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REVIEW

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# Heart–lung interaction in acute respiratory distress syndrome: Pathophysiological insights and stepwise lung- and right ventricular-protective management

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## ABSTRACT:

Acute respiratory distress syndrome (ARDS) imposes a substantial burden on right ventricular (RV) function through increased pulmonary vascular resistance driven by pulmonary vascular injury, hypoxemia, hypercapnia, and the mechanical effects of positive-pressure ventilation. In a subset of patients, this may progress to acute cor pulmonale and is associated with worse outcomes. This narrative review summarizes the pathophysiology of heart–lung interaction in ARDS, the respiratory and hemodynamic effects of prone positioning, and current RV-protective management strategies. Current guidelines support prone positioning in selected patients with moderate-to-severe ARDS, particularly those with severe hypoxemia despite optimized ventilatory support. The 2024 American Thoracic Society (ATS) guideline recommends prone positioning for >12 hours/day in severe ARDS, whereas the 2023 European Society of Intensive Care Medicine (ESICM) guideline and contemporary practice commonly support longer sessions of 16–18 hours, consistent with the PROSEVA protocol. Recent meta-analytic evidence suggests that extended prone positioning may improve oxygenation and reduce mortality, although optimal session duration, patient selection, and complication risk require further study. Prone positioning should be considered a central component of an integrated RV-protective approach that also includes lung-protective ventilation, minimization of driving pressure, individualized positive end-expiratory pressure (PEEP) titration, carbon dioxide control, hemodynamic assessment, and rescue therapies such as inhaled pulmonary vasodilators and veno-venous extracorporeal membrane oxygenation when indicated.

**Keywords:** Acute respiratory distress syndrome; Prone positioning; Right ventricular dysfunction; Heart–lung interaction; Acute cor pulmonale; Right ventricular-protective management

## INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a life-threatening form of acute hypoxemic respiratory failure resulting from diffuse inflammatory lung injury [1]. It is characterized by bilateral pulmonary opacities, impaired gas exchange, and reduced respiratory system compliance, not fully explained by cardiac failure or fluid overload [1]. Despite advances in critical care and the widespread adoption of lung-protective ventilation, moderate-to-severe ARDS remains associated with substantial morbidity and mortality [2, 3]. Increasing evidence suggests that outcomes in ARDS are determined not only by the extent of lung injury but also by its cardiovascular consequences, particularly the burden imposed on right ventricular (RV) function.

The RV is a thin-walled, low-pressure chamber with limited tolerance for acute pressure loading, making it especially vulnerable in ARDS [4]. Several mechanisms converge to increase pulmonary vascular resistance (PVR), including inflammatory pulmonary vascular injury, hypoxic pulmonary vasoconstriction (HPV), microvascular thrombosis, hypercapnia, and the mechanical effects of positive-pressure ventilation [5, 6]. When RV afterload exceeds compensatory reserve, RV dilatation occurs, the interventricular septum shifts toward the left ventricle (LV), LV filling is impaired, and cardiac output may fall. This syndrome, known as acute cor pulmonale (ACP), has been reported in approximately 10 to 30 percent of the patients with ARDS receiving protective ventilation and is associated with worse clinical outcomes [7, 8].

These observations have shifted the management of ARDS from lung protection alone toward an integrated heart-lung approach. Among supportive strategies, prone positioning has a central role. Beyond improving oxygenation, prone positioning may improve ventilation-perfusion matching, reduce regional overdistension, attenuate HPV, lower PVR, and unload the RV [9, 10]. This narrative review summarizes the pathophysiology of heart-lung interaction in ARDS, echocardiographic criteria for ACP, principles of RV-protective mechanical ventilation and individualized PEEP titration, respiratory and hemodynamic effects of prone positioning, and a proposed stepwise approach to integrated RV-protective management.

A narrative literature search was performed using PubMed and EMBASE for publications available up to March 2026. Search terms included acute respiratory distress syndrome, right ventricular dysfunction, acute cor pulmonale, heart-lung interaction, prone positioning, RV-protective ventilation, and extracorporeal membrane oxygenation. Priority was given to randomized controlled trials, prospective observational studies, systematic reviews, meta-analyses, and current international clinical practice guidelines. Relevant peer-reviewed studies published in 2025 and 2026 were incorporated where appropriate and described as recent or emerging evidence.

### KEY MESSAGES:

- ARDS and positive-pressure ventilation increase RV afterload, risking fatal acute cor pulmonale.
- RV protection requires low driving pressure, careful PEEP titration, and hemodynamic monitoring.
- Prone positioning reduces RV afterload and improves ventilation-perfusion matching in severe ARDS. Guidelines recommend prone positioning for at least 12 to 18 hours daily.
- Use norepinephrine or inotropes for RV failure and ECMO for refractory cases.

## NORMAL CARDIOPULMONARY PHYSIOLOGY

Because the cardiac chambers and pulmonary vasculature are enclosed within the thorax, changes in intrathoracic pressure are transmitted to intrathoracic structures and directly influence ventricular preload, afterload, and PVR [11-14]. With each breath, these effects generate predictable heart–lung interactions, although their direction differs between spontaneous breathing and positive-pressure ventilation [11-14].

During spontaneous inspiration, contraction of the diaphragm and inspiratory muscles lowers pleural pressure below atmospheric pressure. This fall in intrathoracic pressure (ITP) increases the pressure gradient for systemic venous return to the right atrium, thereby enhancing RV filling [11]. At the same time, because extrathoracic aortic pressure remains relatively unchanged, LV transmural systolic pressure increases, resulting in a higher effective LV afterload [12]. In healthy individuals, these effects usually produce only a small inspiratory decline in systolic blood pressure. However, when pleural pressure swings become exaggerated, such as in severe bronchospasm or pericardial tamponade, this phenomenon may manifest clinically as pulsus paradoxus [12].

### Positive-pressure mechanical ventilation

Mechanical ventilation applies positive pressure at the airway, which is transmitted through the lungs to the pleural space with each breath. This reverses many of the hemodynamic effects of spontaneous breathing and results in four key circulatory effects [11]:

1. Reduction in RV preload: Elevated ITP compresses the low-pressure veins returning blood to the thorax, thereby reducing the pressure gradient for venous return. As a result, RV end-diastolic volume and stroke volume decrease during mechanical inflation.

