Impairment of hypoxic pulmonary vasoconstriction in acute respiratory distress syndrome

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Shareable abstract (@ERSpublications)
Our review provides a detailed overview of mechanisms underlying the V/Q mismatch in ARDS and its contribution to hypoxaemia, and could help to assess the relevance of treatment options currently being discussed for treatment of ARDS in COVID-19 patients https://bit.ly/3gs2Afj

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Abstract
Acute respiratory distress syndrome (ARDS) is a serious complication of severe systemic or local pulmonary inflammation, such as caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. ARDS is characterised by diffuse alveolar damage that leads to protein-rich pulmonary oedema, local alveolar hypoventilation and atelectasis. Inadequate perfusion of these areas is the main cause of hypoxaemia in ARDS. High perfusion in relation to ventilation (V/Q<1) and shunting (V/Q=0) is not only caused by impaired hypoxic pulmonary vasoconstriction but also redistribution of perfusion from obstructed lung vessels. Rebalancing the pulmonary vascular tone is a therapeutic challenge. Previous clinical trials on inhaled vasodilators (nitric oxide and prostacyclin) to enhance perfusion to high V/Q areas showed beneficial effects on hypoxaemia but not on mortality. However, specific patient populations with pulmonary hypertension may profit from treatment with inhaled vasodilators. Novel treatment targets to decrease perfusion in low V/Q areas showed beneficial effects on hypoxaemia but not on mortality. However, specific patient populations with pulmonary hypertension may profit from treatment with inhaled vasodilators. Novel treatment targets to decrease perfusion in low V/Q areas include epoxyeicosatrienoic acids and specific leukotriene receptors. Still, lung protective ventilation and prone positioning are the best available standard of care. This review focuses on disturbed perfusion in ARDS and aims to provide basic scientists and clinicians with an overview of the vascular alterations and mechanisms of V/Q mismatch, current therapeutic strategies, and experimental approaches.

Clinical definition and current therapeutic options for ARDS
Acute respiratory distress syndrome (ARDS; formerly also called “adult respiratory distress syndrome”) was first described in 1967 [1] and later defined by pulmonary oedema, atelectasis and severe ventilation/perfusion (V/Q) mismatch, which cause hypoxaemia and eventually hypercapnia. ARDS is caused by local or systemic inflammation and delayed mechanisms of repair [2]. Vascular alterations include unbalanced vasoconstriction and vasodilatation of pulmonary vessels leading to both unfavourable blood flow distribution and pulmonary hypertension (PH) [3].

Diagnosis is currently based on the “Berlin definition” of ARDS, including a staging based on the ratio of arterial PaO2 and inspired oxygen fraction (FIO2) [4]. Previous nomenclature distinguished ARDS from “acute lung injury” (ALI). As the term “ALI” remains common in animal studies, we use it in this context in this review.

Despite improvements in ventilation strategies and patient positioning, the in-hospital mortality of ARDS patients is still reported as up to 44% [3]. Importantly, there are currently no specific pharmacological
treatments available to address the pathomechanisms underlying ARDS or the vascular alterations that occur with it [5], which have drawn attention due to the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. This review will describe the vascular alterations resulting in hypoxaemia in ARDS with a specific focus on coronavirus disease 2019 (COVID-19)-induced pathomechanisms and provide an outlook on potential therapies.

General pathomechanisms underlying ARDS
ARDS most commonly develops in the setting of a primary pulmonary insult such as pneumonia (bacterial or viral) or secondary to systemic sepsis. Although the initial clinical phase may differ depending on its aetiology, the common pathophysiological hallmarks of ARDS include an early “exudative” and a later “proliferative” phase (for a recent review please refer to [2]). In brief, the exudative phase, lasting approximately 7 days, is characterised by early and massive epithelial and endothelial damage that leads to increased capillary permeability and a protein-rich exudate, resulting in interstitial and alveolar oedema. The loss of surfactant producing alveolar type II cells facilitates atelectasis. In the later proliferative phase, which can last more than 3 weeks, the release of proliferative and pro-fibrotic mediators activates repair processes and the hyperplasia of alveolar type II cells, eventually leading to interstitial fibrosis [2]. Although the exact pathogenesis and cytokine patterns differ between ARDS caused by bacteria and viruses [6], similar histopathological features are apparent.

V/Q mismatch in ARDS

Hypoxaemia in ARDS
Atelectasis and the obstruction of alveoli with protein-rich fluid cause reduced alveolar oxygen levels and severely hinders oxygenation in ARDS patients (figure 1a). In healthy lungs, redistribution of perfusion (Q) to areas with better ventilation (V) by hypoxic pulmonary vasoconstriction (HPV) results in optimal V/Q matching (V/Q=1) and thus maintains oxygenation (figure 1b) [7]. During ARDS, redistribution of blood flow is severely impaired, characterised by lung areas with high perfusion and low ventilation (V/Q<1, with V/Q=0 called intrapulmonary shunting), and lung areas with high ventilation and low perfusion (V/Q>1, with V/Q→∞ called dead space ventilation) (figure 1c) [7, 8]. Intrapulmonary shunting (V/Q=0) is the major cause of hypoxaemia in ARDS.

