Journal of Intensive Care

REVIEW

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The balance between classical and alternative renin–angiotensin system in ARDS: a narrative review

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Abstract

Acute respiratory distress syndrome (ARDS) is a complex inflammatory condition often requiring admission to intensive care. The renin–angiotensin system (RAS) has emerged as a key modulator of lung inflammation, vascular tone, permeability and pulmonary fibrosis in ARDS. Its effect depend on the activated biochemical pathway during the course of the disease: the classical Angiotensin-Converting Enzyme (ACE)/Angiotensin II/AT1R pathway exerts pro-inflammatory, vasoconstrictive and profibrotic effects, whereas the alternative ACE2/Angiotensin 1–7/MasR axis is associated with anti-inflammatory, vasodilatory and antifibrotic properties. Therapeutic research has largely focused on enhancing the alternative RAS to attenuate inflammation and fibrosis; however, emerging evidence suggests that activation of the classical RAS through exogenous angiotensin II administration may provide clinical benefit in selected etiologies of ARDS, potentially by improving systemic hemodynamic stability and modulating pulmonary vascular resistances. This interplay between the two RAS axes underscores the complexity of their role in ARDS pathophysiology and raises the possibility that selective, stage-dependent modulation of both pathways may represent a new therapeutic approach in this context. This narrative review examines the dual influence of RAS pathways in ARDS and explores the potential for targeted therapeutic interventions at different disease stages.

Keywords Acute respiratory distress syndrome, Renin–angiotensin system, Angiotensin II, ACE2, Angiotensin-(1–7), Inflammation, Pulmonary hemodynamics, Vasopressors

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Introduction

Acute respiratory distress syndrome (ARDS) is a heterogeneous clinical syndrome characterized by acute hypoxemic respiratory failure driven by diffuse inflammatory lung injury, for which effective targeted therapies remain limited [1]. The pathophysiology of ARDS involves a dysregulated inflammatory response, marked by a cytokine release and increased capillary permeability, culminating in diffuse alveolar damage, non-cardiogenic pulmonary edema, reduced lung compliance, loss of aerated lung tissue and impaired gas exchanges [2].

The progression of ARDS follows a pathological trajectory that can be summarized into three distinct phases, although substantial heterogeneity exists depending on the underlying etiology, patient characteristics, comorbidities, and therapeutic interventions. The early phase (i.e. from the onset to day 6) is characterized by interstitial and alveolar edema, endothelial and epithelial damage and the accumulation of neutrophils, macrophages and red blood cells within the alveolar space. The subacute phase (7–14 days) is marked by the initial reabsorption of edema, epithelial repair mediated by alveolar type 2 epithelial cells (AECII), fibroblast infiltration and collagen deposition. Beyond day 14, the late phase emerges, marked by the resolution of the neutrophilic infiltrate and the progression to pulmonary fibrosis [2]. The mechanisms driving progression from early lung injury to fibrotic remodeling and irreversible loss of functional lung parenchyma remain incompletely understood and fibrotic changes do not develop uniformly in all patients with ARDS.

Although ARDS is defined by established diagnostic criteria [3], emerging evidence supports the existence of at least two biologically and clinically meaningful phenotypes, the hyper- and the hypo-inflammatory [4]. In this context, the hyperinflammatory phenotype features more severe clinical manifestations but is more responsive to specific therapeutic strategies, including the use of higher levels of positive end-expiratory pressure (PEEP) [5], a more liberal fluid management approach [6] and anti-inflammatory treatments, such as statins [4, 7].

Furthermore, ARDS is frequently complicated by hemodynamic instability and shock. This circulatory failure may arise from concomitant sepsis, the intrathoracic pressure effects of mechanical ventilation or right ventricular failure (RV) secondary to acute pulmonary hypertension [8, 9]. During the early phase of ARDS, a progressive rise in pulmonary vascular resistance (PVR) often triggers the development of pulmonary hypertension, which significantly increases RV afterload and may ultimately culminate in RV dysfunction or overt acute *cor pulmonale* [10].

Endothelial injury plays a central role by disrupting the homeostatic balance between vasodilatory mediators (e.g., nitric oxide and prostacyclin) and vasoconstrictors (e.g., endothelin-1 and thromboxane A_2) [11]. This functional imbalance is further exacerbated by structural and mechanical obstructions, such as intravascular thrombosis and micro-embolic phenomena, which drastically reduce the functional capacity of the pulmonary vascular bed [12]. Furthermore, lung intravascular neutrophil retention plays a critical role in impairing gas exchange. As recently suggested [13], these trapped neutrophils can mechanically reduce capillary blood flow and trigger microthrombus formation, further exacerbating hypoxemia through a microvascular dysfunction mechanism. Moreover, the occurrence of RV is also strongly associated with adverse clinical outcomes [14]. Ultimately, the presence and severity of cardiovascular dysfunction underscore the profound clinical and biological heterogeneity of ARDS. Identifying these hemodynamic patterns is essential for distinguishing specific sub-phenotypes, which may reflect diverging pathophysiological pathways and necessitate distinct, personalized therapeutic approaches.

The renin–angiotensin system (RAS), a key regulatory network in both physiological and pathological states, exerts effects that extend beyond blood pressure regulation and sodium–water homeostasis [15]. Through its bioactive peptides, RAS influences inflammation, oxidative stress and tissue remodeling across multiple organs, including the lungs [16]. These observations have driven increasing interest in elucidating its role in pulmonary pathophysiology and evaluating its potential as a therapeutic target. While RAS dysregulation has been extensively studies in chronic lung disorders, such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis [17, 18], its role in ARDS remains less clearly defined and, in some contexts, controversial [19].

The aim of this review is therefore to summarize current evidence on the inflammatory and hemodynamic roles of the RAS across the different phases of ARDS and discusses the potential therapeutic implications of targeted RAS modulation.

Basic physiology of the systemic and pulmonary RAS

Renin release by the juxtaglomerular cells is stimulated by reductions in arterial blood pressure and/or circulating blood volume, decreased sodium concentrations into the distal nephron and activation of the sympathetic nervous system [20]. At the systemic level, renin cleaves liver-derived angiotensinogen into the decapeptide Angiotensin I (Ang I). Ang I is subsequently converted into the biologically active octapeptide Angiotensin II (Ang II)

by angiotensin-converting enzyme (ACE), which is abundantly expressed by pulmonary vascular endothelial cells [21]. Ang II mediates its classical effects, i.e. vasoconstriction, stimulation of inflammation and fibrosis, primarily through binding to Ang II type 1 receptor (AT1R).

