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Pathophysiology and pharmacological treatment of pulmonary hypertension in acute respiratory distress syndrome

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ABSTRACT: Pulmonary hypertension (PH) is a characteristic feature of the acute respiratory distress syndrome (ARDS). The magnitude of PH has been shown to correlate with the severity of lung injury in patients with ARDS independently of the severity of associated hypoxaemia and has an adverse prognostic significance.

Early in the histopathological evolution of ARDS, pulmonary vasoconstriction, thromboembolism and interstitial oedema contribute to the development of PH, although pulmonary vascular remodelling probably occurs eventually. Intravenous vasodilator agents lead to an increase in intrapulmonary shunting and systemic hypotension, which can limit their therapeutic use, and have not been shown to improve survival. By contrast, rapidly metabolised vasodilators administered by inhalation induce selective pulmonary vasodilatation and decrease shunting, but again do not appear to confer a survival benefit.

Research aimed at further understanding the mechanisms that underlie pulmonary hypertension, a characteristic feature of the acute respiratory distress syndrome, are expected to provide improvements in pharmacological interventions for the treatment of pulmonary hypertension in the acute respiratory distress syndrome.

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Acute respiratory distress syndrome (ARDS) in adults is defined clinically by the acute onset of respiratory failure, with refractory hypoxaemia (arterial oxygen tension (P_{a,O_2})/inspiratory oxygen fraction (F_{I,O_2}) ratio <26.6 kPa (200 mmHg)) and bilateral infiltrates on frontal chest radiographs that cannot be explained by, but may coexist with, elevated left atrial pressure (occluded pulmonary artery pressure (P_{pa}) <18 mmHg) [1]. These defining features may be seen in context with a wide range of associated severe medical and surgical conditions, not all of which involve the lung directly. ARDS is the extreme manifestation of a spectrum of acute lung injury (ALI). ALI is defined as the same as ARDS but with less severe refractory hypoxaemia ($P_{a,O_2}/F_{I,O_2} <39.9$ kPa (300 mmHg)). The epidemiology of ALI, and its pulmonary vascular complications are poorly characterised and only data relating to pulmonary hypertension (PH) in established ARDS will be discussed hereafter.

PH, due to vasoconstriction and occlusion of the pulmonary microvasculature, is widely recognised as a characteristic feature of ARDS [2, 3]. The presence of PH in patients with ARDS, even following correction for the severity of the associated hypoxaemia, was first described in 1977 [2]. Mean P_{pa} was found to be ~ 3.99 kPa (30 mmHg; range 0.532–1.33 kPa (4–10 mmHg)). Since this early report, PH has been confirmed

in larger cohorts of patients with ARDS and is probably a ubiquitous complication of the syndrome. Indeed, some investigators have suggested that ARDS is unlikely in patients with a $P_{pa} <2.66$ kPa (20 mmHg) [1, 4–8].

Clinical implications

PH contributes to impaired right ventricular performance and cardiac output in ARDS patients, leading to a reduction in systemic oxygen delivery [9]. In the setting of associated multiple organ dysfunction, PH may therefore further impair tissue oxygen utilisation and contribute to an increase in organ dysfunction. A correlation between elevations in P_{pa} and pulmonary oedema has also been demonstrated [10]. Thus, pulmonary interstitial oedema may cause vascular compression and an increase in P_{pa} can promote oedema formation if vasoconstriction develops distal to the site of increased vascular permeability. Secondly, the magnitude of PH has also been shown to correlate with the severity of lung injury [11]. Thus, resolution of ARDS is accompanied by an improvement in PH, whereas progressive PH has been shown to be associated with a poor outcome [2, 7, 11]. A multicentre trial in the USA collected haemodynamic data from 153

patients with ARDS for 7 consecutive days [7]. Although P_{pa} was comparable for all subjects at enrolment, it increased steadily over the 7 study days only in those who failed to survive (mean P_{pa} 33 mmHg in nonsurvivors *versus* 29 mmHg in survivors, $p < 0.05$).