2. Increase in RV afterload: PVR follows a U-shaped relationship with lung volume, reaching its lowest point near functional residual capacity (FRC) and rising at both low and high lung volumes. Tidal inflation above FRC compresses intra-alveolar capillaries; when alveolar pressure exceeds pulmonary venous pressure, Zone 2 conditions may develop, increasing impedance to RV ejection.
3. Augmentation of LV preload: Positive-pressure lung inflation mobilizes blood from the pulmonary microcirculation toward the left atrium, generating a transient early-inspiratory increase in LV filling that precedes the downstream consequences of reduced RV output.
4. Reduction in LV afterload: Positive ITP surrounding the LV reduces LV transmural systolic pressure and, consequently, myocardial wall stress. This afterload reduction facilitates LV ejection and is a principal mechanism by which noninvasive positive-pressure ventilation provides hemodynamic support in acute decompensated heart failure.

The magnitude of these effects depends on tidal volume, positive end-expiratory pressure (PEEP), respiratory rate, lung compliance, and the filling state of each ventricle [11, 12]. In healthy individuals, these changes are modest and well tolerated. In ARDS, however, in which PVR is already elevated and RV reserve may be limited, these mechanical stresses are amplified and may become clinically significant.

## PATHOPHYSIOLOGY OF HEART–LUNG INTERACTION IN ARDS

In ARDS, lung injury is heterogeneous: dependent regions are consolidated and edematous, whereas non-dependent regions remain relatively aerated. This heterogeneity increases PVR through two major mechanisms. First, widespread endothelial injury and intravascular microthrombi, driven by systemic inflammation such as tumor necrosis factor-α, interleukin-1β, and interleukin-6, reduce the pulmonary capillary cross-sectional area [5]. Second, alveolar hypoxia in consolidated regions triggers HPV. Although HPV normally diverts blood flow away from poorly ventilated lung units, inflammatory dysregulation in ARDS may impair this adaptive response, contributing to persistent intrapulmonary shunt (Qs/Qt) and increased overall PVR [6]. The net result is a marked increase in RV afterload that may exceed the adaptive capacity of the normal RV.

The U-shaped relationship between PVR and lung volume is particularly important in ARDS. Because the injured lung contains both atelectatic dependent zones and overdistended non-dependent zones, both extremes of this curve may coexist simultaneously, further increasing RV afterload [13]. In addition, positive-pressure ventilation raises ITP, thereby reducing venous return and compromising RV preload [11]. This creates a clinical dilemma: the PEEP and tidal volume required to maintain oxygenation may increase RV afterload, whereas insufficient ventilatory support allows hypoxemia and hypercapnia to worsen pulmonary vasoconstriction.

Systemic hypoxemia triggers sympathetic activation, increases myocardial oxygen demand while reducing oxygen supply, and may contribute to RV ischemia [6]. Permissive hypercapnia, which may occur during low-tidal-volume ventilation, can further raise PVR because hypercapnic acidosis increases mean pulmonary arterial pressure (mPAP) and impairs RV contractility [14]. Hypercapnic acidosis also has divergent vascular effects: while it causes pulmonary vasoconstriction and increases RV afterload, it may simultaneously induce systemic vasodilation, lowering mean arterial pressure and reducing the perfusion pressure gradient available for RV coronary blood flow. This dual vascular effect underscores the clinical importance of correcting severe hypercapnia in patients with established or suspected RV dysfunction.

RV failure may then worsen pulmonary edema and gas exchange through ventricular interdependence, also known as the reverse Bernheim effect [15, 16]. As the acutely dilated RV shifts the interventricular septum leftward into the LV cavity, LV diastolic compliance decreases and LV filling is impaired. This may increase left-sided filling pressure despite reduced effective LV preload, thereby augmenting pulmonary capillary hydrostatic pressure and superimposing a cardiogenic component on pre-existing inflammatory pulmonary edema [17]. The result is a self-perpetuating cycle in which RV failure worsens pulmonary edema, gas exchange deteriorates, hypoxemia and hypercapnia deepen, PVR rises, and RV afterload is amplified.

In this review, RV dysfunction refers to any detectable impairment of RV size or function without overt hemodynamic compromise. RV failure denotes a clinical state in which RV dysfunction results in reduced cardiac output and systemic hypoperfusion. ACP specifically refers to the echocardiographic combination of RV dilatation with paradoxical septal motion arising from acute pressure overload.

When PVR rises acutely, the RV initially adapts through dilatation, a process termed heterometric adaptation. Within the constraint of the pericardium, RV dilatation further shifts the interventricular septum leftward, reduces LV end-diastolic volume, impairs LV filling, and decreases stroke volume and cardiac output [17]. This hemodynamic deterioration characterizes ACP. Echocardiographically, ACP is commonly defined by the combination of RV dilatation, usually an RV end-diastolic area/LV end-diastolic area (RVEDA/LVEDA) ratio > 0.6, and paradoxical systolic septal motion or septal dyskinesia [7, 8]. When ACP is present, even modest reductions in pulmonary vascular loading may translate into clinically meaningful improvements in cardiac output and systemic perfusion, as illustrated in Figure 1.

## MECHANICAL VENTILATION: RV-PROTECTIVE PRINCIPLES

Traditional lung-protective mechanical ventilation, targeting tidal volumes of 4–6 mL/kg predicted body weight (PBW) and limiting plateau pressure to ≤ 30 $cmH_2O$, has substantially reduced ventilator-induced lung injury (VILI) and underpins current ARDS guidelines [2]. How-