Ang II can be further metabolized into Angiotensin 1–7 (Ang-(1–7)) by angiotensin-converting enzyme 2 (ACE2) [22], a carboxypeptidase sharing approximately 40% identity and 61% similarity with ACE [23]. ACE2, although predominantly expressed in other organs (such as the heart and kidney) [24], within the lungs is primarily expressed in Clara cells and type II alveolar cells (AECII) [25]. Ang-(1–7) exerts its biological actions via binding to the Ang II type 1 receptor (AT2R) and Mas receptor (MasR), promoting vasodilation through nitric oxide (NO) release and exerting anti-inflammatory, antifibrotic and antiproliferative effects [26–28]. Notably, Ang II can also bind to AT2R, albeit with lower affinity, thereby modulating its own biological activity. AT2R expression is typically low under physiological conditions but becomes upregulated under pathological conditions, such as COPD, where it appears to mediate protective effects [29, 30].

Beyond angiotensin metabolism, ACE2 is also involved in the degradation of des-Arg^9-bradykinin (DABK), a pro-inflammatory peptide that activates bradykinin B1 receptors expressed in the distal airways. Reduced ACE2 activity results in increased DABK availability, thereby amplifying neutrophil recruitment and airway inflammation [31]. Although the renin–angiotensin system is often conceptualized as a dual-axis network, comprising a classical ACE/Ang II/AT1R pathway promoting vasoconstriction, inflammation and fibrosis, and an alternative ACE2/Ang-(1–7)/MasR pathway mediating vasodilation and tissue protection, this framework likely oversimplifies the true complexity of RAS regulation. The system is better described as a highly interconnected and dynamically regulated network, in which enzymes, peptides and receptors interact bidirectionally. An additional layer of regulation is provided by the dipeptidyl peptidase 3 (DPP3), a zinc-dependent cytosolic metalloprotease ubiquitously expressed in human cells. Following cellular injury, apoptosis or necrosis, DDP3 may be released into the circulation [32], where it degrades peptides from both RAS axes. Specifically, DPP3 converts Ang II to angiotensin IV (Ang IV), thereby attenuating Ang II–mediated pulmonary vasoconstriction, while also hydrolyzing Ang-(1–7) to Angiotensin-(3–7) and subsequently angiotensin-(5–7); thereby, downregulating the alternative pathway as well [33, 34]. Disruption of this finely balanced network can shift RAS signaling toward inflammation, vascular dysfunction and lung injury, features that are highly relevant in ARDS.

Apart DPP3, other peptidases could degrade Ang II, including the conversion of Ang II to Ang III by aminopeptidase A and subsequently to Ang IV by aminopeptidase N. These two enzymes, expressed across various tissues and in the bloodstream, can be overexpressed in conditions such as sepsis and septic shock, thereby contributing to further RAS dysfunction [35].

In summary, within the intricate interplay of RAS pathways, the lung plays a central regulatory role. It serves as the principal site of ACE expression and a major contributor to systemic Ang II generation [21], while simultaneously acting as a counter-regulatory organ through ACE2-mediated conversion of Ang II into Ang-(1–7) and degradation of other bioactive peptides [25]. This dual role positions the lung as a key modulator of both systemic and pulmonary RAS activity, with important implications for acute and chronic lung diseases.

Role of RAS in lung inflammation

During the early phase of ARDS, activated macrophages and alveolar epithelial cells release neutrophil chemoattractants, notably interleukin (IL)-8, which drive neutrophil migration from the pulmonary microvasculature into the alveolar space. Activated neutrophils subsequently produce proinflammatory cytokines, including IL-1β, IL-6, IL-18, and tumor necrosis factor (TNF)-α, as well as reactive oxygen species (ROS), thereby amplifying the hyperinflammatory *milieu* that characterizes the early stage of ARDS [36]. An imbalance between the classical and alternative RAS axes may therefore exacerbate and sustain pulmonary inflammation. Platelet–leukocyte aggregate formation, complement activation and upregulation of tissue factor further exacerbate microvascular inflammation and immune-thrombosis. In parallel with localized pulmonary injury, a systemic inflammatory response develops, contributing to multiple organ dysfunction that frequently accompanies severe ARDS [37]. While initially adaptive, sustained inflammatory signaling perpetuates barrier disruption and promotes extrapulmonary organ involvement. Furthermore, largely through the upregulation of TGF-β signaling, it primes the lung for a subsequent fibroproliferative response—a hallmark of the late fibrotic stage of ARDS [19].

Classical RAS

Extensive evidence from clinical and preclinical studies has established Ang II as a central mediator of inflammatory alveolar injury in ARDS and this effect is largely driven by unopposed activation of the ACE/Ang II/AT1R axis within the injured alveolar compartment [38] (Fig. 1). Specifically, Ang II induces dose-dependent apoptosis of AECs via AT1R activation, thus directly compromising the epithelial barrier integrity [39, 40].