Hypoxic pulmonary vasoconstriction and pulmonary hypertension in acute respiratory distress syndrome

The canine oleic acid model of lung injury, which bears close pathophysiological and histological similarities to clinical ARDS, is characterised by a significant redistribution of pulmonary blood flow from dependent to nondependent lung regions [12]. This redistribution results from hypoxic pulmonary vasoconstriction (HPV), a mechanism that diverts blood flow from hypoxic to normoxic lung regions, thereby helping to preserve gas exchange. Moreover, preventing this redistribution can increase the deterioration in oxygenation [13]. Similarly, in patients with ARDS, the characteristic refractory hypoxaemia is primarily the result of intrapulmonary shunting and increased ventilation/perfusion (V/Q) mismatch [14], which is further exacerbated by the administration of intravenous vasodilators [15]. Thus, while the increase in P_{pa} attributable to HPV increases right ventricular afterload, it is a consequence of a physiological reflex designed to preserve V/Q mismatch and attenuate arterial hypoxaemia. However, PH persists in ARDS, even after severe hypoxaemia has been corrected. Whether HPV persists or not in such patients remains unclear. HPV is a relatively weak mechanism for the homeostatic control of alveolar oxygenation [16]. Several other studies of HPV's overall efficiency have produced variable results [16–18]. ARDS has even been reported to inhibit or abolish HPV. In these patients, the blunted pulmonary vascular response to hypoxia has been attributed to the release of endogenous vasodilator substances *e.g.* nitric oxide (NO) and prostaglandin (PG) I_2 [19]. Whilst the exact mechanisms of HPV are still being evaluated [20], it is clear that NO attenuates the response of pulmonary arteries to hypoxaemia both *in vitro* and *in vivo* [21]. In addition, it was observed recently that the increase in P_{pa} in lung injury, is inhibited by low-dose endotoxin and metabolic alkalosis, factors known to inhibit HPV [22]. This inhibition was incomplete, however, which may reflect the effects on the pulmonary circulation, not only of functional (*e.g.* active vasoconstriction), but also of anatomical factors that are not rapidly reversible (table 1) [23].

Nonhypoxia increases in pulmonary vascular tone in acute respiratory distress syndrome

In healthy individuals the endothelium exerts an active control over the tone of the underlying vascular smooth muscle via the synthesis and release of a wide variety of substances (fig. 1). These substances include NO, cyclooxygenase (COX) products including thromboxane (TX) A_2

Fig. 1. – Schematic illustration demonstrating some of the major functional changes in the pulmonary circulation in a) vascular smooth muscle and b) endothelium, in patients with acute respiratory distress syndrome. LPS: lipopolysaccharide; NO: nitric oxide; iNOS: inducible nitric oxide synthase; eNOS: endothelial nitric oxide synthase; ET: endothelin; ECE: endothelin converting enzyme; COX: cyclooxygenase; PG: prostaglandin; IL: interleukin; TNF: tumour necrosis factor.

PGI $_2$, leukotrienes (LTs), endothelins (ETs), and platelet-activating factor (PAF) [24]. During lung injury, the pulmonary circulation is exposed to the widespread release of these constricting and dilating mediators, the net effect is an increase in the vascular tone. Inhibitors of COX [25, 26] and of NO synthesis or their effects, have been shown to further increase P_{pa} in experimental lung injury [27]. Intravenous infusion of endotoxin in sheep causes P_{pa} to rise within several minutes, which remains raised for hours [28]. Furthermore, endotoxin infusion causes an increase in the levels of PAF [29]. Pretreatment with PAF antagonists inhibits both the rise in TXA $_2$ and the pulmonary pressor response to endotoxin [30].

Cyclooxygenase metabolism

Arachidonic acid is the precursor of a variety of vasoactive and inflammatory mediators implicated in the pathogenesis of

Table 1. – Factors contributing to pulmonary hypertension in acute respiratory distress syndrome

Functional	Mediator-induced vasoconstriction
	Hypoxic pulmonary vasoconstriction
Structural	Vascular compression by oedema fluid or fibrosis
	Vascular wall remodelling
	Thromboembolism
	Reduced lung volume