FIGURE 1 Mechanism of ventilation/perfusion (V/Q) mismatch in acute respiratory distress syndrome (ARDS). a) ARDS is characterised by diffuse alveolar damage leading to oedema and atelectasis. The computed tomography scan performed in supine position of the patient demonstrates bilateral dense consolidations (*) in the most dependent region and normal attenuation in the non-dependent region of the lung. b) In healthy lungs alveolar hypoxia (e.g. due to hypoventilation) leads to hypoxic pulmonary vasoconstriction (HPV) of precapillary vessels matching the perfusion (Q) to regional ventilation (V) and thus optimising arterial oxygenation. c) In ARDS a disbalance of vasoconstriction in well ventilated areas and vasodilation in poorly ventilated areas (due to inhibition of HPV) results in blood flow redistribution from well to poorly ventilated alveoli and a V/Q mismatch leading to hypoxaemia. Further factors contributing to low perfusion of well-ventilated alveoli are vascular obstruction by oedema, infiltration, and (micro)thrombosis. In the schematic, the size of vessels indicates amount of blood flow. CO: cardiac output; PvO2: mixed venous partial pressure of O2.
of hypoxaemia in ARDS, and probably to a lesser extent areas of a low V/Q ratio (V/Q<1) [9–11]. Hypoxaemia may be further aggravated by PH and low cardiac output, leading to decreased mixed venous oxygen content (PvO2) which severely impairs arterial Po2 in areas of intrapulmonary shunting (figure 1c) [8]. In contrast, diffusion limitation plays a minor role in ARDS and can be corrected by high FiO2 (table 1) [7, 8].

A low V/Q ratio and/or intrapulmonary shunting is caused by hypoventilation due to altered lung mechanics, airway obliteration and alveolar infiltration, or by perfusion alterations. While ventilation strategies address hypoventilation, currently 6.6% of patients with severe ARDS develop refractory hypoxaemia and require veno–venous extracorporeal membrane oxygenation (ECMO) [12], which is the only effective therapy for intrapulmonary shunting. Thus, new therapeutic approaches addressing the pulmonary vascular component of V/Q (mis)matching are required.

Relative hyperperfusion of poorly ventilated lung areas (low V/Q areas)

In healthy lungs, V/Q matching is optimised by HPV, a rapid, widely conserved physiological response by the precapillary pulmonary arteries to alveolar hypoxia [13]. Naturally, the efficiency of HPV for correcting the V/Q mismatch decreases with the extent of the hypoxic lung region [14].

Theoretical models and investigations in ARDS patients employing pulmonary vasodilators and the multiple inert gas elimination technique (MIGET) suggested that functional HPV can improve V/Q matching and thereby PO2 by approximately 20 mmHg in ARDS [15]. Moreover, studies applying an FiO2 of 1.0 suggested that HPV is present in ARDS patients [16].

Partially functional HPV may explain why low V/Q areas seem to contribute much less to hypoxaemia than shunting in atelectatic areas, where HPV may not be efficient enough to completely restrain blood flow [9–11]. Using MIGET, up to 50% of the cardiac output has been detected to be shunt flow in ARDS patients. Importantly, the amount of blood flow to consolidated areas determined by dynamic computed tomography correlated with the extent of hypoxaemia of the patients [11].

In addition to shunting due to impaired HPV, intrapulmonary shunting caused by pulmonary capillary distention or opening of intrapulmonary arteriovenous anastomoses was described in 26% of patients with ARDS and correlated with the hyperdynamic state of ARDS patients [17]. Thus, opening of intrapulmonary arteriovenous anastomosis may contribute to shunting in ARDS.

Data from animal models support that impaired HPV and V/Q mismatch cause hypoxaemia in ARDS. Systemic (i.v. or i.p.) or intratracheal (i.t.) administration of lipopolysaccharide (LPS) has been used frequently as a model for in vivo septic ARDS [18]. LPS, also known as endotoxin, is a toll-like receptor 4 agonist expressed by Gram-negative bacteria and is a major stimulus of the immune system. In vivo LPS administration increased basal pulmonary artery pressure (PAP) and attenuated HPV in various species, ranging from mice to horses [18]. Importantly, inhibition of HPV occurred even at concentrations 10x lower than the concentration that caused an elevation of baseline PAP, and attenuation of HPV was reported to last longer than baseline PAP elevation [19].

### Table 1: Causes of hypoxaemia in ARDS, response to oxygen supplementation and differentiation from other diseases

| Cause of hypoxaemia | PA–aO2 | PaO2 response to increased FiO2 | Typical pathological condition |
|---------------------|--------|--------------------------------|------------------------------|
| **Global pulmonary limitations** |        |                                |                              |
| Diffusion limitation (decreased exchange area, increased diffusion distance) | Increased | Improved | Interstitial lung diseases; aggravation during exercise (low PaO2 and short erythrocyte transit time) |
| Global hypoventilation | Normal | Improved | Muscular diseases, ventilatory failure |
| Decreased PaO2 | Normal | Improved | High altitude |
| **Local pulmonary limitations** |        |                                |                              |
| Low V/Q | Increased | Improved | COPD, ARDS, perfusion redistribution from areas with high V/Q (e.g. pulmonary embolism) |
| Shunt (V/Q=0) | Increased | Minimal improvement | Atelectasis; aggravation by low PvO2 (e.g. low CO) |

PA–aO2: alveolar–arterial O2 tension difference; PaO2: arterial partial pressure of O2; FiO2: inspiratory O2 fraction; PvO2: mixed venous partial pressure of O2; PpO2: partial pressure of O2 in inspired gas; V/Q: ratio of alveolar ventilation to perfusion; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; CO: cardiac output. Adapted from [7].

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Hypoperfusion of well-ventilated lung areas (high V/Q areas)

Redistribution of perfusion from obstructed vessels located in well-ventilated areas to poorly ventilated areas promotes V/Q mismatch. Functional and structural factors contribute to low perfusion in well-oxygenated areas. These factors include intravascular occlusion by microthrombi, extravascular compression of vessels by oedema and atelectasis, and (in later stages) interstitial fibrosis and vascular wall remodelling [20, 21].