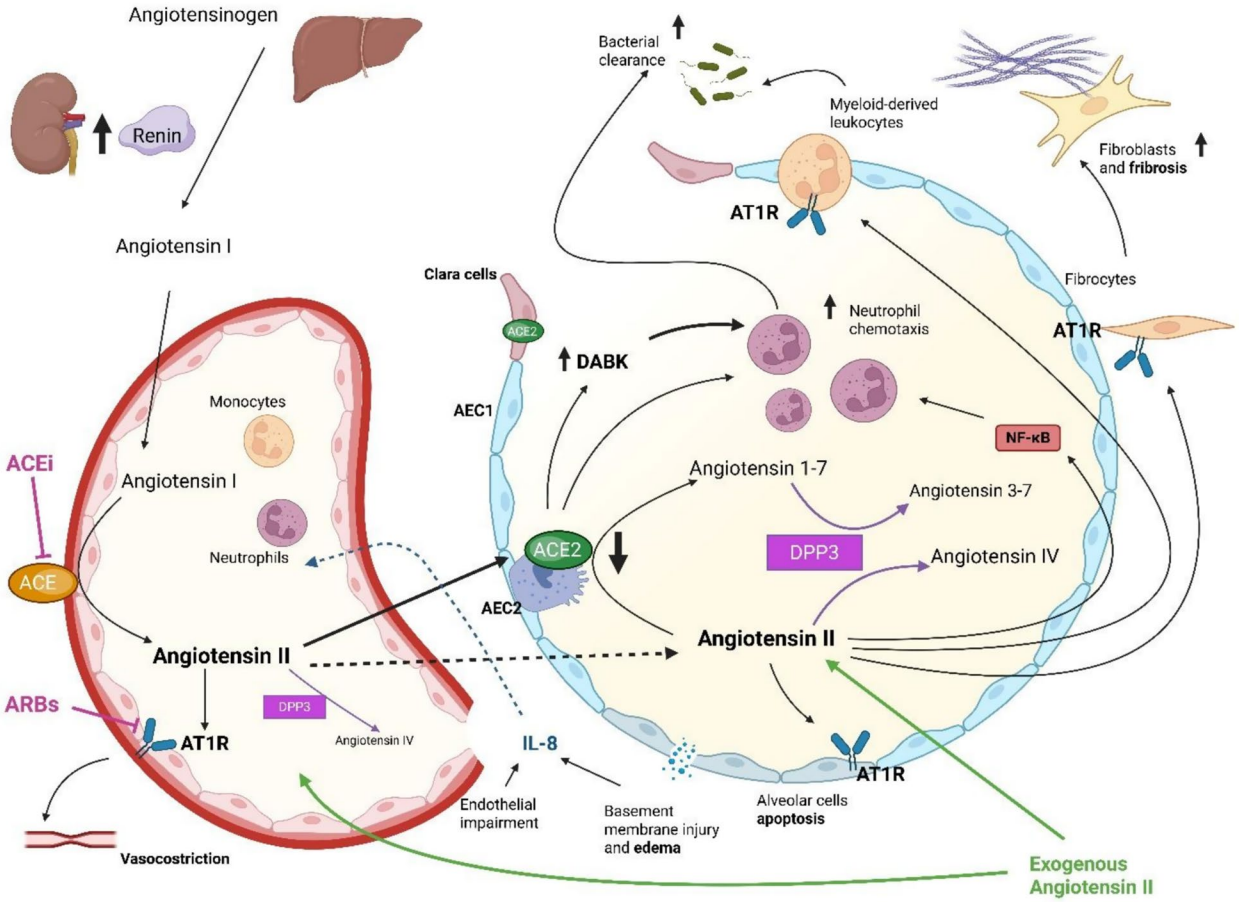

Fig. 1 Pulmonary classical RAS in lung injury. ACE (in orange) expression in pulmonary endothelial cells promotes the conversion of Ang I to Ang II, which primarily binds to AT1R. This receptor, present on pulmonary vascular smooth muscle cells and AEC1, mediates vasoconstriction and induces dose-dependent apoptosis of AEC1, leading to alveolar edema and enhanced recruitment of inflammatory cells through Ang II–induced NF-κB activation. Reduced ACE2 (in green) expression results in DABK accumulation, promoting neutrophil recruitment and the release of inflammatory mediators in the distal airways. AT1R expression on myeloid leukocytes contributes to bacterial clearance, while AT1R activation on fibrocytes by Ang II drives fibrocyte activation and pulmonary fibrosis in later stages. Finally, DPP3 (in purple) degrades Ang II into Ang IV, thereby attenuating pulmonary vasoconstriction. ACEi and ARBs (in pink) inhibit Ang II production and activity, respectively; while exogenous Ang II administration (in green) amplifies the classical RAS. *ACE* angiotensin-converting enzyme, *ACE2* angiotensin-converting enzyme 2, *AEC1* alveolar epithelial cells type 1, *Ang* angiotensin, *AT1R* angiotensin II type 1 receptor, *DABK* des-Arg9-bradykinin, *DPP3* dipeptidyl peptidase 3, *IL* interleukin, *NF-kB* nuclear factor kappa-light-chain-enhancer of activated B cells, *RAS* renin–angiotensin system. ↑: increased activity/expression. ↓: decreased activity/expression ⊥: inhibited activity/expression

In addition, Ang II enhances inflammatory signaling by activating NF-κB [41], stimulating cytokine release and promoting the recruitment of macrophages and neutrophils [40, 42]. These mechanisms have also been implicated in ventilator-induced lung injury (VILI), wherein mechanical ventilation upregulates ACE activity and Ang II generation, in parallel with increased AT1R expression [43–45].

Preclinical evidence suggests that excessive activation of the classical RAS pathway may exert deleterious effects on the lung, as pharmacological inhibition of RAS signaling has been shown to attenuate experimental acute lung injury [42]. Clinical evidence regarding the effects of ACE inhibitors (ACEi) and angiotensin II type 1 receptor blockers (ARBs) on outcomes in ARDS and VILI remains inconclusive; moreover, their use in critically ill patients is largely precluded by hypotension, in addition to their long duration of action and potential to exacerbate renal dysfunction [46, 47].

These effects of classical RAS activation are context- and time-dependent, as they appear highly dependent on disease stage. However, during the early phases of ARDS, activation of the classical pro-inflammatory RAS cascade may serve an adaptive or protective role.

In experimental models of sepsis, exogenous Ang II administration enhanced host immune defense by engaging AT1R on myeloid-derived leukocytes, thereby promoting phagocytosis, ROS production and pro-inflammatory cytokine release, ultimately improving bacterial clearance [48]. Similarly, in the pulmonary compartment, reduced ACE2 expression, reflecting relative predominance of the classical RAS axis, facilitates neutrophil recruitment, a key component of innate immune defense against respiratory pathogens [49, 50]. In addition, diminished ACE2 activity leads to increased availability of DABK, which stimulates airway epithelial cells to release inflammatory mediators and further amplifies neutrophil infiltration during bacterial infection [31]

Alternative RAS and role of ACE2

The ACE2/Ang-(1–7)/MasR axis counterbalances AT1R-mediated signaling by promoting anti-inflammatory, vasodilatory and barrier-protective effects [51] (Fig. 2). Through the conversion of Ang II into Ang-(1–7), ACE2 limits pro-inflammatory cytokine release, attenuates neutrophil recruitment and preserves endothelial integrity [52]. Importantly, infectious and inflammatory conditions frequently impair ACE2 activity. Reduced ACE2 expression has been reported in bacterial pneumonia, influenza and other viral respiratory infections; although pathogen-specific mechanisms differ, ACE2 downregulation appears to represent a shared response to pulmonary inflammation [53]. ACE2 downregulation, a mechanism observed in various forms of ARDS, has emerged as one