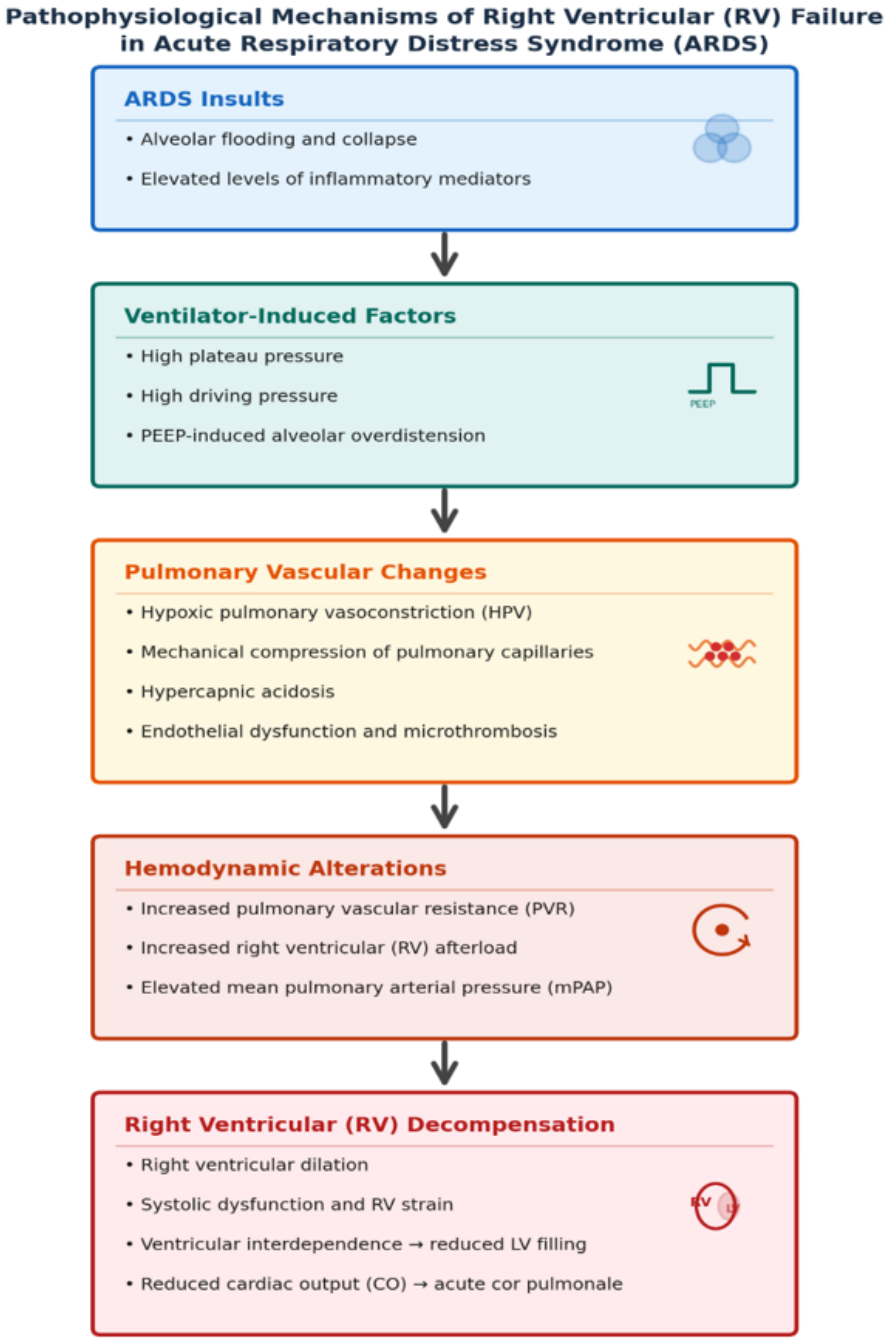



**Figure 1.** Pathophysiology of right ventricular (RV) failure in ARDS. Three converging mechanisms elevate pulmonary vascular resistance (PVR), leading to RV pressure overload, ventricular interdependence, and acute cor pulmonale.

**Abbreviations:** ARDS: acute respiratory distress syndrome; ACP: acute cor pulmonale; HPV: hypoxic pulmonary vasoconstriction; LV: left ventricle; PVR: pulmonary vascular resistance; RV: right ventricle.

ever, standard lung-protective targets do not uniformly protect the right ventricle and, under some conditions, may increase RV afterload [18, 19]. A useful conceptual framework distinguishes three categories of ventilatory goals: (1) shared principles that simultaneously protect both the lung and the RV (e.g., limiting tidal volume, avoiding overdistension); (2) lung-specific targets that do not inherently account for RV load; and (3) RV-specific targets that require active adjustment beyond standard lung protection [19]. Recognizing this distinction enables clinicians to anticipate and manage conflicts between pulmonary and cardiac goals at the bedside (Table 1).

Among RV-relevant ventilatory variables, elevated driving pressure (ΔP = plateau pressure − PEEP) is strongly associated with ACP; in one study, ΔP ≥18 $cmH_2O$ independently predicted ACP. Therefore, active minimization of driving pressure, commonly targeting ≤15 $cmH_2O$ when feasible, is a reasonable goal in patients with known or suspected RV compromise [19]. PEEP titration presents a parallel challenge. PEEP selected solely to improve oxygenation may cause alveolar overdistension and increase non-Zone 3 conditions, thereby elevating RV afterload. Conversely, insufficient PEEP permits cyclic atelectasis, hypoxemia, and HPV. Therefore, PEEP should be individualized according to lung recruitability and RV response rather than oxygenation alone. Individualizing PEEP to lung recruitability, assessed by the recruitment-to-inflation (R/I) ratio or electrical impedance tomography (EIT), allows optimization of the PVR–lung volume relationship and supports both lung and RV protection [18, 19]. This concept aligns with the proposal to move beyond simply "open up the lung and keep the lung open" toward "open up the lung and keep the lung vessels open," emphasizing that optimal PEEP should recruit alveoli while preserving pulmonary vascular patency [18]. EIT achieves this by identifying the individual crossing point between alveolar overdistension and cyclic collapse on regional compliance curves, thereby locating the optimal PEEP that minimizes RV afterload more precisely than oxygenation-based titration alone [18, 19].

Hypercapnia is another important modifiable contributor to RV afterload. Although permissive hypercapnia is often accepted during lung-protective ventilation, $PaCO_2$ ≥ 48 mmHg has been associated with ACP. In patients with established or suspected RV dysfunction, unnecessary hypercapnia should be avoided, and $PaCO_2$ should be reduced when feasible without increasing injurious ventilatory stress. Increasing respiratory rate may lower $PaCO_2$, but excessive rates may shorten expiratory time, promote intrinsic PEEP, increase mechanical power, and expose the RV to more frequent cycles of peak afterload. Conversely, excessively low rates may worsen $CO_2$ retention. Respiratory rate should therefore be individualized according to $PaCO_2$, pH, intrinsic PEEP, mechanical power, and RV response [19]. Assisted ventilation may reduce mean transpulmonary pressure and RV afterload when respiratory effort is controlled; however, excessive spontaneous effort may increase transpulmonary pressure swings and worsen lung injury or RV loading [19].