Primary sensing and signalling mechanism underlying HPV and alterations in ARDS

HPV is a unique and intrinsic mechanism of the precapillary pulmonary vessels which – in contrast to systemic vessels – constrict in response to hypoxia. Establishing a successful treatment specifically to enhance HPV in hypoxic alveoli requires an understanding of the sensor and signalling mechanisms that underlie HPV, as well as modulating factors and how they are affected by ARDS (figure 2). Acute hypoxia (lasting seconds to minutes) induces rapid vasoconstriction (acute phase of HPV) which is suggested to adapt blood flow to alveolar ventilation on a breath-to-breath basis and is fully reversible seconds after re-exposure to normoxia. In contrast, sustained HPV (lasting minutes to hours) initiates long-term adaptation of the pulmonary vasculature to chronic hypoxia, including pulmonary vascular remodelling. It has been shown that the underlying mechanisms responding to acute, prolonged and chronic hypoxia are different [22, 23].

While pulmonary arterial smooth muscle cells (PASMC) of the small resistance arteries were identified as the primary effector and sensor site for acute HPV, the exact role of the endothelium as a trigger for HPV, e.g. by transmitting signals via specific gap junctions containing connexin 40 (and involving epoxyeicosatrienoic acids (EETs) and sphingosine-1-phosphate) is under debate [24]. Undoubtedly, the endothelium modulates the strength of HPV, which is crucial for the fine-tuning of V/Q matching in vivo [24, 25]. During prolonged hypoxia, the endothelium and calcium sensitisation of the contractile apparatus via the Rho-kinase may be of particular importance [22].

While the physiological significance of HPV is unquestioned, the exact oxygen sensing and signalling mechanisms underlying HPV are not yet fully elucidated [13, 23, 25] (figure 2a). Although there is a broad consensus that mitochondria are the essential oxygen sensors underlying HPV, and that an intracellular calcium increase via plasmalemmal ion channels in PASMC triggers HPV, various hypotheses on the primary mitochondrial sensing mechanisms and the connection between the sensor and effector mechanisms have been proposed. Recent studies suggest that hypoxia-induced changes in the mitochondrial redox state cause a release of mitochondrial reactive oxygen species (ROS) from complex III of the mitochondrial respiratory chain, triggering HPV [26, 27]. Lung-specific modulation of cytochrome C oxidase (complex IV, CIV) through the expression of a specific isoform of subunit 4 within CIV promotes ROS release and is probably responsible for the unique reaction of PASMC to acute hypoxia [28]. Another hypothesis suggests that a more reduced cellular redox state mediates the hypoxia-induced intracellular calcium increase [29]. Moreover, changes in the AMP/ATP ratio may play a role [30]. It is probable that multiple localised signals – dependent on oxygen levels and time – accumulate until they reach a threshold for triggering HPV [13, 26, 28]. Regardless of the initial signal, downstream inhibition of different potassium channels induces membrane depolarisation and subsequent extracellular calcium entry via voltage-dependent L-type calcium channels, resulting in contraction [13, 23].

Additional types of ion channels are involved in HPV, including store-operated and receptor-operated calcium channels such as the transient receptor potential canonical channel type 6 (TRPC6), the transient receptor potential vanilloid 4 channel and the cystic fibrosis transmembrane conductance regulator (CFTR), which both could form a complex with TRPC6 during hypoxia [24, 25].

Currently, the role of primary oxygen-sensing mechanisms and most of the channels for regulation of HPV in ARDS remains unclear. In particular, downregulation of gap junctions or CFTR during inflammation may contribute to disturbance of HPV [24]. Moreover, potassium channels may qualify as targets for enhancing HPV signalling. Inhibitors of voltage-dependent potassium (Kv) channels, such as 4-aminopyridine, are possible sensitisers of hypoxic Kᵥ-channel inhibition and restored HPV in isolated lungs in LPS-preconditioned mice [31]. Inhibition of the vasodilatory Kᵥ-ATP channels with PNU-37883A was found to restore HPV in isolated lungs from endotoxaemic mice, while HPV among non-endotoxaemic controls was not altered [32]. However, a previous clinical trial with the Kᵥ-ATP channel inhibitor glibenclamide, focussing on systemic hypotension, failed [33]. Almitrine, which was suggested to inhibit calcium-dependent potassium channels or act on mitochondrial oxygen sensing [34], was shown to enhance HPV and the ventilatory response to hypoxia. Several clinical trials in ARDS have been performed with almitrine (see below).
Primary mechanisms of HPV

Modulators of HPV

CFTR

TRPC6

TRPV4

Kv

Kv

GJ

GJ

EC

PASMC

K+ +

Na+

Ca2+

Ca2+

DAG

PLC

GJ

GJ

Hypoxia

V/Q=1

V/Q<1

V/Q>1

Decreased HPV:

Local inflammation

NO   , PGI2   , EET   ?

Vasoconstriction

TXA2   , ATII   , ET-1

V/Q=1

V/Q<1

V/Q>1

V/Q=1

V/Q<1

V/Q>1

Colour codes:

Clinical trial

Act as vasoconstrictor/vasodilator

↑↓ Regulation in ARDS

↑↓ Animal study

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Endothelial modulators of HPV and pulmonary vascular pressure in ARDS

HPV in ARDS is largely (dis)regulated by inflammatory mediators affecting the pulmonary endothelium. The primary endothelial factors modulating HPV include nitric oxide (NO), endothelin-1 (ET-1), and the arachidonic acid (AA) metabolite prostacyclin (PGI₂) (figure 2b). For therapeutic use it is important to consider that the systemic use of most pulmonary vasoactive substances affects basal pulmonary pressure and HPV, which may have opposing effects on the desired therapeutic aims, enhancement of HPV or alleviation of PH (see table 2 [35–56]). Importantly, because the healthy pulmonary circulation is a low-resistance circuit, pulmonary vasodilators may have only limited effects in healthy volunteers, in contrast to patients with increased pulmonary vascular resistance (PVR).