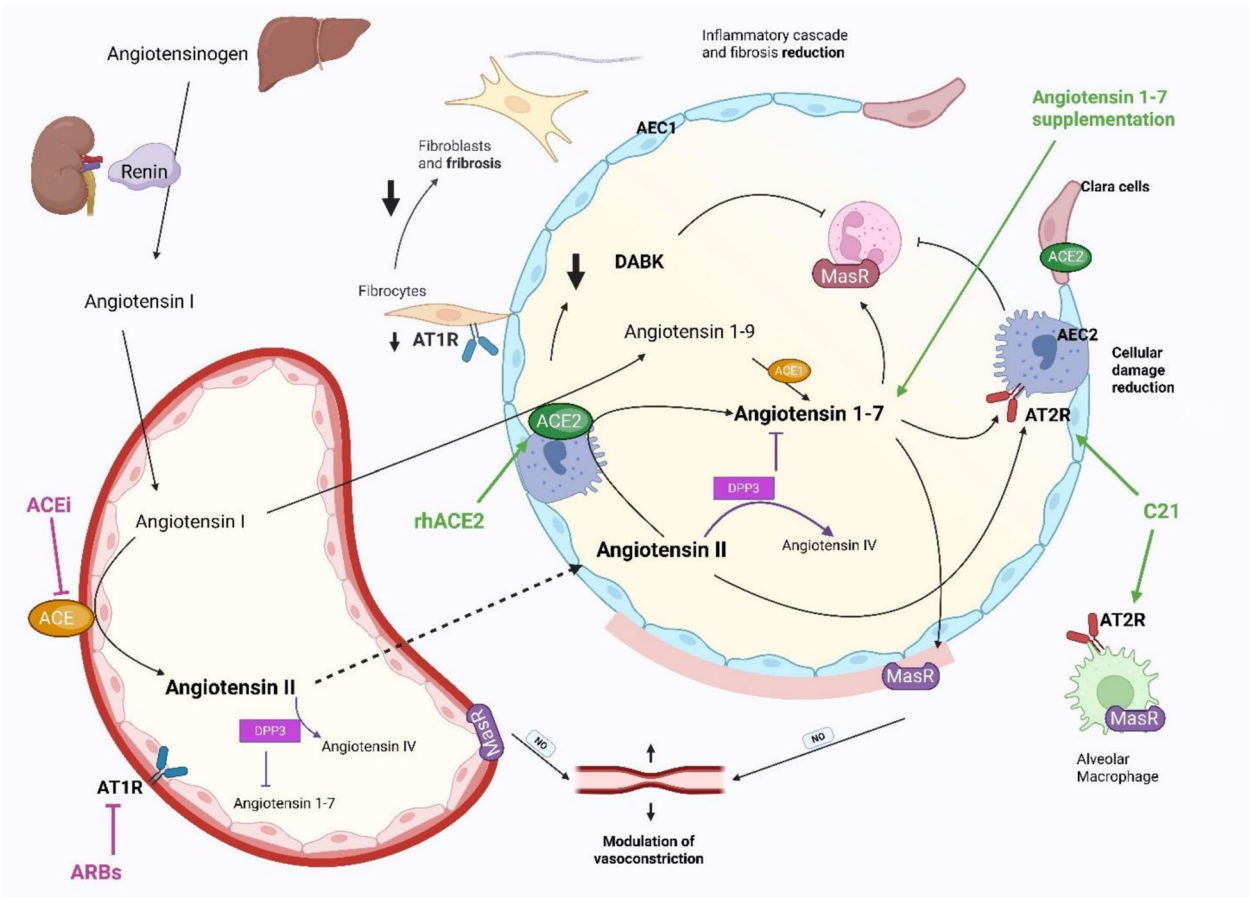

Fig. 2 Pulmonary alternative RAS in lung injury. ACE2 (in green), primarily present in AECII and Clara cells, converts Ang I to Ang-(1–9), which is subsequently converted to Ang-(1–7) by ACE (in orange), and Ang II to Ang-(1–7). Ang-(1–7) binds to MasR expressed on bronchial and vascular smooth muscle cells, promoting vasodilation. Its anti-inflammatory effects occur through three main mechanisms: binding of Ang-(1–7) to AT2R expressed on AECII and alveolar macrophages; interaction of Ang-(1–7) with MasR on immune cells; ACE2-mediated hydrolysis of DABK. Conversely, DPP3 (in purple), released into the circulation following cellular apoptosis, hydrolyzes and inactivates Ang-(1–7). The alternative RAS can be enhanced through exogenous administration of Ang-(1–7), recombinant human ACE2, or AT2R agonists such as compound 21 (C21). *AECII* alveolar type 2 epithelial cells, *Ang* angiotensin, *AT2R* angiotensin II type 2 receptor, *C21* compound 21, *MasR* Mas receptor, *rhACE2* recombinant human ACE2. ↑: increased activity/expression. ↓: decreased activity/expression ⊥: inhibited activity/expression

of the most significant pathophysiological drivers in Coronavirus infection.

ACE2 exists in both membrane-bound (mACE2) and soluble (sACE2) forms. The extracellular domain of mACE2 can be cleaved from the cell surface and released as sACE2 into the interstitial space and circulation, either constitutively or in response to inflammatory stimuli. This process is primarily mediated by the metalloprotease ADAM17, which is widely expressed, including in pulmonary tissue [54, 55]. This mechanism is particularly relevant during coronavirus infections, as mACE2, highly expressed on AECII, serves as the cellular entry receptor for both SARS-CoV and SARS-CoV-2, enabling viral internalization and replication [56]. Viral binding to the spike protein induces mACE2 internalization and downregulation, a process that may reduce susceptibility to subsequent intracellular co-infection [57–59], while ADAM17-dependent shedding further decreases surface mACE2 expression [60, 61]. Notably, only mACE2 facilitates viral entry, whereas sACE2 retains the ability to bind viral particles without permitting cellular internalization, potentially acting as a decoy receptor [62, 63].

Reduced ACE2 activity is thought to favor sustained activation of pro-inflammatory RAS signaling. This imbalance prolongs dominance of the classical RAS axis, thereby promoting persistent inflammation, tissue injury and progression toward fibrotic remodeling [19]. Recent preclinical studies support the therapeutic relevance of the alternative ACE2/Ang-(1–7)/MasR pathway in severe infectious ARDS. In experimental models, exogenous Ang-(1–7) administration significantly improved survival in pneumococcal pneumonia and prevented systemic sepsis [64], likely through enhancement of macrophage-mediated bacterial clearance [65], while simultaneously limiting neutrophil-driven inflammation and preserving epithelial barrier function [66].

Interactions between classical and alternative RAS in the lung: the role of DPP3

Rather than a strictly sequential transition, the balance between the ACE/Ang II/AT1R axis and the ACE2/Ang 1–7/MasR axis appears to be highly dynamic and rapidly responsive to cellular injury [18]. As a matter of fact, under physiological conditions, the concurrent activation of the pro-inflammatory ACE/Ang II/AT1R axis are counterbalanced by the ACE2/Ang-(1–7)/MasR pathway, thereby maintaining pulmonary homeostasis. This finely regulated equilibrium is frequently disrupted during infectious or mechanical insults, such as pneumonia or mechanical ventilation, leading to dysregulated RAS signaling and lung injury [38]. In this context, dipeptidyl peptidase 3 (DPP3), which is released in large amounts following cellular injury and apoptosis, has emerged as an additional contributor to RAS imbalance [32, 33].