PH in ARDS. Arachidonic acid is liberated from membrane phospholipids by phospholipase A₂, and is subsequently metabolised by either COX, to form PGI₂ and TXA₂, or lipoxygenase, to form LTs. PGI₂ is a potent vasodilator, whereas TXA₂ is a potent vasoconstrictor. The balance between the release of these two prostanoids therefore contributes to pulmonary vascular tone [31]. Endothelial cells mainly form PGI₂, whereas platelets and to a lesser extent neutrophils, are the main sources of TXA₂. However, as neither neutrophil [32] nor platelet [33] depletion have been shown to abolish PH completely in experimental ARDS, it is likely that other possible sources of TXA₂ (e.g. endothelium, macrophages, eosinophils) contribute. In animal models, serum levels of TXB₂, the product of TXA₂ metabolism, rose concurrently with *Ppa*. Further, pretreatment with COX inhibitors prevented the release of TXA₂ [34] and attenuated the rise in *Ppa* [35]. Clinical studies in patients with ARDS have shown increased levels of circulating TXA₂ in bronchoalveolar lavage fluid (BALF) [36]. TXA₂ has also been shown to initiate the microvascular thrombosis that is responsible for perfusion abnormalities and recurrent ischaemia-reperfusion injury to the lung. Similarly, the vasoconstrictive effects of TXA₂ contribute to impaired gas exchange [31], however, these are probably not the sole mediators of PH in lung injury as dazoxiben, a specific TXA-synthase inhibitor, does not alter *Ppa* in patients with ARDS [36]. Additionally, COX inhibitors block the acute PH associated with endotoxin infusion, but fail to prevent the rise in *Ppa* that occurs several hours later. Likewise, in animal models of lung injury, TXA synthase inhibition decreased pulmonary oedema formation and inhibited microembolism, but only partially reduced PH [37]. In these circumstances, arachidonic acid metabolism may be shunted towards the lipoxygenase pathway, resulting in increased release of LTs [38].

Lipoxygenase metabolism

LTs are derived from arachidonic acid by 5-lipoxygenase. LTB₄ is a potent neutrophil chemokine, whilst LTC₄ and LTD₄ cause pulmonary vasoconstriction, increased capillary permeability and pulmonary oedema formation. Clinical studies have demonstrated that increased levels of LTs have been found in the BALF taken from patients with ARDS [39]. It has also been shown that 5-lipoxygenase metabolites were elevated in BALF from sheep challenged with endotoxin [40, 41]. However, the acute pulmonary hypertensive response to endotoxin infusion is only partially inhibited by 5-lipoxygenase inhibitors [40, 41] or by LT antagonists [42–44]. Ketoconazole is an imidazole antifungal agent that inhibits TXA synthase and 5-lipoxygenase without inhibiting COX. Therefore, it may have a dual anti-inflammatory action in ARDS, through the inhibition of inflammatory eicosanoid synthesis, thereby directing COX products down other, less inflammatory paths

e.g. those synthesising PGI₂ or PGE₁ [45]. In four trials using enteric ketoconazole to treat patients at risk of developing, or with established ARDS, a reduction in the incidence of acute respiratory failure in high-risk surgical patients and other critically ill patients was found [46–48]. By contrast, in patients with established ARDS, no differences were found regarding in-hospital mortality, or markers of gas exchange between the ketoconazole and placebo groups [49].

Endothelins

The release of ETs may also contribute to the pulmonary vasoconstrictor response. ET-1, a 21 amino-acid peptide, is formed from big ET-1 by the action of membrane bound metalloproteases called ET-converting enzyme [50]. ET-1 is both a potent vasoconstrictor and a comitogen/proliferation factor for vascular smooth muscle [51], and has been implicated in the pathogenesis of PH [52]. Although the main source of ET-1 is considered to be the endothelium [50], many cell types have been shown to release this peptide *in vitro*, including vascular smooth muscle, cultured from systemic vessels [53]. However, it is unclear whether ET-1 has a primary pathogenetic role or whether it is a secondary mediator that perpetuates the inflammatory response in ARDS. ET expression is upregulated in lung tissue from patients with PH [54]. Increased circulating levels of ET-1 have been detected in patients with ARDS. A comparison of the vasopressor response to ET-1 infusion in the ARDS group with that of healthy controls suggested that the increased circulating levels were due to both reduced clearance and net ET-1 release by the pulmonary circulation [55]. An autocrine role for ET-1 in human pulmonary artery smooth muscle was recently postulated, with important implications for the pathogenesis of human pulmonary vascular remodelling in ARDS of prolonged duration [51].