Alongside ventilatory titration, parallel monitoring of RV function is essential for personalizing these strategies. Bedside echocardiography remains the cornerstone of RV assessment, with key parameters including the RV-to-LV end-diastolic area ratio (RVEDA/LVEDA; >0.6 indicating RV dilatation), tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and RV global longitudinal strain (GLS) [20]. Pulmonary artery catheterization may provide complementary assessment when echocardiography is insufficient, shock is unexplained, or continuous hemodynamic monitoring is needed [20]. Together, these modalities guide iterative ventilatory and pharmacological titration to optimize RV loading conditions and support a physiology-based approach to RV protection in ARDS (Figure 3).

It is important to acknowledge that the evidence supporting specific RV-protective ventilation targets remains largely observational and physiologically derived, rather than based on randomized controlled trials with RV outcomes as primary endpoints. The rationale for minimizing driving pressure is supported by robust observational evidence, including the analysis by Amato et al., which showed that driving pressure was more strongly associated with survival than tidal volume or plateau pressure alone [21]. However, a specific target such as driving pressure ≤15 $cmH_2O$ has not been incorporated into current clinical practice guidelines and should be understood as an evidence-informed clinical target. Specific PEEP targets for RV protection are similarly derived from physiological reasoning and observational studies. Recent publications by Slobod et al. provide emerging insights into RV-protective ventilation strategies [19, 20], but this approach requires further prospective validation. Clinicians should therefore apply these targets with awareness of their evidence base and individualize decisions using bedside respiratory and hemodynamic assessment.

## RESPIRATORY MECHANICS OF PRONE POSITIONING

In the supine position, the weight of the heart and ventral lung compresses the dorsal, dependent lung, generating a steep vertical pleural pressure gradient that promotes dependent alveolar collapse. When the patient is turned prone, this compressive force is redistributed to the anterior chest wall, which is stiffer than the posterior chest wall. The result is a more homogeneous pleural pressure distribution, more even regional transpulmonary pressures, and recruitment of previously collapsed dorsal alveoli with less overdistension of non-dependent regions [9].

As lung inflation becomes more uniform, cyclic atelectasis and regional alveolar overdistension, which are important drivers of VILI, are reduced. Driving pressure and mechanical power may also decrease as compliance improves in the recruited dorsal zones [21]. At the same time, prone positioning improves ventilation–perfusion (V/Q) matching: ventilation shifts toward the dorsal lung as compliance is restored, while pulmonary perfusion tends to

**Table 1.** Ventilatory targets and considerations for lung-protective versus lung + right ventricular-protective ventilation in ARDS.

| Parameter | Lung-protective target | Lung + RV-protective target | Comment/Rationale |
|---|---|---|---|
| Tidal volume | 6 mL/kg PBW; reduce to 4–5 mL/kg if needed | Same target; avoid excessive tidal inflation | Shared goal; limits VILI and reduces RV stroke work |
| Plateau pressure | ≤ 30 $cmH_2O$ | Consider lower Plateau pressure ≤28 $cmH_2O$ when RV compromise is present | Lower alveolar pressure may reduce pulmonary vascular compression and RV afterload |
| Driving pressure | Limit when possible | Actively minimize driving pressure; commonly aim ≤15 $cmH_2O$ when feasible | Driving pressure ≥18 $cmH_2O$ independently predicts ACP |
| PEEP | Often oxygenation-guided | Individualize using recruitability and RV response; consider recruitment-to-inflation ratio or electrical impedance tomography | Excessive PEEP may cause overdistension; insufficient PEEP may permit atelectasis and HPV |
| $PaCO_2$/pH | Permissive hypercapnia acceptable | Avoid $PaCO_2$ ≥48 mmHg when RV compromise is present | Hypercapnia promotes pulmonary vasoconstriction and increases RV afterload |
| Respiratory rate | Adjusted to balance $PaCO_2$ and driving pressure | Individualize; avoid excessive respiratory rate and intrinsic PEEP | Excessive respiratory rate may increase mechanical power and RV loading; low respiratory rate may worsen hypercapnia |
| Ventilation mode | Passive or assisted ventilation | Assisted ventilation may be useful if effort is controlled; excessive effort may be harmful. | Assisted ventilation reduces mean transpulmonary pressure and RV afterload. |
| RV monitoring | Not routine in all patients | Use echocardiography when RV dysfunction is suspected; consider PA catheter selectively | Guides individualized ventilator and hemodynamic titration |

**Abbreviations:** RV: right ventricle; ARDS: acute respiratory distress syndrome; ACP: acute cor pulmonale; PBW: predicted body weight; VILI: ventilator-induced lung injury; PEEP: positive end-expiratory pressure; HPV: hypoxic pulmonary vasoconstriction; PA: pulmonary artery.

remain preferentially distributed toward dorsal lung regions because of the anatomical distribution of the pulmonary vasculature. As ventilation and perfusion become better aligned in the dorsal lung, intrapulmonary shunt decreases and arterial oxygenation improves [9, 10].

## HEMODYNAMIC IMPACT OF PRONE POSITIONING

### RV afterload reduction

Prone positioning may reduce PVR through several complementary mechanisms. First, improved V/Q matching and oxygenation may attenuate HPV. Second, reduced regional overdistension may relieve compression of intra-alveolar capillaries. Third, recruitment of previously collapsed dorsal lung regions may restore radial traction on extra-alveolar vessels, thereby reducing their resistance [9, 22]. Together, these effects may reduce PVR and mPAP, thereby lowering RV afterload.

### Venous return and intra-abdominal pressure

Turning the patient prone may increase intra-abdominal pressure (IAP), particularly if the abdomen is compressed against the mattress. Moderate increases in IAP may mobilize blood from the splanchnic venous reservoir and increase mean systemic filling pressure, potentially supporting venous return. However, excessive abdominal compression can impede venous return, underscoring the importance of positioning strategies that allow the abdomen to move freely. Accordingly, careful support of the thorax and pelvis to avoid abdominal compression is important during prone positioning [23].