Through its ability to convert and inactivate Ang II into Ang IV, DPP3 appears to play a significant role in the loss of compensatory systemic vasoconstriction, ultimately leading to refractory shock [67]. Indeed, elevated circulating DPP3 concentrations have demonstrated prognostic relevance in critically ill patients. In a post hoc analysis of the AdrenOSS-1 trial, which included patients with sepsis and septic shock predominantly of pulmonary origin, high DPP3 levels at admission were strongly associated with 28-day mortality. Moreover, early reductions in DPP3 concentrations correlated with improved organ function, whereas persistently elevated levels were linked to ongoing organ dysfunction and increased mortality [68].

DPP3 has also been evaluated in a European multicenter prospective cohort study involving critically ill patients with COVID-19. In this population, in which mACE2 already serves as the viral entry receptor mediating binding and internalization, DPP3 concentrations on ICU admission were significantly higher in non-survivors than in 28-day survivors, with this difference becoming progressively more pronounced over time, particularly on days 3 and 7. These findings support the hypothesis that DPP3 may be released by injured pulmonary cells and contribute to RAS dysregulation in severe viral lung injury [69]. Given that DPP3 can degrade peptides from both the classical and alternative RAS pathways, its inhibition may restore endogenous Ang II availability, potentially improving pulmonary hemodynamics and/or increase Ang-(1–7) levels, thereby enhancing anti-inflammatory and barrier-protective effects. However, DPP3 represents only one component of a broader network of nonspecific peptidases involved in RAS peptide regulation. Other enzymes with overlapping proteolytic activity, such as neprilysin (NEP), have also been identified and may play complementary roles in modulating RAS signaling during acute lung injury [70].

Furthermore, data from the AKIKI 2 study population, which included patients with severe acute kidney injury (KDIGO 3), revealed that circulating DPP3 levels correlate significantly with 28-day mortality [71]. Similarly, a recent publication supports the pathophysiological role of DPP3 in the development of catecholamine-refractory shock [72]. Specifically, high DPP3 activity may explain the hyporesponsiveness of some patients to exogenous Angiotensin II administration, as the rapid enzymatic degradation of the peptide by DPP3 prevents its vasopressor effect.

In conclusion, since circulating DPP3 levels are significantly higher in septic and cardiogenic shock due to extensive cellular necrosis, this enzyme appears to play

a more prominent pathophysiological role in bacterial sepsis-correlated ARDS [65]. Nevertheless, while DPP3 is not the primary mechanism involved in viral internalization, elevated circulating values have also been documented in severe COVID-19 [66], likely reflecting the amplitude of cellular damage. Consequently, the overlap in DPP3 elevation across these conditions suggests that this biomarker may lack the specificity required to reliably distinguish between bacterial and viral ARDS etiologies, acting instead as a common indicator of the severity of cellular injury.

Therapeutic options

Overall, these observations highlight the multifaceted role of the RAS in ARDS, functioning not only as a regulator of vascular tone but also as a key modulator of pulmonary inflammation and fibrotic remodeling. This temporal complexity has pivotal implications for therapeutic targeting. During the early phase of ARDS, activation of the classical RAS axis appears to contribute to host defense by facilitating recruitment of immune-competent cells and Ang-II may also influence hypoxic pulmonary vasoconstriction. However, sustained or excessive stimulation of this pathway may promote exaggerated inflammatory responses, epithelial cell apoptosis and progression toward fibrotic lung injury. In contrast, timely activation of the alternative RAS axis during later phases may help restore immune balance by modulating cytokine production, limiting tissue damage and attenuating fibrogenesis. These dynamics support the concept of stage-specific RAS modulation as a potential therapeutic strategy in ARDS [19]. In this context, recent experimental and clinical studies have explored a range of therapeutic approaches targeting the RAS, spanning from inhibition of the classical pathway to selective enhancement of alternative RAS components at defined stages of ARDS progression. The main evidence regarding the use of pharmacological agents related to the RAS in the adult population with pneumonia and ARDS is summarized in Table 1.

ACE inhibitors and AT1R blockers

Several preclinical studies have demonstrated that inhibition of the classical RAS axis through angiotensin-converting enzyme inhibitors (ACEi) or ARBs attenuates key pathological features of ARDS, including pulmonary edema, alveolar epithelial apoptosis and endothelial barrier dysfunction [73–76]. Comparable protective effects have been reported in experimental models of VILI, where ACEi or ARB administration reduced inflammatory lung injury and vascular permeability [42, 43, 45].

Signals of potential clinical benefit have also emerged from observational studies. In a retrospective cohort of patients hospitalized with community-acquired pneumonia, chronic ACEi therapy was associated with reduced 30-day mortality [77]. Moreover, ACEi and ARB use has been linked to a lower incidence of pneumonia in older adults initiating antihypertensive therapy [78], as well as reduced risk of pneumonia and disease exacerbations in patients with COPD [79–81] and diabetes mellitus [82].

During the COVID-19 pandemic, substantial uncertainty arose regarding the continuation of RAS inhibitors (RASi) in infected patients. Conflicting results were initially reported [83]; however, several large analyses suggested a neutral or potentially protective effect. In a cohort study of 148 COVID-19 patients adjusted for major confounders, ACEi/ARB use was independently associated with lower rates of ICU admission, invasive mechanical ventilation and mortality [47]. Similarly, a large meta-analysis including more than 100,000 patients reported an association between ACEi/ARB therapy and reduced mortality and adverse outcomes, particularly among patients with hypertension [46]. Importantly, multiple retrospective studies in non-critically ill COVID-19 patients found no benefit from discontinuing chronic ACEi or ARB therapy [84, 85].

Nevertheless, extrapolation of these findings to patients with established ARDS should be approached with caution. ARDS patients differ substantially in both disease severity and pathophysiology and the hemodynamic effects of ACEi and ARBs may be poorly tolerated in this population. In mechanically ventilated and vasopressor-dependent patients, de novo initiation of RASi carries a significant risk of hypotension and cardiovascular instability, potentially offsetting any anti-inflammatory benefit. This concern is supported by a large multicenter randomized controlled trial in critically ill patients, in which initiation of ACEi or ARB therapy was associated with a high probability of worse outcomes, leading to premature trial termination [86]. In summary, although experimental data support a potential protective role of RAS inhibition in inflammatory lung injury, robust clinical evidence in severe ARDS remains limited. The systemic hemodynamic consequences of ACEi and ARB therapy currently constrain their applicability in critically ill patients, underscoring the need for alternative strategies that allow selective and stage-specific modulation of the RAS without compromising cardiovascular stability.