Increased release of vasodilators: NO

NO signalling as a target in sepsis and ARDS has a long history, as excessive NO production is the cause of systemic hypotension. Patients with ARDS exhale higher concentrations of NO than healthy controls [57], suggesting a pulmonary source of NO in ARDS. NO originating primarily from endothelial NO synthase (eNOS) attenuates HPV [58]. Consequently, NOS inhibition augmented HPV in animals [58–60] and healthy volunteers [61].

In models of ALI inhibition of downstream NO signalling and NO release from eNOS or inducible NOS (iNOS) restored HPV [62] and protected against ALI and/or hypoxaemia [63, 64], respectively. In humans, iNOS expression was increased in bronchoalveolar lavage (BAL) cells in healthy volunteers after instillation of LPS [65] and in BAL macrophages from (septic) ARDS patients [66].
Despite these promising results on NOS inhibition from preclinical models, clinical trials with different unselective NOS inhibitors, like 546C88, in ARDS failed due to increased mortality. Study design and the lack of selectivity may have contributed to the failure of the study [67].

Other therapeutic approaches employing NO scavengers or addressing uncoupling of NOS and related superoxide production were not able to show beneficial effects in septic shock and intensive care unit patients [68, 69].

In summary, attempts thus far to modulate NO signalling with the purpose of improving HPV and attenuating inflammation in ARDS have failed in clinical trials.

**TABLE 2. Pharmacological factors that may affect hypoxic pulmonary vasoconstriction (HPV)**

| Pulmonary vasodilatory drugs | Pulmonary vasoconstrictive drugs |
|-------------------------------|---------------------------------|
| Soluble guanylate cyclase (sGC) activators, PDE5 inhibitors: decreased V/Q matching/oxygenation in COPD-PH but not in fibrosis patients or healthy volunteers [35–37]. | Catecholamines with positive inotropic effects and systemic vasoconstriction (α1 receptor stimulation): norepinephrine, phenylephrine, enhance HPV; epinephrine can dose-dependent inhibit HPV due to effects on β2-receptors [38]. |
| NO donors: i.v. application did not impair V/Q matching in healthy volunteers [39] but oxygenation in ARDS patients [40]; inhaled NO can improve V/Q matching [41, 42] (see text). | Nitrous oxide: the effects on HPV are unclear; it may increase basal PAP [38]. |
| Prostacyclins and prostacyclin analogs: i.v. application decreased oxygenation and increased shunting in ARDS patients [43]; inhaled iloprost can improve V/Q matching in ARDS [42] (see text). | Vasopressin: systemic vasoconstriction, suggested to decrease the PVR/SVR ratio in low doses [44]. |
| Endothelin receptor antagonists: decreased oxygenation in COPD patients [45]. | Calcium channel inhibitors: s.l. nifedipine may attenuate V/Q matching in hypoxic or COPD lungs [39, 46, 47]; i.v. diltiazem decreased V/Q matching in ARDS patients [48]. |
| ACE inhibitors/ATII receptor blockers: vasodilatory in volunteers with an activated renin–angiotensin system [49]; lisinopril [50] and losartan [51] decreased HPV in healthy volunteers. | ACE inhibitors/ATII receptor blockers: vasodilatory in volunteers with an activated renin–angiotensin system [49]; lisinopril [50] and losartan [51] decreased HPV in healthy volunteers. |
| Vasodilators with positive inotropic effects and systemic vasodilation: dobutamine (β1-adrenergic) inhibits HPV [38], milrinone (PDE3 inhibitor) [52]; inhaled β2-agonists may affect V/Q matching, primarily in asthmatics [53]. | ACE inhibitors/ATII receptor blockers: vasodilatory in volunteers with an activated renin–angiotensin system [49]; lisinopril [50] and losartan [51] decreased HPV in healthy volunteers. |
| Other drugs decreasing HPV | Drugs specifically enhancing HPV |
| Volatile anaesthetics (e.g. halothane, isoflurane and sevoflurane): inhibit HPV and impair oxygenation to varying degrees during one-lung ventilation [38, 54]. | Almitrine: at low doses, enhances HPV via an unknown mechanism, at least partially via Ca2+-dependent K+ channels [55] (see text). |
| Acetazolamide (uncertain mechanism, unrelated to carbonic anhydrase) [56]. | Acetazolamide (uncertain mechanism, unrelated to carbonic anhydrase) [56]. |

ACE: angiotensin converting enzyme; ARDS: acute respiratory distress syndrome; ATII: angiotensin II; COPD: chronic obstructive pulmonary disease; NO: nitric oxide; PAP: pulmonary artery pressure; PDE: phosphodiesterase; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; V/Q: ventilation/perfusion.

Despite these promising results on NOS inhibition from preclinical models, clinical trials with different unselective NOS inhibitors, like 546C88, in ARDS failed due to increased mortality. Study design and the lack of selectivity may have contributed to the failure of the study [67].

Other therapeutic approaches employing NO scavengers or addressing uncoupling of NOS and related superoxide production were not able to show beneficial effects in septic shock and intensive care unit patients [68, 69].