Pulmonary vascular remodelling in acute respiratory distress syndrome

Early in the course of ARDS, pulmonary vasoconstriction, thromboembolism and interstitial oedema, all of which are potentially reversible, act together to elevate pulmonary vascular resistance (PVR). In the subacute and chronic phases of ARDS, fibrocellular intimal proliferation occurs, involving predominantly small muscular arteries, but also veins and lymphatics (table 2) [3]. Here, the vascular lumens are compromised by concentric arrangements of fibrin, myointimal and hyperplastic endothelial cells, mucopolysaccharides, and collagen. This proliferation is considered to represent the sequelae of endothelial injury and repair, it is a significant contributor to the reduction of the vascular luminal area and reduces background filling on pulmonary angiographs

Table 2. – Spectrum of pulmonary vascular dysfunction in acute respiratory distress syndrome

Target	Mechanism	Consequence
Resistance vessel	Dysregulated vasodilatation/ vasoconstriction	Pulmonary hypertension Ventilation/perfusion mismatch Loss of hypoxic pulmonary vasoconstriction
Microvasculature	Endothelial inflammation	Increased permeability/oedema Leukocyte activation and tissue invasion
	Extravascular compression	Intravascular thrombosis Increased dead space Pulmonary hypertension
Postcapillary venule	Vasoconstriction and compression Endothelial inflammation	Increased permeability/oedema Increased permeability/oedema

performed *post mortem*. Obstruction of venous and lymphatic channels further increases intracapillary pressure, contributing to the accumulation of interstitial oedema fluid, as well as impeding its removal from the lung [3]. In the late, fibroproliferative phases of ARDS, more permanent structural changes consequent on vascular remodelling of the pulmonary vasculature, with medial hypertrophy and a reduction in luminal diameter contribute to PH [3]. The thickness of the media relative to the vascular diameter increases, which correlates with the extent of parenchymal honeycombing and haemorrhage [56]. Arterial tortuosity occurs as a result of distortion by irregular contracting fibrous tissue. The increased anatomical concentration of pulmonary blood vessels measured in patients in the late stage of ARDS has been suggested to reflect the combined effects of abnormal dilatation, tortuosity and crowding of vessels, rather than a restoration or regrowth of normal arteries [3].

Thromboembolism in acute respiratory distress syndrome

Post mortem studies have shown that thromboemboli are the most consistently observed vascular lesions in patients with ARDS and are present in 95% of cases [3]. These may be either embolic, or formed *in situ*. In ARDS it is likely that both mechanisms of clot deposition occur. Macrothrombi (in arteries >1 mm in diameter) are found in as many as 86% of patients through *post mortem* examination or angiography and are more prevalent in patients who die in the early phases of the syndrome [3]. Moreover, the number of macrothrombi, have been shown to correlate with the number of filling defects seen on *ante mortem* angiographs [3, 57]. Microthrombi, which have a similar prevalence to macrothrombi, contribute to the reduction in peripheral arterial fillings on *post mortem* pulmonary angiograms and are distributed throughout all phases of ARDS [3].

Therapy for pulmonary hypotension in acute respiratory distress syndrome

Intravenous vasodilators

If cardiac function is limited as a result of increased right ventricular afterload, reductions in PVR may prove therapeutically beneficial. Endogenous vasodilators released as part of the inflammatory process modulate the increase in P_{pa} , but contribute to the deterioration in gas exchange, presumably by dilating vessels in hypoxic lung regions (*i.e.* inhibiting HPV) [19]. Blockade of COX and NO have been shown to improve P_{a,O_2} by reducing intrapulmonary shunt in animals with oleic acid-induced pulmonary oedema [19, 25–27]. In clinical practice, several intravenous vasodilators have been administered in patients with ARDS, with the aim of increasing cardiac output and hence oxygen delivery. However, intravenous vasodilators have two drawbacks that limit their therapeutic utility. Most lack selectivity for the pulmonary circulation, and may therefore cause systemic hypotension. Secondly, intravenous vasodilators act on all pulmonary vessels, in both ventilated and nonventilated areas. The net effect is to increase shunt fraction, which leads to a deterioration in oxygenation [58, 59].