Recombinant human ACE2

Several preclinical investigations have explored the potential protective role of exogenous ACE2 administration in experimental models of ARDS. In animal studies, treatment with human recombinant ACE2 (rhACE2) attenuated the severity of acute lung injury, as reflected by reductions in lung elastance and lung wet-to-dry

Table 1 Summary of main clinical evidence on RAS pharmacological agents in the treatment of adult population with pneumonia and ARDS

Study design	Population	Outcomes/Effects of treatment	Benefit (Yes/No)	COVID-19 (Yes/No)	Refs.
1. ACE inhibitors and AT1R blockers					
Retrospective cohort study	787 adult patients with community-acquired pneumonia (194 on ACE-i chronic treatment)	↓ 30-days mortality in patients on chronic ACE-i treatment	Yes	No	[77]
Retrospective cohort study	254.485 patients (≥ 65 yo.) with a new prescription of anti-hypertensive drugs	↓ Risk of hospitalization for pneumonia within 90-days from the anti-hypertensive drug prescription in patients under ACE-i or ARBs	Yes	No	[78]
Retrospective nested case–control study	375 adult COPD patients	↓ Risk of pneumonia in patients under ACE-i/ARBs	Yes	No	[79]
Retrospective cohort study	215.225 patients with an emerging hypertension diagnosis	ACE-i significantly reduces the incidence of infectious (pneumonia, influenza), inflammatory (COPD) and structural lung disease ARBs significantly reduce the incidence of structural lung disease	Yes	No	[80]
Retrospective comparative study	12.452 patients with a new prescription of ACE-i/ARBs within 90 days after COPD diagnosis	↓ Risk of pneumonia, COPD severe exacerbations and mortality in ARBs vs ACE-i	Yes (for ARBs)	No	[81]
Longitudinal observational study	1.482 patients with type 2 diabetes	↓ Risk of pneumonia and influenza in patients under ACE-i/ARBs	Yes	No	[82]
Systematic review and meta-analysis	101.949 patients with diagnosis of COVID-19	↓ Mortality and incidence of severe adverse events in patients under ACE-i/ARBs	Yes	Yes	[46]
Retrospective observational cohort study	148 hypertensive patients with diagnosis of COVID-19	↓ ICU admission, intubation rate and mortality in patients under ACE-i/ARBs	Yes	Yes	[47]
Retrospective observational study	11.205 patients with diagnosis of COVID-19	↓ All-cause mortality, invasive and non-invasive mechanical ventilation and ICU admission for patients under ACE-i/ARBs	Yes	Yes	[84]
Retrospective cohort study	625 hypertensive patients with COVID-19 under ACE-i/ARBs	Higher mortality rate in patients who discontinued the chronic ARBs therapy	Yes	Yes	[85]
Multicenter randomized clinical trial	779 COVID-19 patients	Initiation of ACE-i/ARBs in critically ill COVID-19 patients worsened organ support-free days and clinical outcomes	No	Yes	[86]
2. Recombinant human ACE2					
Randomized clinical trial (phase II)	39 ARDS patients under mechanical ventilation for < 72 h (19 rhACE2 0.4 mg/kg twice daily for 3 days vs 20 placebo)	No difference in PaO_2/FiO_2, oxygenation index and SOFA score Prematurely stopped following a pre-planned futility analysis	No	No	[91]
Case report	1 severe ARDS due to COVID-19 treated with rhACE2 (0.4 mg/Kg)	–	–	Yes	[92]
3. MasR agonists					
Randomized pilot study	22 COVID-19 patients requiring supplemental oxygen treated with Ang (1–7)/TXA-127 (0.5 mg/kg/day for 10 days)	Prematurely stopped due to decreasing admission rates and low length of stay; no serious adverse events observed	No	Yes	[88]

Table 1 (continued)

Study design	Population	Outcomes/Effects of treatment	Benefit (Yes/No)	COVID-19 (Yes/No)	Refs.
Two randomized controlled trial	543 COVID-19 patients a) 170 patients TXA-127 (0.5 mg/kg/day for 5 days) vs 173 placebo b) 145 patients treated TRV-027 (12 mg/h continuous intravenous infusion for 5 days) vs 145 placebo	TXA-127 and TRV-027 did not improve oxygen-free days; no difference in 28-days mortality	No	Yes	[95]
Randomized controlled trial (phase 1–2)	COVID-19 patients admitted to ICU - Phase 1: 28 patients Ang (1–7) 5 mcg/Kg/day up to 10 mcg/Kg/day after 24 h - Phase 2: 33 patients Ang (1–7) [10 mcg/Kg/day for max 7 days] vs 45 placebo	Prematurely ended due to low recruitment rate Phase 1: one case of bradycardia Phase 2: no differences in oxygen-free days between groups	No	Yes	[97]
Randomized controlled trial (phase 2–3)	238 adults patients hospitalized for severe COVID-19 - 126 oral BIO101 (350 mg twice daily) vs 107 placebo	BIO101 significantly reduced the risk of death and respiratory failure	Yes	Yes	[101]
4. AT2R agonists					
Randomized controlled trial (phase 2)	COVID-19 patients: - 51 C21 (100 mg twice daily for 7 days) vs 55 placebo	No reduction in C-reactive protein Post hoc analysis marked a reduction of requirement for oxygen at day 14 in patients randomized to C21	Yes	Yes	[104]

weight ratios compared with placebo-treated controls [87]. The beneficial effects of rhACE2, including mitigation of fibrotic remodeling and improvement in pulmonary mechanics, have been consistently demonstrated across multiple preclinical models of lung injury, including bleomycin-induced lung injury [88], SARS-CoV-1 infection [56], H5N1 influenza [89] and respiratory syncytial virus infection [90].

Translation of these findings into clinical practice, however, has yielded limited success. The safety, pharmacokinetics, and biological effects of rhACE2 were evaluated in a pilot randomized trial in patients with ARDS. In this study, conducted by Khan et al., participants were randomized to receive escalating doses of rhACE2 followed by twice daily administration or placebo. Although rhACE2 was well tolerated and resulted in a marked reduction in circulating Ang II levels with a concomitant increase in Ang-(1–7), these biochemical effects did not translate into measurable clinical benefit, leading to early termination of the trial [91]. Clinical experience with rhACE2 in COVID-19–related ARDS remains sparse. Evidence is currently limited to a single case report describing its use in a patient with severe COVID-19–associated ARDS [92], as well as preliminary, unpublished data from a randomized controlled trial (NCT04335136), in which the primary composite endpoint of all-cause mortality or need for invasive mechanical ventilation by day 28 or hospital discharge did not differ significantly between treatment groups.