In summary, attempts thus far to modulate NO signalling with the purpose of improving HPV and attenuating inflammation in ARDS have failed in clinical trials.

**Imbalance of AA-derived vasodilative and vasoconstrictive mediators: PGI2 and thromboxane**

AA metabolites are generated mostly from phospholipids by phospholipase A2 and are paracrine inflammatory intermediates released by various cell types. AA can be metabolised to different vasoactive mediators by cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 enzymes. Notably, the effects of AA metabolites on HPV are highly variable and species- and age-dependent (for an extended review, see [70]). This review focusses on the clinically most relevant AA derivatives.

In this regard, balanced levels of vasoconstrictor thromboxane A2 (TXA2) and vasodilator PGI2 (both downstream of COX) are most important for regulating pulmonary vascular tone. TXA2 is generated by platelets via the TXA2 synthase, acts via the T prostaglandin receptor and induces vasoconstriction in PASMCl. In contrast, PGI2 is produced mainly in endothelial cells via the prostacyclin synthase, acts via prostaglandin I2 receptors and induces vasodilation, anti-inflammatory effects, and decreased platelet aggregation [71]. The strong vasodilatory effect of PGI2 is exploited for treatment of PH; however, this is at the expense of increased shunting and decreased systemic pressure when applied systemically in patients [72]. Interestingly, in sepsis and ARDS patients, TXA2 as well as PGI2 are increased [73, 74]. Animal experiments indicate that
a high, fast peak of TXA\(_2\) may cause the increase in basal PAP after LPS application, but that the later peak of PGI\(_2\) may cause impairment of HPV [19]. However, neither COX nor TXA\(_2\) synthase inhibition affected acute HPV in healthy volunteers [75], or improved outcome in septic patients [76, 77].

In contrast, the vasodilatory effects of PGI\(_2\) are used for treatment of PH and V/Q mismatch when applied via the inhalative route, thereby only reaching well-ventilated lung areas and enhancing perfusion to lung regions with high V/Q values (see section “Pharmacological approach for treatment of V/Q mismatch and PH”).

**Decreased release of vasoconstrictive AA-derived mediators downstream of cytochrome P450: EETs**

EETs are generated in various cell types, including endothelial and smooth muscle cells, by Cyp450 epoxygenases (especially CYP2C and CYP2J) from AA, and are degraded by soluble epoxide hydrolase (sEH) [24]. EETs are short-lived mediators that have gained attention as they promote vasorelaxation of systemic vessels but induce vasoconstriction of pulmonary vessels *ex vivo* [78] and *in vivo* in hypoxia in animal models [79], and thus may account for the specific vasoconstrictive effect of hypoxia in the pulmonary vasculature [24]. However, the effects of EETs may depend on the experimental setup and the presence of sensitising factors [80]. Genetical approaches to reduce EET generation significantly reduced HPV in mice [81], while enhanced EET levels by deletion of EET-degrading sEH resulted in potentiation of HPV [79], with unaltered basal pulmonary pressures. Of note, contrary results exist: in left main-stem bronchial occlusion experiments healthy control mice with deletion or inhibition of sEH had no alterations in hypoxic blood redistribution [82]. In ALI, EET levels in lung tissue of rodents were decreased, and deletion or inhibition of sEH was found to protect mice from LPS-induced impairment of HPV and hypoxaemia [82], as well as pulmonary oedema [83]. Currently, sEH inhibitors are tested in healthy volunteers and smokers in an initial phase 1 study (ClinicalTrials.gov identifier NCT01762774). Here sEH inhibition with GSK2256294 resulted in restored systemic vasodilation *in vivo* [84], although clinical data on HPV remain untested.

**Increased release of vasoconstrictors/inflammatory mediators: endothelin**

Endothelin (ET-1) is a highly potent vasoconstrictor released by the endothelium. Its production and release are stimulated by inflammatory mediators and hypoxia and decreased by the vasodilatory mediators NO and PGI\(_2\) [71]. While endothelial cells express ET\(_{B1}\) receptors, leading to vasorelaxation, ET\(_A\) and ET\(_{B2}\) receptors on PASMC induce vasoconstriction, as well as proinflammatory and proliferative effects [71]. ET-receptor inhibitors are frequently used for treatment of PH in humans.

With regard to HPV, both selective ET\(_{A}\)-receptor or unselective ET\(_A/ET_{B}\)-receptor blockade inhibited HPV in animals [85, 86] and humans [87]. In ARDS patients, elevated circulating ET-1 levels are probably caused by pulmonary release [88]. Similar results exist from septic animal models [89], showing additional ET\(_A\)-receptor upregulation and ET\(_B\)-receptor downregulation in lung tissue [90]. ET-receptor blockers disturbed V/Q matching after systemic application in a study on sepsis in piglets [89] but improved right-to-left-shunting and arterial oxygenation after inhalation in an ALI model [91]. In humans, the relevance of ET-receptor blockade for causing a V/Q mismatch is unclear. In healthy volunteers, bosentan, a dual ET-receptor antagonist, attenuated the increase in PAP during hypoxia but did not affect blood gases [87]. So far, a single case report describes the use of bosentan as a rescue treatment for refractory hypoxaemia and PH in a patient with ARDS. In this patient, bosentan rapidly lowered the right ventricular (RV) systolic pressure and subsequently improved oxygenation [92]. In such cases, vasodilation of well-ventilated areas and increased cardiac output may outweigh the negative effects of inhibition of HPV.