Prostaglandin E_1

PGE_1 is a prostanoid vasodilator, which inhibits platelet aggregation, impairs neutrophil chemotaxis and release of toxic products, and decreases macrophage activation. In one

large-scale, randomised, controlled trial, PGE_1 reduced P_{pa} and increased cardiac output in patients with ARDS, indicating unequivocal pulmonary vasodilation. However, P_{a,O_2} decreased by 22% as the result of an increase in true shunt from 21% to 35% [60]. Further, PGE_1 has not been shown to afford a survival benefit in ARDS, despite significantly reducing PVR [6]. The potentially adverse effects of PGE_1 on systemic blood pressure, cardiac rhythm, and gas exchange therefore limit its use as a pulmonary vasodilator in ARDS.

Intravenous prostaglandin I_2

PGI_2 is an endothelium-derived prostanoid vasodilator that also inhibits platelet aggregation and neutrophil adhesion. Epoprostenol, a synthetic analogue of PGI_2 , has recently been shown to improve survival in patients with primary pulmonary hypertension (PPH) [61]. This is probably through its properties as a selective vasodilator [62] and more speculatively by its ability to reverse vascular remodelling and platelet adhesion [63]. However, in patients with ARDS, intravenous PGI_2 led to an increase in intrapulmonary shunting, a deterioration in oxygenation, and systemic hypotension despite its reduction of P_{pa} [64]. The side-effect profile of prostacyclin therapy, therefore limits its use as a pulmonary vasodilator in ARDS.

Other intravenous vasodilators

Increases in shunt have also been reported in patients with ARDS after the administration of other intravenous vasodilators, including nitroprusside [65], isoproterenol, and diltiazem [17].

Inhaled vasodilators

Vasodilators administered into the respiratory tract by inhalation, only access ventilated alveoli. Drug delivery by this route is therefore theoretically attractive, since recruitment of pulmonary blood flow to ventilated lung units improves V'/Q' matching and therefore arterial oxygenation; in addition P_{pa} is reduced [66, 67]. Directly accessing the pulmonary circulation by inhalation also tends to limit the systemic effects of vasodilators (table 3).

Inhaled nitric oxide

NO is a ubiquitous biological mediator implicated in modulating vascular resistance [68]. Interestingly however, the concentration of NO in exhaled air is lower in patients with ARDS compared with controls, despite the marked alveolar inflammation that is characteristic of the syndrome [69]. Various isoforms of NO synthase convert L-arginine to

Table 3. – Comparison of the theoretical effects of a putative short acting vasodilator, administered intravenously or by inhalation

	Intravenous	Inhaled
Systemic blood pressure [#]	Decreased	Unchanged
Intrapulmonary shunt	Increased	Decreased

[#]: the effects on the systemic circulation will be influenced by the site of intravenous administration (*i.e.* peripheral venous versus pulmonary artery) and the duration of action the drug has in circulation.

L-citrulline and NO in the presence of oxygen and several cofactors [70]. Once produced, NO is freely diffusible and enters the pulmonary smooth muscle cells to activate soluble guanylate cyclase and produce guanosine 3,5-cyclic monophosphate (cGMP) [70]. NO is rapidly inactivated by avid binding to haemoglobin, thus reducing its vasoactive half-life to milliseconds and obviating the possibility of systemic vasodilation.

In animal models, inhaled NO at concentrations of 5–80 parts per million (ppm) has been shown to produce selective and rapidly reversible pulmonary vasodilation [71, 72], and in appropriate models, to improve V'/Q' matching and increase arterial oxygenation [73–75]. Furthermore in experimental preparations, inhaled NO decreases both pulmonary oedema formation and neutrophil sequestration in the lung [75, 76]. The response to inhaled NO in a porcine model of early ARDS has been shown to depend on the pre-existing distribution of pulmonary blood flow, being most beneficial in septic animals with a large intrapulmonary shunt [13]. However, as ARDS evolved, this benefit was lost with impaired diffusion of NO into the pulmonary circulation [77].