Allowing the abdomen to move freely during prone positioning also improves diaphragmatic excursion during inspiration and facilitates ventilation redistribution toward the dorsal lung regions, where pulmonary perfusion is preferentially maintained. The improved dorsal ventilation-perfusion alignment may reduce HPV and contribute to the oxygenation benefit of prone positioning.

### Restoration of ventriculo-arterial coupling

As RV afterload falls, RV dilatation may improve, interventricular septal shift may lessen, and LV filling and stroke volume may increase [17, 22], as depicted in Figure 2. These changes can be assessed at the bedside with echocardiography (Table 2). A recent single-center study by Cheong et al. (2025), using speckle-tracking echocardiography, reported improvement in RV global longitudinal strain and RV free-wall strain during prone positioning, suggesting RV unloading [24]. These findings support the concept of improved RV loading conditions during prone positioning, although the broader literature remains heterogeneous and improvements in measured RV function are not uniform across studies.

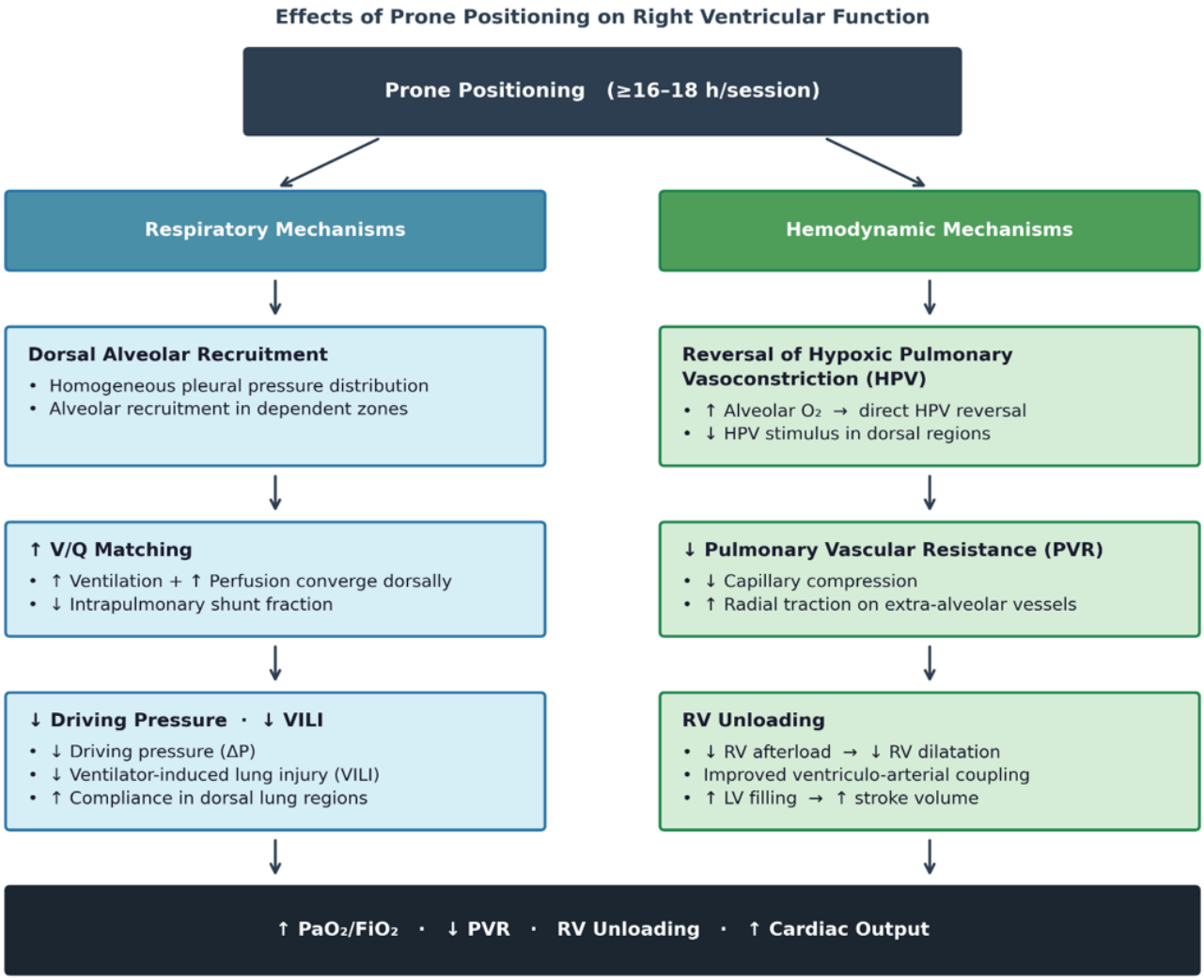



**Figure 2.** Dual benefit of prone positioning in ARDS. Respiratory and hemodynamic mechanisms converge to reduce PVR, unload the RV, and improve ventriculo-arterial coupling.

**Abbreviations:** ARDS: acute respiratory distress syndrome; IAP: intra-abdominal pressure; PVR: pulmonary vascular resistance; RV: right ventricle; V/Q: ventilation-perfusion.

**Table 2.** Echocardiographic parameters and expected changes during prone positioning in patients with acute respiratory distress syndrome.

| Parameter | Expected change during prone positioning | Clinical interpretation |
|---|---|---|
| Tricuspid annular plane systolic excursion (TAPSE) | Increases | Suggests improved RV longitudinal systolic function |
| RV/LV end-diastolic area ratio (RVEDA/LVEDA) | Decreases | Suggests reduced RV dilatation and less interventricular septal shift |
| RV global longitudinal strain (GLS) | Becomes more negative | Suggests improved RV systolic performance |
| RV free-wall strain (RVFWS) | Becomes more negative | Suggests improved RV contractility and reduced RV loading |

For strain parameters, improvement is reflected by more negative values. **Abbreviations:** GLS: global longitudinal strain; RV: right ventricle; RVEDA/LVEDA: right/left ventricular end-diastolic area ratio; RVFWS: RV free-wall strain; TAPSE: tricuspid annular plane systolic excursion.