**AA-derived inflammatory mediators downstream of lipoxygenase: leukotrienes**

Recently, the AA metabolite leukotriene B\(_4\) (LTB\(_4\)) has gained attention for treating PH [93]. Importantly, leukotrienes are not classical “endothelial” modulators of HPV, as their expression is normally restricted to immune cells like macrophages, but – at least under pathophysiological conditions – the endothelium can be a source of leukotrienes [94]. LTB\(_4\) and the group of cysteinyl leukotrienes (cysLTs: LTC\(_4\), LTD\(_4\) and LTE\(_4\)) are generated by 5-LOX. While LTB\(_4\) acts primarily via LTB\(_4\) receptor 1, cysLTs act via cysLT-receptor 1 (cysLTR1) causing oedema formation, but also smooth muscle contraction and cell proliferation [95]. Leukotriene levels were elevated in BAL fluid and/or lung tissue from rodents with ALI [95] and patients with ARDS [96].

In different murine ALI models, inhibition of 5-LOX or cysLTR1 inhibited HPV impairment [95] and V/Q mismatch [97]. In contrast, inhibition of cysLTR1 strongly attenuated HPV in isolated lungs, most probably via direct inhibition of smooth muscle contraction [98]. Thus, in ARDS general anti-inflammatory effects of cysLTR1 blockade probably outweigh their effects on smooth muscle contraction. In this regard, montelukast, a cysLTR1 receptor inhibitor used to treat asthma, showed
beneficial effects in an animal model of ALI [99]. Currently, a clinical trial is planned to investigate the effects of montelukast on reducing the risk of acute care visits and hospital admissions among patients infected with SARS-CoV-2 (NCT04389411).

**The role of further inflammatory cytokines**

Inflammatory cytokines may affect the pulmonary vascular tone indirectly via release of endothelial mediators such as NO, PGI₂, ET-1 and angiotensin II (ATII) [100] or directly via interaction of vasoconstrictive signalling pathways in PASMC [101]. Some data exist regarding cytokine-induced gene regulation in PASMC which may result in changes of the vascular tone or reactivity [102]. However, investigations of direct effects of cytokines specifically on pulmonary vessels in HPV are limited. For one of the most relevant cytokines, interleukin-6 (IL-6), it was shown that incubation of isolated pulmonary arterial rings with IL-6 resulted in inhibition of HPV, albeit the mechanism remains unclear [103]. Definitely, improvement of inflammation should have beneficial effects on V/Q matching irrespectively of direct or indirect effects on the pulmonary vasculature. Emerging therapeutic approaches to limit inflammation in ARDS are summarised elsewhere [104].

**Systemic, humoral and pharmacological factors affecting HPV**

Several systemic and therapeutic factors can modulate HPV, thereby possibly affecting oxygenation in ARDS.

**Physical and physiological factors**

Hypercapnia and hyperoxia are probably the clinically most relevant factors that may affect HPV. Hypercapnia increased HPV and improved V/Q matching in animal models [23, 60], and enhanced normoxic PAP [105] and HPV [106] in humans, contributing to V/Q matching [107]. Hyperoxia in healthy volunteers did not change HPV after 8 h of exposure [108] nor did acute hyperoxic ventilation affect the PVR [109]. Interestingly, in ALI, hyperoxic ventilation enhanced intrapulmonary shunting due to alveolar collapse [110].

**Drugs interfering with HPV**

The vast majority of frequently used vasoactive drugs in clinical use have the potential to interfere with HPV (see table 2).

For the detailed effects of anaesthesia, please refer to recent reviews [38, 54]. An overview of the effects of inotropic, inodilator and vasopressor drugs on pulmonary and systemic circulation is given elsewhere (for a review, see [111]). Numerous substances also affect HPV in animal models [23, 70].

**Hormonal modulators: ATII**

ATII is synthesised by the angiotensin-converting enzyme (ACE) located in pulmonary endothelial cells and expresses vasoconstrictive and inflammatory effects via the angiotensin-receptor 1 (ATR1). ACE2 (mainly expressed on alveolar epithelial cells, endothelial cells and PASMCs) metabolises ATII to AT1-7, which activates vasodilatory and anti-inflammatory signalling [112]. In animals with ALI, vasoconstrictive ATII signalling was upregulated due to increased ACE activity, and impaired ACE2 activity [113, 114]. Along these lines, BAL levels of ACE were elevated in ARDS patients [115]. Preclinical studies have used ACE inhibitors, ATR1 blockers or the application of AT1-7 to reduce inflammation and ALI and improve oxygenation [113, 116, 117]. Recombinant ACE2-attenuated perfusion heterogeneity, arterial hypoxaemia and PH in LPS challenged pigs [114]. However, in ARDS patients a trial with recombinant human ACE2 (rhACE2) did not show beneficial effects on haemodynamics or the $P_{\text{aO}_2}/F_{\text{I}O_2}$ ratio in ARDS patients [118]. A very small clinical trial with enalapril, an ACE inhibitor, also failed [119].

**Dysregulation of HPV in SARS-CoV-2 infection**

Low V/Q areas and shunting both seem to be a particular problem in COVID-19 patients. In ARDS due to SARS-CoV-2, typical histological features of ARDS are found, including injury of the alveolar epithelium, hyaline membrane formation and hyperplasia of alveolar type II cells [118]. However, additional specific features such as severe endothelial injury and increased prevalence of alveolar capillary microthrombi in pathological samples of COVID-19 patients may explain the pronounced effect of SARS-CoV-2 on the pulmonary circulation [119].