In 1993, in patients with ARDS, 18 ppm inhaled NO was shown to induce small but significant decrements in mean P_{pa} , PVR and shunt fraction, without affecting cardiac output or systemic blood pressure. Oxygenation improved significantly over the population as a whole, although individual responsiveness was variable. NO was inhaled for 3–53 days without loss of beneficial haemodynamic effect or evidence of toxicity [64]. In subsequent studies, NO was shown to increase the $P_{a,O_2}/F_{I,O_2}$ ratio, decrease the pulmonary shunt fraction and reduce PVR [60, 66]. Doses that improved gas exchange (0.06–0.25 ppm), were found to be lower than the doses that reduced P_{pa} (5–20 ppm).

However, the results of two multicentre, randomised, controlled trials comparing inhaled NO with conventional therapy in ARDS failed to show a mortality benefit of this therapy (table 4) [78, 79]. In a total of 177 ARDS patients at 30 centres, an acute increase in P_{a,O_2} was observed in 60% of the patients receiving NO, compared with 24% of those exposed to placebo. This improvement in oxygenation resulted in a decrease in the intensity of mechanical ventilation over the first 4 days which was not sustained thereafter. There were no differences between the groups in terms of overall mortality, the number of days alive off mechanical ventilation, or the number of days alive meeting the oxygen requirement for extubation [78]. A second, European multicentre (43 sites) trial, which enrolled 260 medical and surgical patients with ARDS known to respond favourably to NO, revealed a 30 day mortality of 45% for treated patients, compared with 38% for controls [79]. The mortality rate in those not responding

to NO (and therefore not randomised) was also 45%. After huge enthusiasm for and widespread use of this therapeutic strategy, the results of these studies clearly fail to support the routine use of inhaled NO in the treatment of patients with ARDS. Furthermore, it is difficult to predict which patients will respond to inhaled NO or not [69]. Methaemoglobinaemia decreased platelet aggregation and, when abruptly discontinued, rebound deterioration in arterial oxygenation and elevation of PH were also significant possible side-effects [60, 66]. Finally, it has been demonstrated that any benefit in oxygenation does not last longer than 24 h (table 4) [80, 81].

Inhaled (nebulised) prostaglandin I_2

Nebulised PGI_2 , which acts through an increase in the level of the second messenger intracellular cyclic adenosine monophosphate (cAMP), has been evaluated as an inhaled pulmonary vasodilator. In contrast to NO, nebulised PGI_2 does not require sophisticated equipment for its administration. In small-scale studies, nebulised PGI_2 induced selective pulmonary vasodilation and redistributed blood flow from areas of shunt to well-ventilated regions, thereby improving $P_{a,O_2}/F_{I,O_2}$ ratio [82, 83]. These studies demonstrated decreases in P_{pa} to those seen with inhaled NO [82, 83], but cardiac output and right ventricular function remained unchanged [83]. However, PGI_2 , like NO, has not been shown to improve survival in ARDS patients. Moreover, the sustained physiological improvement has been modest in many studies [64, 84]. Recent therapeutic strategies in PPH have reported significant benefits with oral PGI_2 analogues [85], but evidence for their use in ARDS is lacking.

Almitrene bismesylate

Further attempts to manipulate pulmonary vascular tone with the purpose of improving gas exchange have been made by administering a combination of drugs that augment HPV with inhaled NO. The use of pulmonary vasoconstrictors in patients with ARDS can lead to improved gas exchange if HPV is restored. However, they are superficially unattractive because of their negative effect on P_{pa} and right ventricular function. In these circumstances, constricting the shunting vascular bed whilst simultaneously vasodilating well-ventilated areas would be therapeutically attractive [86–88]. Almitrine, a peripheral chemoreceptor agonist, improves V'/Q' matching in patients with chronic obstructive pulmonary disease, presumably through an enhancement of HPV [89]. Recently, almitrine has been shown to improve gas exchange in patients with ARDS without decreasing cardiac output, despite increasing

Table 4. – Randomised controlled trials of inhaled nitric oxide (NO) in patients with acuterespiratory distress syndrome