## CLINICAL GUIDELINES AND IMPLEMENTATION

Both the 2024 American Thoracic Society (ATS) guideline and 2023 European Society of Intensive Care Medicine (ESICM) guideline support prone positioning in selected adults with moderate-to-severe ARDS, particularly those with severe hypoxemia despite optimized ventilatory support. In clinical practice, prone positioning is typically considered in intubated patients with $PaO_2/FiO_2 < 150$ mmHg despite optimized ventilatory support, commonly $FiO_2 \geq 0.6$ and PEEP ≥5 $cmH_2O$ [25, 26]. Early implementation is generally favored, particularly within the first 48 hours after intubation, when lung recruitability may be greater and before prolonged supine ventilation compounds lung and RV stress. From a heart–lung interaction perspective, earlier prone positioning may reduce cumulative RV loading from persistent HPV, regional overdistension, and lung heterogeneity.

Regarding session duration, the 2024 ATS guideline recommends prone positioning for >12 hours per day in patients with severe ARDS [25]. This threshold is supported by prior meta-analyses, including those by Sud et al. and Munshi et al., which found that mortality benefit was most evident when prone positioning was applied for at least 12 hours daily [27, 28]. The 2023 ESICM guideline and contemporary clinical practice commonly target longer sessions, often 16–18 hours per session, consistent with the protocol used in the PROSEVA trial [26]. From a heart–lung interaction standpoint, maintaining prone positioning for an adequate duration may be important because improvement in V/Q matching, dorsal lung recruitment, and RV unloading may not be sustained if patients are returned to the supine position too early. Recent meta-analytic evidence suggests that extended prone positioning may improve oxygenation and reduce mortality, although the optimal session duration, patient selection, and complication risk require further study [29]. Prolonged sessions also require careful attention to pressure injury prevention, airway security, vascular access, ocular protection, and staff workload.

Safe implementation requires a standardized multidisciplinary protocol, including pre-proning assessment, securement of the endotracheal tube and vascular lines, eye and pressure-area protection, coordinated turning, and scheduled reassessment of oxygenation, ventilatory mechanics, hemodynamics, and skin integrity. In patients with suspected RV dysfunction, echocardiographic reassessment after prone positioning may help determine whether oxygenation improvement is accompanied by RV unloading.

Safe prone positioning also requires systematic prevention and monitoring of known complications. Pressure injuries involving the face, anterior chest, and bony prominences are common and require protective padding, scheduled positional adjustments within each session, and regular skin assessment. Facial and conjunctival edema may occur during prolonged sessions. Accidental extubation and central line displacement should be prevented by rigorous securement of all endotracheal tubes, vascular lines, and drains before each turn. Brachial plexus injury may result from improper arm positioning and can be minimized by using a standardized arm placement protocol. Transient hemodynamic instability may occur during the turning procedure but usually resolves once the prone position is established [23].

## INTEGRATED RV-PROTECTIVE MANAGEMENT: A PRACTICAL SUMMARY

Prone positioning should be implemented as part of a broader RV-protective bundle (Figure 3) rather than as an isolated oxygenation maneuver. Each element of this integrated strategy targets a distinct component of the heart-lung interaction pathway: limiting tidal volume and plateau pressure helps reduce VILI-related increases in PVR; individualized PEEP titration aims to optimize the PVR–lung volume relationship; and carbon dioxide ($CO_2$) control helps limit hypercapnic pulmonary vasoconstriction. Additional components include:

1. Use low tidal volume ventilation at approximately 6 mL/kg predicted body weight (PBW), with reduction to 4–5 mL/kg PBW when needed to limit plateau or driving pressure [2].
2. Limit plateau pressure and actively minimize driving pressure; in patients with RV compromise, consider lower targets such as plateau pressure ≤28 $cmH_2O$ and driving pressure ≤15 $cmH_2O$ when feasible [2, 19].
3. Avoid unnecessary hypercapnia in patients with suspected or established RV dysfunction; $PaCO_2$ ≥48 mmHg has been associated with ACP, and severe hypercapnic acidosis (pH < 7.20) should be corrected [14, 19].
4. Individualize PEEP to balance recruitment against overdistension and RV loading; neither uniformly high nor uniformly low PEEP is appropriate across all ARDS phenotypes [13].
5. Neuromuscular blockade: Short-term neuromuscular blockade may be considered in selected patients with severe ARDS, refractory hypoxemia, ventilator dyssynchrony, or excessive inspiratory effort, although routine use has not consistently improved mortality [2].

## RESCUE THERAPIES FOR REFRACTORY RV FAILURE

### Inhaled pulmonary vasodilators

When optimized ventilation and prone positioning fail to correct refractory hypoxemia, hypercapnia, or RV failure, rescue therapies may be considered in selected patients. Inhaled nitric oxide (iNO) or inhaled prostacyclins (e.g., iloprost or epoprostenol) may be used as short-term adjunctive rescue therapies, particularly when severe hypoxemia or RV afterload remains problematic despite optimization. Because they are delivered to ventilated alveoli, these agents preferentially dilate pulmonary vessels in better-ventilated lung regions, which may improve V/Q

