralazine in acute PE.

Limitations

This review contains some limitations to consider. Firstly, the broad diversity of animal models of PE makes it difficult to compare results directly between them. Species, emboli material and measurements and outcomes differ significantly among the included studies. Interpretation and translation must be done with caution. Secondly, the vast majority of the clinical publications are case reports with possible publication biases and accordingly, the level of evidence is low.

Summary

Several mechanisms of PE-induced pulmonary vasoconstriction are well described and represent potential therapeutic targets for pulmonary vasodilation in PE. Many of those were tested in animal models, which differ substantially in the choice of species and embolic material. Only a small number of case reports and clinical trials exist despite the treatment options have been available for decades.

Further research in pulmonary vasodilation as an adjunct to anticoagulation in acute PE is warranted but needs to be in pathophysiological relevant models and prospective clinical trials.

Authors' contribution

All authors participated in design and aim. MDL did the screening of papers and drafted the article. AA is the guarantor. All authors contributed substantially to and approved the final version of the article.


Conflict of interest

The author(s) declare that there is no conflict of interest.

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Supplemental material

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Appendix I. Search strategy

We searched MEDLINE via PubMed and Embase for relevant articles with latest update September 13th 2019. We used the following search strategies for PubMed: (acute pulmonary embolism OR “Pulmonary Embolism”[Mesh]) AND (“Vasodilation”[Mesh] OR “Vasodilator Agents”[Mesh] OR “Hydralazine”[Mesh] OR “Phosphodiesterase Inhibitors”[Mesh] OR “Sildenafil Citrate”[Mesh] OR “Soluble Guanylyl Cyclase”[Mesh] OR “Guanylate Cyclase”[Mesh] OR “riociguat” [Supplementary Concept] OR “Endothelin Receptor Antagonists”[Mesh] OR “Nitric Oxide”[Mesh] OR “Nitroprusside”[Mesh] OR “Nitroglycerin”[Mesh] OR “Prostaglandins”[Mesh] OR “Epoprostenol”[Mesh] OR hydralazine OR endothelin receptor antagonist OR bosentan OR tezosentan OR macitentan OR prostacyclin OR epoprostenol OR prostaglandins OR sildenafil OR tadalafil OR phosphodiesterase-5 inhibitor OR riociguat OR soluble guanylyl cyclase OR inhaled nitric oxide) and for Embase: (‘hydralazine’/exp OR ‘phosphodiesterase inhibitor’/exp OR ‘sildenafil’/exp OR ‘tadalafil’/exp OR ‘riociguat’/exp OR ‘guanylate cyclase activator’/exp OR ‘guanylate cyclase’/exp OR ‘endothelin receptor antagonist’/exp OR ‘bosentan’/exp OR ‘tezosentan’/exp OR ‘macitentan’/exp OR ‘nitric oxide’/exp OR ‘inhaled nitric oxide’/exp OR ‘nitroprusside sodium’/exp OR ‘glyceryl trinitrate’/exp OR ‘prostaglandin’/exp OR ‘prostacyclin derivate’/exp OR ‘iloprost’/exp OR ‘prostaglandin h2’/exp OR ‘prostaglandin e2’/exp OR ‘prostaglandin e1’/exp OR ‘prostaglandin derivate’/exp) AND (‘acute pulmonary embolism’/exp OR ‘lung embolism’/exp) AND (‘article’/it OR ‘article in press’/it).

Titles and abstracts were screened for relevance by MDL. If eligible, the article was read and deemed for inclusion or not. References were reviewed for further hits.

Articles were included if they described a medical intervention causing pulmonary vasodilation in acute PE including air embolism using a clinically relevant drug. No specific needs for comparison were required (either control group or repeated measurements). Any hemodynamic outcome was accepted. Both human and animal studies were included no matter the year of publication. Only English papers were included.

Exclusion criteria included studies on chronic thromboembolic pulmonary hypertension (CTEPH) and the other causes of pulmonary hypertension (PH) within the World

Health Organization classification of PH; studies that investigated causes in PE-induced pulmonary vasoconstriction but did not intervene; and animal models that did not have an actual embolism (toxins or pharmacologically induced acute PH, e.g. by a thromboxane analog), and studies on isolated perfused lungs. We did not include studies on inodilators in this review. Case reports without sufficient description of hemodynamic effects of the vasodilatory agent were excluded. We excluded abstracts, conference papers, comments, editorials, and reviews.

Due to the broad variety of PE-models and outcome measures, no specific synthesis of outcome or meta-analysis was possible. We sum up hemodynamic findings in Tables 1 to 4.