Early in the pandemic, severe intrapulmonary shunting in COVID-19 ARDS was described in a small Italian cohort [120]. Later, two phenotypes of COVID-19 patients have been proposed: one in a probably early stage of the disease with high compliance of the lung, low amount of non-aerated tissue and low V/Q matching, the other with a more classical ARDS presentation and right-to-left shunting in non-aerated
positive end-expiratory pressure (PEEP) ventilation is used to improve lung recruitment by opening caused by a decrease of ventilator-induced lung injury and not better oxygenation [140]. Furthermore, thereby improving oxygenation (figure 3a). However, the improvement of survival was suggested to be to recruitment of dorsal (larger) lung areas for ventilation and abandoning the (smaller) ventral lung areas, effects on V/Q matching and RV dysfunction [139]. The beneficial effects of prone positioning are related positioning has been accepted as the best standard of care [8, 137, 138]. Both strategies exert beneficial pressures to avoid respirator-associated lung injury and decrease atelectasis. With severe ARDS, prone current knowledge of SARS-CoV-2 on the pulmonary vasculature [131, 132]. Several resistance, thus interfering with physiological V/Q matching, as outlined above. Recent reviews have summarised the current knowledge of SARS-CoV-2 on the pulmonary vasculature [131, 132]. Several ongoing clinical studies are investigating whether drugs targeting angiotensin signalling affect SARS-CoV-2 infection outcomes (e.g. NCT04408326, NCT04337190, NCT04335786 and NCT04340557). Specifically, rhACE2 is discussed as a potential therapeutic for patients with early SARS-CoV-2 infection as in these patients it may additionally block viral entry into cells [133].

The role of PH in ARDS
Despite a decrease of HPV, dysregulation of vasoactive factors (see above) and mechanical vascular obstruction can cause the development of PH and, subsequently, RV dysfunction; these well-known complications of ARDS can limit oxygen delivery and contribute to organ dysfunction [24, 70, 134]. In later stages of ARDS, fibrous intimal proliferative lesions [135], as well as smooth muscle hypertrophy and neomuscularisation of formerly non-muscularised vessels, have been reported [135, 136]. The mechanisms that drive vascular remodelling are most probably similar to other chronic lung diseases associated with PH, with a major role of proliferative/mitogenic endothelial mediators such as ET-1 and inflammatory mediators [20, 101]. Here various cytokines, e.g. IL-6, have been shown to be a major contributor to PH development [2, 20, 102]. Additionally, therapeutic factors may promote PH. Positive pressure ventilation can impair RV dysfunction by decreasing RV preload and increasing afterload by augmented extrinsic vascular compression [2, 20]. Accordingly, even during lung-protective ventilation, a prevalence of cor pulmonale of approximately 20–25% has been described in ARDS patients. PH is of specific relevance in the context of V/Q mismatch, as therapeutic approaches that alleviate PH may severely disturb V/Q mismatch and vice versa enhancement of HPV disturbs pulmonary haemodynamics and may augment PH. Thus, the development of therapeutic approaches to improve HPV and simultaneously alleviate PH is crucial.

Non-pharmacological approach for treatment of V/Q mismatch
Currently, ARDS treatment focusses on lung-protective ventilation using low tidal volumes and airway pressures to avoid respirator-associated lung injury and decrease atelectasis. With severe ARDS, prone positioning has been accepted as the best standard of care [8, 137, 138]. Both strategies exert beneficial effects on V/Q matching and RV dysfunction [139]. The beneficial effects of prone positioning are related to recruitment of dorsal (larger) lung areas for ventilation and abandoning the (smaller) ventral lung areas, thereby improving oxygenation (figure 3a). However, the improvement of survival was suggested to be caused by a decrease of ventilator-induced lung injury and not better oxygenation [140]. Furthermore, positive end-expiratory pressure (PEEP) ventilation is used to improve lung recruitment by opening
atelectasis, which can improve V/Q matching in these areas. However, PEEP ventilation may disturb V/Q matching [141], as it can cause hyperinflation of previously well-aerated alveoli and restrict perfusion in these areas, thereby causing an area of high V/Q ratio and redistribution of perfusion to non-aerated tissue or toward dependent lung regions with higher perfusion pressure due to gravity (figure 3b). In a recent study using lung protective ventilation with PEEP, a heterogeneous response in a small patient population has been shown with individual different benefit during PEEP [8].

Further options for improving gas exchange in very severe ARDS cases are ECMO and extracorporeal CO₂ removal; both techniques are used by experienced multidisciplinary teams in trained centres [2, 142].

**Pharmacological approach for treatment of V/Q mismatch and PH**

Most pharmacological treatment approaches to improve clinical outcome or prevent ARDS have failed in clinical trials (for a review, see [2]). Discouraging results from anti-inflammatory drugs such as...
glucocorticoids, which increased mortality in early studies, have prevented further large-scale trials for a long time [2]. Recently, a multicentre randomised trial enrolling 277 patients with established moderate-to-severe ARDS showed that early administration of dexamethasone reduced duration of mechanical ventilation and overall mortality [143]. Accordingly, studies using corticoids for treatment in the current SARS-CoV-2 pandemic have been initiated, with the first promising results being published [144]. Prospective meta-analysis of seven randomised trials enrolling 1703 critically ill COVID-19 patients showed that administration of systemic corticoids resulted in lower 28-day all-cause mortality [145].

Another approach to improve V/Q matching and simultaneously decrease PH in ARDS consists of increasing perfusion in well-ventilated areas through inhaled vasodilators such as NO or PGI2. Inhaled NO (iNO) improved blood flow redistribution, shunting and oxygenation in preclinical studies [146, 147] and in clinical trials and additionally reduced PVR in patients [41, 42]. However, later studies have indicated no beneficial effect on mortality in adult and paediatric ARDS patients but a potentially harmful effect on renal function, especially among elderly patients [148]. Notably, study design and heterogeneous patient population in some of these studies were criticised.