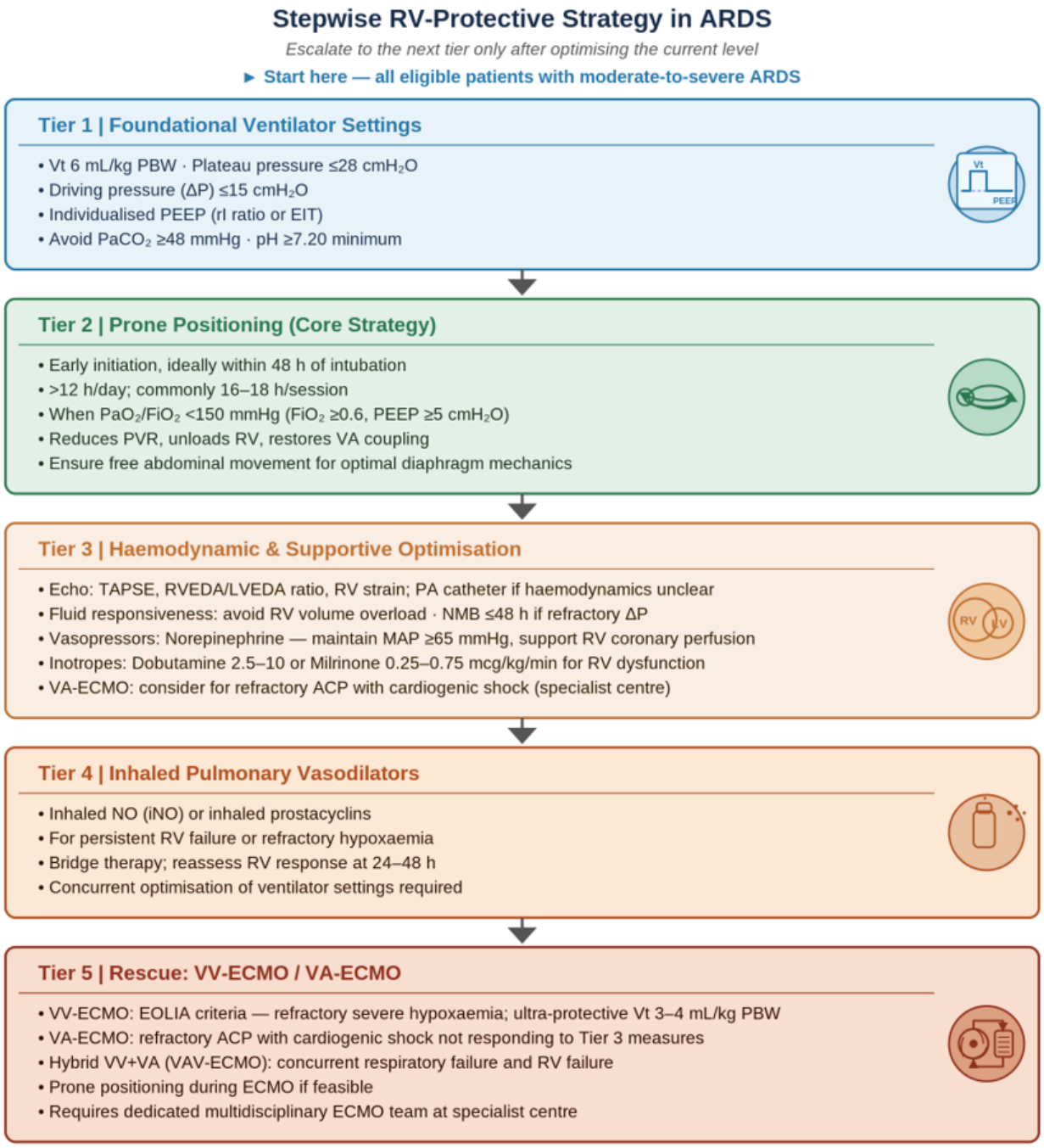



**Figure 3.** Stepwise RV-protective strategy in ARDS. The figure illustrates a stepwise escalation from foundational ventilator optimization to prone positioning, hemodynamic optimization, and rescue therapies. Tier 3, hemodynamic optimization, includes assessment of fluid responsiveness, avoidance of volume overload, vasopressor support with norepinephrine to maintain mean arterial pressure and preserve RV coronary perfusion pressure, and cautious addition of dobutamine or milrinone when echocardiography demonstrates severe RV contractile dysfunction. Tier 5 includes rescue extracorporeal support; VV-ECMO may be considered for refractory hypoxemia or hypercapnia, whereas VA-ECMO or advanced ECMO configurations may be considered when refractory ACP is complicated by hemodynamic collapse.

EOLIA-like eligibility criteria for VV-ECMO include $PaO_2/FiO_2$ <50 mmHg for >3 h, < 80 mmHg for >6 h, or pH <7.25 with $PaCO_2$ ≥60 mmHg for >6 h despite optimized ventilation. **Abbreviations:** ARDS: acute respiratory distress syndrome; EIT: electrical impedance tomography; PEEP: positive end-expiratory pressure; PBW: predicted body weight; r/I: recruitment-to-inflation ratio; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion; RVEDA/LVEDA: right/left ventricular end-diastolic area ratio; VV-ECMO: veno-venous extracorporeal membrane oxygenation; ΔP: driving pressure.

matching and reduce RV afterload without substantial systemic hypotension [6]. However, randomized trials have not demonstrated a mortality benefit; therefore, inhaled pulmonary vasodilators should be regarded as temporary rescue therapies or bridges to more definitive support.

### Vasopressors and inotropic support

In patients with ACP, maintaining adequate systemic vascular resistance and RV coronary perfusion pressure is a critical priority. The RV depends on a sufficient pressure gradient between mean arterial pressure (MAP) and RV end-diastolic pressure (RVEDP) to sustain coronary blood flow. When systemic hypotension accompanies ACP, norepinephrine is the preferred first-line vasopressor because it restores systemic vascular resistance and increases MAP, thereby preserving RV coronary perfusion pressure without substantially worsening pulmonary vascular tone [17, 30]. Vasopressin may be added as an adjunct because of its systemic vasoconstrictor effect and potentially favorable pulmonary vascular profile in ACP [30, 31].

When RV contractility is severely impaired, cautious inotropic support may be required. Dobutamine, a predominantly beta-1 adrenergic agonist, augments RV contractility and may reduce RV filling pressure, but it can cause systemic hypotension and tachycardia, often requiring concurrent vasopressor support [30, 31]. Milrinone, a phosphodiesterase type 3 inhibitor with both inotropic and pulmonary vasodilatory properties, may improve RV contractility and reduce RV afterload, although systemic hypotension may similarly necessitate concurrent vasopressor therapy [31]. The choice of vasoactive agent should be guided by hemodynamic assessment, including MAP, heart rate, and echocardiographic evaluation of RV size and contractility. A practical approach is to use norepinephrine as the primary vasopressor to maintain adequate MAP and preserve RV coronary perfusion, then add an inotrope when echocardiographic evidence of severe RV contractile dysfunction persists despite adequate perfusion pressure [17, 30]. The vasoactive agents used in ACP, their hemodynamic profiles, and key clinical considerations are summarized in Table 3.