Collectively, these findings suggest that while rhACE2 effectively modulates RAS peptide balance and demonstrates robust protective effects in preclinical models, its clinical efficacy in established ARDS has yet to be demonstrated. Further investigation is needed to determine whether timing of administration, patient selection, or disease phenotype may influence the therapeutic potential of ACE2-based strategies.

MasR agonists

Preclinical studies have also demonstrated that administration of Ang-(1–7) may confer protective effects in experimental models of acute lung injury. In lipopolysaccharide-induced lung injury, Ang-(1–7) attenuated pulmonary inflammation, at least in part through downregulation of AT1R expression, and was associated with reduced progression toward early pulmonary fibrosis [93].

The therapeutic relevance of the ACE2/Ang-(1–7) axis was further explored in a rat model of hydrochloric acid–induced acute lung injury. In this experimental setting, Ang-(1–7) administration mitigated the decline in arterial oxygenation, reduced leukocyte and polymorphonuclear cell counts in bronchoalveolar lavage fluid and decreased collagen deposition within lung tissue. Notably, these effects occurred without significant changes in alveolar cytokine concentrations, suggesting a predominant role in modulating cellular recruitment and tissue remodeling rather than directly suppressing cytokine release [28].

In the clinical context of COVID-19–associated lung injury, a pilot study evaluated the safety of synthetic Ang-(1–7) (TXA-127) in patients requiring supplemental oxygen [94]. This was followed by two large randomized controlled trials investigating modulation of the MasR pathway. One trial tested TXA-127, while the other evaluated TRV027, an AT1R-biased ligand that functionally enhances MasR signaling by shifting downstream pathway activation [95]. Neither study demonstrated a significant benefit on oxygen-free days, although concerns have been raised regarding the dosing strategies employed and the absence of systematic measurements of circulating RAS peptides, which may have limited interpretation of pharmacodynamic effects [96].

Consistent findings were reported in a phase 1–2 randomized trial in which continuous infusion of Ang-(1–7) failed to improve the primary clinical endpoint, despite favorable signals observed in selected secondary outcomes [97]. Nonetheless, recent preclinical evidence continues to support the therapeutic relevance of this pathway, showing that Ang-(1–7) significantly reduces pulmonary inflammation and tissue injury in experimental beta-coronavirus infection models [98]. Moreover, innovative delivery strategies, including intranasal liposomal formulations, have demonstrated efficacy in reducing both viral load and lung inflammation [99] suggesting that localized administration may overcome some limitations observed with systemic approaches.

Beyond peptide-based therapies, alternative pharmacological strategies targeting the alternative RAS axis have emerged. BIO101, a pharmaceutical formulation of the hormone 20-hydroxyecdysone (20E), acts in vitro as a MasR agonist [100] and has shown encouraging results in patients with severe COVID-19. Its efficacy and safety were recently evaluated in a randomized controlled trial involving 126 hospitalized adults with severe disease, in which BIO101 (350 mg twice daily) was associated with a significant reduction in the risk of respiratory failure and death compared with placebo, without an increase in adverse events [101]. Collectively, these data highlight the therapeutic promise of targeting the alternative RAS pathway, while underscoring the importance of appropriate dosing, patient selection, and delivery strategies to fully translate preclinical benefits into clinical efficacy.

AT2R agonists

Given their anti-inflammatory and antifibrotic properties, direct stimulation of the AT2R has emerged as a potential therapeutic strategy in lung injury. AT2R activation may counteract many of the deleterious effects mediated by AT1R signaling. This concept is supported by preclinical investigations of the selective AT2R agonist compound 21 (C21), which has demonstrated beneficial effects in multiple experimental models. In particular, C21 attenuated pulmonary vascular remodeling and right ventricular fibrosis in animal models of pulmonary hypertension [102] and significantly reduced inflammation and fibrotic remodeling in bleomycin-induced lung injury [103].

Importantly, among the AT2R agonists evaluated in experimental studies, C21 is currently the only compound that has advanced to clinical testing. Although a phase II trial investigating C21 in patients with fibrotic lung disease was terminated prematurely, the compound was subsequently evaluated in a phase II randomized controlled trial involving hospitalized patients with COVID-19. While the study did not demonstrate a significant effect on the primary endpoint of C-reactive protein (CRP) reduction, secondary analyses revealed a lower proportion of patients requiring supplemental oxygen at day 7 in the C21 group compared with placebo, suggesting a potential clinical signal warranting further investigation [104]. Other AT2R agonists remain confined to the preclinical domain. Among these, CGP42112 is the most extensively studied. Initially identified in 1989 [105] and originally developed as an AT1R antagonist [106], CGP42112 was later characterized as a selective AT2R agonist [107]. In experimental models, CGP42112 has shown favorable effects, including attenuation of cardiac fibrosis and modulation of tissue remodeling processes [108]. However, despite these promising findings, CGP42112 has not yet progressed to evaluation in human clinical trials. Overall, AT2R agonism represents a biologically plausible and mechanistically attractive approach to modulating inflammation and fibrosis in acute and chronic lung injury. Nevertheless, the translation of these experimental findings into clinically meaningful therapies remains limited, underscoring the need for further well-designed clinical trials to define optimal patient populations, dosing strategies and therapeutic windows.

Anti-DPP3

Circulating DPP3 may complicate RAS dysregulation by hydrolyzing peptides from both the classical and alternative pathways, thereby contributing to the persistence of refractory shock. Recently, a humanized monoclonal antibody that binds DPP3 and inhibits its enzymatic activity, Procizumab, was evaluated in a phase 1 study involving healthy subjects (NCT06331884). Beyond clinical trials, the rescue use of procizumab has been reported in three terminally ill patients with refractory shock and multi-organ failure due to septic cardiomyopathy [109]. In these cases, administration was well-tolerated and associated not only with a rapid reduction in DPP3 activity but also with decreased norepinephrine requirements and lactate levels. Notably, treated patients also showed a significant improvement in respiratory function, as measured by the PaO_2/FiO_2 ratio. Although still experimental and requiring validation in phase 2 and 3 trials, Procizumab could emerge as a promising therapeutic tool for ARDS, particularly in scenarios where excessive DPP3 release exacerbates multi-organ dysfunction.

RAS in ARDS patients with shock

Hemodynamic instability is a frequent complication in critically ill patients with ARDS, with more than 60% developing circulatory failure and requiring vasopressor support, a condition consistently associated with increased mortality [14]. The mechanisms underlying hemodynamic impairment in ARDS are multifactorial [8]. In this setting, Ang-II may confer potential benefits on both hemodynamic and respiratory function by restoring vascular tone in vasodilatory shock, improving mean arterial pressure and organ perfusion and modulating pulmonary vascular resistance (PVR).