Currently, iNO is recommended only for selected patient populations, such as those with acute cor pulmonale [142]. Nevertheless, iNO remains a commonly used rescue therapy for ARDS patients [142]. In COVID-19 patients, several small retrospective studies report the use of iNO; however, with limited success in improving oxygenation or the $P_{aO_2}/FiO_2$ ratio [149–151]. Pulmonary vascular endothelial dysfunction and microthrombi, both hallmarks of SARS-CoV-2-induced lung damage, may impair iNO-induced pulmonary vasodilation [151]. The application of iNO may be favourable under specific conditions, as illustrated in a case series of five patients with PH or in patients with severe hypoxaemia and signs of RV strain [152]. Large-scale clinical trials are currently being performed; however, no outcomes have been yet released [153]. Beneficial effects similar to iNO were reported for inhaled aerosolised PGI2, although it was only tested in small cohorts of ARDS [42]. General use of inhaled PGI2 is currently not recommended; however, the Thllo study (NCT03111212), a prospective, randomised, multicentre trial, is currently recruiting patients to evaluate the effects of PGI2 in a larger cohort [154].

An optimal treatment for improving V/Q matching requires sufficient specificity to enhance HPV without promoting PH. A small clinical trial with almitrine (a drug formerly approved for treating COPD that has been shown to enhance the central ventilator response and HPV in animal models of ALI [155, 156]) found that almitrine with or without iNO increased $P_{aO_2}$ and improved perfusion redistribution in ARDS patients at low doses but increased PAP at higher doses [157, 158]. Furthermore, in combination with inhalative anaesthesia, almitrine may fail to improve $P_{aO_2}$ [159]. Oral almitrine was withdrawn from the market in 2013 because of its potential to cause peripheral neuropathy and weight loss (>15%) in patients after long-term use [160]. Nevertheless, a recent single-centre case series enrolled 25 patients with severe ARDS on ECMO treatment. Almitrine improved $P_{aO_2}/FiO_2$ in 18 patients and no adverse events were observed [12]. In a recent small case series of 17 patients with early hypoxaemic SARS-CoV-2 induced pneumonia, almitrine improved $P_{aO_2}$ in 80% of prone and supine-positioned patients [161]. In a recent larger trial, almitrine was used in most cases in combination with iNO and improved oxygenation in SARS-CoV-2 ARDS without adverse effects. Interestingly, this trial defined specific responders to the treatment (about 2/3 of the patients) which showed an improvement of the $P_{aO_2}/FiO_2$ ratio of at least 20%; however, no statistical significant difference in 28-day mortality rates between responders and non-responders was detected [162]. Thus the value of almitrine for use of ARDS treatment needs to be carefully evaluated, in particular in the face of the severe adverse effects in the past and the lack of effect on mortality.

Currently, no specific therapy for RV dysfunction in ARDS exists. Prone positioning, lung-protective ventilation, individually optimised PEEP settings, and limiting hypercapnia have been suggested as essentials for treating PH and RV dysfunction [163, 164]. The role of specific pulmonary vasodilators such as phosphodiesterase 5 inhibitors or endothelin receptor antagonists in the treatment of PH in ARDS remains unclear; however, their use may be limited by worsening oxygenation due to impaired HPV [165, 166].

**Conclusion: treatment of V/Q mismatch in ARDS – rebalancing vascular function**

Vascular dysfunction in ARDS is caused by inflammatory and mechanical factors disrupting pulmonary blood flow distribution, thereby impairing pulmonary gas exchange and RV function. Tropism of certain viruses such as SARS-CoV-2 towards the pulmonary vasculature may enhance pulmonary vascular dysfunction. Currently, no approved pharmacological therapy to specifically address blood flow distribution in ARDS is available. A simple strategy to improve V/Q matching and decrease PVR is the use of iNO or inhaled aerosolised PGI2. Unfortunately, larger clinical trials remain ongoing or have shown
improved oxygenation without any benefit on mortality. Advanced study design may answer the question of whether treatment of hypoxaemia also can improve mortality under specific conditions. Patients with a good chance to recover under a causative treatment of the ARDS (e.g. by antibiotics) should be preferentially included. In these patients, treatment of hypoxaemia could serve as a bridge to recovery and may avoid the necessity of ECMO treatment and/or may decrease mortality. Furthermore, alternative endpoints that may be affected by prolonged hypoxaemia, such as neurological outcome, could be defined. Most importantly, specific subpopulations such as patients with RV dysfunction may benefit more greatly from inhaled vasodilators as they improve V/Q matching and attenuate RV afterload.

Although treatment of V/Q mismatch and PH merely alleviates symptoms and does not cure ARDS, treating life-threatening hypoxaemia as a bridge to recovery will remain a promising therapeutic aim until specific treatments for ARDS are established. Thus, further basic research and clinical trials on treating V/Q mismatch and PH in ARDS are warranted. In this regard, application of inhaled vasoactive substance (e.g. iNO) in combination with substances that enhance HPV may be most promising to effectively address V/Q matching and minimise the risk of causing PH. However, currently there is a lack of well-tolerated clinically available substances that specifically enhance HPV. It needs to be further investigated if novel targets including epoxyeicosatrienoic acids and specific leukotriene receptors can improve V/Q matching without deleterious effects on pulmonary haemodynamics. Preclinical investigations should focus on specific oxygen sensing mechanisms, such as ion channels (e.g. TRPC channels) and clearly delineate effects on HPV and general pulmonary hemodynamics in ARDS.

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