### Veno-venous extracorporeal membrane oxygenation

VV-ECMO is an important rescue therapy for selected patients with severe ARDS and refractory hypoxemia when conventional management is insufficient and eligibility criteria, such as those used in the EOLIA trial, are met [32]. EOLIA-like entry criteria include a $PaO_2/FiO_2$ ratio <50 mmHg for more than 3 hours or <80 mmHg for more than 6 hours, or an arterial pH <7.25 with $PaCO_2$ ≥60 mmHg persisting for more than 6 hours despite optimized ventilation. By partially or completely supporting gas exchange, VV-ECMO can rapidly improve hypoxemia and hypercapnia, facilitate ultra-protective ventilation, and reduce RV loading conditions [33]. It also facilitates ultra-protective ventilation strategies, such as very low tidal volumes and lower driving pressures, while PEEP is individualized to maintain recruitment without overdistension. Whether prone positioning should be continued during VV-ECMO remains uncertain. Although prone positioning during ECMO may improve recruitment and oxygenation in selected patients, the PRONECMO randomized clinical trial did not improve time to successful ECMO weaning compared with supine management [34]. Therefore, prone positioning during ECMO should be individualized and performed only with appropriate expertise, staffing, and safeguards to minimize complications such as cannula displacement [34].

**Table 3.** Vasoactive agents used in acute cor pulmonale: primary class, hemodynamic effects, and key clinical considerations.

| Agent | Class | MAP effect | PVR effect | Key consideration in ACP |
|---|---|---|---|---|
| Norepinephrine | Alpha-1/beta-1 agonist | Increases | Neutral to mild increase | First-line vasopressor in hypotensive ACP. Restores systemic vascular resistance and RV coronary perfusion pressure. Can be combined with inotropes. |
| Vasopressin | V1 agonist | Increases | Neutral to possible decrease at low dose | Adjunct to norepinephrine. May support MAP with potentially favorable pulmonary vascular effects and lower arrhythmia risk. |
| Dobutamine | Predominantly Beta-1 agonist | May decrease | May decrease | Augments RV contractility but may cause tachycardia and systemic hypotension; usually requires adequate vasopressor support. |
| Milrinone | PDE-3 inhibitor | May decrease | Decreases | Inotrope with pulmonary vasodilatory effect. Systemic hypotension is common; a concurrent vasopressor may be required. |

**Abbreviations:** ACP: acute cor pulmonale; MAP: mean arterial pressure; PDE-3: phosphodiesterase type 3; PVR: pulmonary vascular resistance; RV: right ventricle; V1: vasopressin V1 receptor.

### Veno-arterial extracorporeal membrane oxygenation in severe acute cor pulmonale

In the most severe presentations of ACP, particularly when refractory cardiogenic shock or cardiac arrest complicates severe ARDS despite optimized ventilation, prone positioning, inhaled pulmonary vasodilators, and pharmacological hemodynamic support, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) may be considered as a form of mechanical circulatory support [35]. Unlike VV-ECMO, which primarily addresses gas exchange failure without directly augmenting systemic blood flow, VA-ECMO drains deoxygenated venous blood, oxygenates it extracorporeally, and returns it to the systemic arterial circulation. This can support systemic perfusion, partially unload the failing RV, reverse tissue hypoperfusion, and serve as a bridge to recovery, decision-making, or other definitive therapies [35].

However, VA-ECMO in ARDS-associated ACP carries important limitations. The arterial return increases LV afterload, which may worsen LV distension and require LV unloading or venting strategies. Additional risks include systemic thromboembolism, limb ischemia from the arterial cannulation, bleeding, and the need for anticoagulation in patients who may already have coagulopathy. In patients already supported with VV-ECMO for ARDS in whom refractory ACP subsequently develops, conversion to veno-pulmonary arterial ECMO, in which the return cannula is positioned in the pulmonary artery rather than the systemic artery, has been reported as an alternative strategy that selectively unloads the RV while directing oxygenated blood into the pulmonary circulation [35]. The evidence base for these approaches remains limited primarily to case series, and patient selection should be guided by multidisciplinary evaluation at centers with appropriate expertise, considering disease reversibility, contraindications, and institutional experience [17, 35].

## PRACTICAL BEDSIDE PEARLS

1. Monitor RV function with bedside echocardiography in mechanically ventilated patients with moderate to severe ARDS, particularly when shock, severe hypoxemia, hypercapnia, or high ventilatory pressures are present. An RVEDA/LVEDA ratio > 0.6 with paradoxical septal motion defines ACP and should prompt RV-focused management adjustments.
2. Observational data support lower driving pressure as a clinically meaningful target, with ≤15 $cmH_2O$ often used as an evidence-informed goal when feasible. PEEP should be titrated according to lung recruitability and RV response rather than oxygenation alone, using the R/I ratio or EIT when available.
3. Avoid unnecessary hypercapnia in patients with RV compromise. A $PaCO_2 \geq 48$ mmHg has been associated with ACP. When severe hypercapnia is present, consider reducing instrumental dead space, such as switching from an HME to a heated humidifier, before increasing tidal volume or respiratory rate.
4. Prone positioning benefits both the lungs and the RV. After turning prone, reassess oxygenation, ventilatory mechanics, hemodynamics, and RV function when feasible to determine whether oxygenation improvement is accompanied by RV unloading.
5. In ACP with systemic hypotension, use norepinephrine to restore mean arterial pressure and preserve RV coronary perfusion pressure. Add dobutamine or milrinone only when echocardiography confirms severe RV contractile dysfunction and systemic blood pressure is adequately supported.
6. In the most severe cases of ACP with refractory shock, consult an ECMO team early. VV-ECMO may be considered for refractory hypoxemia or hypercapnia, whereas VA-ECMO or advanced ECMO configurations may be considered for hemodynamic collapse not responsive to pharmacological support.

## CONCLUSION

ARDS is a syndrome of cardiopulmonary failure, not pulmonary failure alone. Elevated PVR, RV pressure overload, and ventricular interdependence evolve in parallel with the underlying lung injury and should be considered together in management. Prone positioning remains one of the most important non-pharmacological interventions in moderate-to-severe ARDS because it promotes lung recruitment, reduces driving pressure, improves V/Q matching, and may help unload the RV. Current evidence supports early and prolonged prone positioning in appropriate patients, although the optimal duration remains uncertain and prolonged sessions require careful prevention of complications. Safe implementation requires a multidisciplinary protocol, including preparation, airway and line security, pressure-area protection, bedside monitoring, and careful repositioning. When prone positioning and ventilator optimization are insufficient, adjunctive therapies such as inhaled pulmonary vasodilators and VV-ECMO should be considered in selected patients. Applying a heart–lung framework may help clinicians individualize ventilatory, hemodynamic, and rescue strategies in ARDS.

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