Following publication of the ATHOS-3 trial, pharmaceutical-grade Ang-II became available for second-line vasopressor therapy in patients with vasodilatory shock [110]. During the COVID-19 pandemic, several observational studies subsequently evaluated its effects on respiratory function and gas exchange. In a small single-center compassionate-use pilot study involving 16 mechanically ventilated patients, Ang-II administration was associated with significant improvements in arterial oxygenation, the SpO_2/FiO_2 ratio, and a reduction in FiO_2 requirements [111]. Two subsequent multicenter observational studies reported improved oxygenation and a more rapid decrease in FiO_2 and $PaCO_2$ among patients receiving Ang-II compared with standard care, although these physiological benefits did not translate into improved survival [112, 113].

A post hoc analysis of the ATHOS-3 trial focusing on 81 patients with ARDS showed that the 34 individuals treated with Ang-II experienced a significant increase in the PaO_2/FiO_2 ratio and a reduction in the oxygenation index compared with placebo. These effects occurred independently of ventilator settings, as no significant differences were observed in PEEP, ventilatory ratio or minute ventilation between groups [114]. Consistent findings were reported in another

post hoc analysis of a retrospective multicentre cohort including 254 non-COVID-19 ARDS patients (ARTEMIS-O_2) [115].

The mechanisms underlying these improvements remain incompletely understood. However, several studies suggest that Ang-II may exert specific effects on the pulmonary vasculature that are at least partially dissociated from its systemic vasoconstrictive action. In addition, potential anti-inflammatory effects mediated through AT2R activation or via conversion of Ang-II to Ang-(1–7) by ACE2 cannot be excluded [33, 114].

Given its AT1R-mediated vasoconstrictive properties, the impact of Ang-II on PVR and hypoxic pulmonary vasoconstriction is of particular relevance in ARDS. Experimental studies have demonstrated divergent pulmonary vascular effects of norepinephrine and Ang-II. Norepinephrine, through α_1-adrenergic stimulation, acts as a global pulmonary vasoconstrictor affecting both arteries and veins, resulting in a proportionally greater increase in PVR compared with systemic vascular resistance [116]. This was supported by a clinical study in mechanically ventilated patients with septic shock, in which high-dose norepinephrine infusion (mean dose of 0.32 µg/kg*min) significantly increased PVR compared with dopamine, without affecting RV ejection fraction [117]. In contrast, experimental studies in isolated canine lungs demonstrated that Ang-II induces vasoconstriction predominantly at the level of pulmonary arteries, with minimal effect on pulmonary venules under resting conditions; when venules were pre-contracted, Ang II elicited a modest vasodilatory response [118].

Some experimental evidence suggests that alveolar hypoxia may attenuate Ang II–mediated pulmonary vasoconstriction, potentially through modulation of hypoxic pulmonary vasoconstriction and improved ventilation–perfusion matching [119]. This hypothesis is supported by studies in healthy volunteers exposed to hypoxia, in which administration of AT1R antagonists (saralasin or losartan) inhibited hypoxic vasoconstriction [120, 121]. In a prospective observational study of 45 mechanically ventilated patients, plasma Ang II concentrations were not associated with the development of pulmonary hypertension or RV failure as assessed by echocardiography [122].

Finally, concerns regarding a potentially deleterious effect of Ang II on pulmonary hemodynamics were challenged by a secondary analysis of a multicentre feasibility study (A-TRAK) conducted in 58 patients following cardiac surgery. In this cohort, Ang II administration did not increase PVR compared with norepinephrine [123].

Future perspectives

To translate these therapeutic strategies into clinical practice, the identification of specific, clinically applicable biomarkers is essential for a precision medicine approach in ARDS. In this context, monitoring plasma renin activity or, more specifically, circulating Angiotensin II levels could identify patients with a depleted RAS profile who are most likely to benefit from exogenous Angiotensin II infusion [124]. Similarly, measuring circulating DPP3 concentrations [68] would be crucial for selecting candidates for anti-DPP3 antibody (procizumab) therapy, ensuring that treatment is targeted at individuals with high enzymatic activity that compromises cardiovascular and respiratory stability. Implementing such diagnostic strategies would allow for stage-specific and phenotype-driven interventions, potentially improving survival outcomes.

Conclusions

The RAS appears to contribute to ARDS pathophysiology through its intertwined roles in inflammation, vascular regulation and lung injury. The dynamic balance between its classical and alternative pathways suggests that stage-specific RAS modulation may offer therapeutic benefit. In patients with ARDS complicated by hemodynamic instability, exogenous Ang-II may improve systemic perfusion and oxygenation without adversely affecting PVR.

The marked heterogeneity of ARDS, across etiologies disease stages and hemodynamic profiles, likely explains the variable efficacy observed with RAS-directed therapies in clinical studies. This highlights the importance of biomarker-guided patient stratification to identify those most likely to benefit. Future efforts should focus on achieving selective, time-dependent modulation of RAS signaling while minimizing systemic adverse effects.

Abbreviations

20E	20-Hydroxyecdysone
ACE	Angiotensin-converting enzyme
ACE2	Angiotensin-converting enzyme 2
mACE2	Membrane-ACE2
sACE2	Soluble-ACE2
ACEi	ACE inhibitors
AECII	Alveolar type 2 epithelial cells
Ang	Angiotensin
ARBs	AT1R blockers
ARDS	Acute respiratory distress syndrome
AT1R	Angiotensin II type 1 receptor
AT2R	Angiotensin II type 2 receptor
C21	Compound 21
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
DABK	Des-Arg9-bradykinin
DPP3	Dipeptidyl peptidase 3
IL	Interleukin
MasR	Mas receptor
NEP	Neprilysin
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells

NO	Nitric oxide
PEEP	Positive end-expiratory pressure
PVR	Pulmonary vascular resistance
RAS	Renin–angiotensin system
RASi	RAS inhibitors
rhACE2	Recombinant human ACE2
ROS	Reactive oxygen species
RV	Right ventricle/ventricular
TNF-α	Tumor necrosis factor α
VILI	Ventilator-induced lung injury

Acknowledgements
None.

Author contributions
C.D. and I.S.Z. equally contributed to this work. C.D., I.S.Z., A.C. and V.B. wrote the draft. F.A. and F.S.T. made substantial contributions to the conception of the manuscript. F.A., F.S.T., S.S., S.S. and G.S. reviewed and revised the manuscript. All authors reviewed and approved the final version.

Funding
None.

Data availability
No datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 8 March 2026 Accepted: 7 May 2026
Published online: 14 May 2026

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