First author [ref.]	Patients n	Inhaled NO dose ppm	Duration days	Outcome
LUNDIN [79]	260	2–40	30	Development of severe respiratory failure less (2.2% versus 10.3%) in NO treated group. Mortality not altered (44% versus 40% control).
DELLINGER [78]	177	1.25–80	28	P_{a,O_2} increased >20% in first 4 h in 60% of patients treated with NO and 24% of controls. F_{I,O_2} and intensity of ventilation could be reduced in first 4 days. No difference in mortality (30% versus 32–38% in NO-treated groups).
MICHAEL [80]	40	5–20	3	NO improved $P_{a,O_2}/F_{I,O_2}$ by at least 20% and allowed a decrease in F_{I,O_2} of at least 0.15 only in the first 24 h in more treated patients than controls.
TRONCY [81]	30	0.5–40	30	NO improved oxygenation, only in the first 24 h in more treated patients than controls. Mortality (60% versus 67% in control) not altered.

ppm: parts per million; F_{I,O_2} : inspiratory oxygen fraction; P_{a,O_2} : arterial oxygen tension.

right ventricular afterload [90]. Further, the combination of almitrine with inhaled NO had additive effects on arterial oxygenation, with no increase in P_{pa} [67]. One study found that the administration of NO or almitrine increased P_{a,O_2} by 9.9 and 13.4 kPa (75 and 101 mmHg) respectively, but by 23.3 kPa (175 mmHg) after administration of both [88]. In a further series of 17 patients, NO caused a modest, but non-significant improvement in $P_{a,O_2}/F_{I,O_2}$ ratio from 11.7 ± 3.9 to 13.0 ± 4.9 kPa (88 ± 30 to 98 ± 37 mmHg), whereas the combination of NO and almitrine caused a significant increase in the $P_{a,O_2}/F_{I,O_2}$ ratio from 12.2 ± 3.3 to 17.29 ± 7.4 kPa (92 ± 25 to 130 ± 56 mmHg) [91]. Combined therapy also caused a significant decrease in the P_{pa} , similar to that induced by inhaled NO alone. It therefore appears that almitrine improves oxygenation and augments the effects of inhaled NO. However, its effects to date have only been determined in nonrandomised trials. Further studies are required prior to almitrine being a recommended form of therapy.

Oral vasodilators and antiproliferative agents

Endothelin-receptor antagonists

Recent therapeutic strategies in PPH have reported significant benefits from the administration of an oral ET-receptor antagonist, bosentan [92]. Small, but beneficial effects, in exercise capacity were demonstrated in a trial involving 213 patients, suggesting that ET-receptor blockade has a therapeutic role in some patients with PPH. However, the duration of the 16-week trial was insufficient to test for a difference in mortality, and there was an increased incidence of hepatic dysfunction at a higher dose of ET-receptor blockade. Evidence for supporting its application in ARDS is presently lacking.

Sildenafil

The use of sildenafil, a phosphodiesterase type-5 inhibitor, has recently been reported in 16 patients with PH secondary to lung fibrosis [93], in which it was shown to be a more selective pulmonary vasodilator than PGI_2 . However, unlike NO, systemic blood pressure fell in patients who received sildenafil but not inhaled NO. At present, there is no evidence to support the use of sildenafil in patients with ARDS. However, by inhibiting phosphodiesterase type 5, sildenafil stabilises cGMP (the second messenger of NO), unlike prostacyclins, that act through an increase in cAMP. Clinical studies are therefore needed to assess the potential additive effects of simultaneous increase in cGMP and cAMP by combining these two classes of drugs.

Summary

Pulmonary hypertension appears to be a ubiquitous complication of acute respiratory distress syndrome. Pulmonary hypertension contributes to impaired right ventricular performance, reduced cardiac output and is associated with an increase in the mortality. Pharmacological manipulation of pulmonary vascular tone is feasible in patients with acute respiratory distress syndrome, but without a proven mortality benefit. The properties of the ideal pulmonary vasodilator include selectivity for the pulmonary circulation, no impairment in hypoxic pulmonary vasoconstriction, ease of administration, and lack of adverse systemic effects. Research aimed at further elucidating the mechanisms underlying pulmonary

hypertension in acute respiratory distress syndrome can be expected to provide improvements in the results of pharmacological interventions. Furthermore, the incorporation of new treatments into the armamentarium should be based on the results from well-designed and carefully performed clinical trials that demonstrate convincing evidence of both safety and efficacy.

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