JACC: ADVANCES VOL. ■, NO. ■, 2025

STATE-OF-THE-ART REVIEW

Navigating Hypoxemic Respiratory Failure in Critically Ill Cardiac Patients

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ABSTRACT

Acute respiratory failure is a common reason for admission to cardiac intensive care units and the prevalence of respiratory failure in this cohort is increasing over time. Hypoxemia can occur due to a variety of mechanisms; the most common cause in the cardiac intensive care units remains cardiogenic pulmonary edema, but other etiologies, such as pneumonia and acute respiratory distress syndrome, are also common. This article provides an update on mechanisms of hypoxemia among patients with cardiac critical illness, heart lung interactions during spontaneous and positive pressure ventilation, optimization of sedation and ventilation for cardiac patients including novel ventilation strategies, and management of refractory hypoxemia among patients with cardiac critical illness. (JACC Adv. 2025;■:101616)

Acute respiratory failure is a common reason for admission to cardiac intensive care units (CICUs)[1,2] and the prevalence of respiratory failure is increasing. In their tertiary care CICUs, Jentzer and colleagues described a rising prevalence of respiratory failure, from 15% in 2007 to 38% in 2018.[3] Acute respiratory failure is an umbrella term encompassing acute hypoxemic respiratory failure (AHRF) and hypercarbic failure. Hypoxemia, or a partial pressure of oxygen in arterial blood (PaO_2) below the normal range of 80-100 mm Hg, frequently leads to hypoxia, a failure of oxygenation at the tissue level. AHRF is often defined as a PaO_2 to fraction of inspiratory oxygen <300. This narrative review focuses on the pathophysiology, epidemiology, and management of AHRF for patients with significant left ventricle (LV) or right ventricle (RV) dysfunction.

Physiologic mechanisms of hypoxemia in patients with cardiac critical illness are multifold and synergistic. They include ventilation/perfusion (V/Q) mismatch, or an imbalance between ventilation and perfusion in the lungs. An extreme V/Q mismatch occurs with right to left shunts, either due to anatomical intracardiac shunts, such as atrial and ventricular septal defects, or physiologic shunts from alveolar disorders (ie, atelectasis, cardiogenic or noncardiogenic pulmonary edema, or pneumonia). The other extreme is physiologic dead space due to decreased perfusion of gas exchange surfaces (ie, large pulmonary embolism). Other important

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received September 25, 2024; revised manuscript received December 2, 2024, accepted December 10, 2024.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2025.101616

ABBREVIATIONS AND ACRONYMS

AHRF = acute hypoxemic respiratory failure

ARDS = acute respiratory distress syndrome

CICU = cardiac intensive care unit

CS = cardiogenic shock

ECMO = extracorporeal membrane oxygenation

FiO_2 = fraction of inspiratory oxygen

IL = interleukin

IMV = invasive mechanical ventilation

iNO = inhaled nitric oxide

LTVV = low tidal volume ventilation

LV = left ventricle

PaO_2 = partial pressure of oxygen in arterial blood

PEEP = positive end expiratory pressure

PPV = positive pressure ventilation

RV = right ventricle

SBT = spontaneous breathing trial

V/Q = ventilation/perfusion

mechanisms of hypoxemia include diffusion impairment at the alveolar-pulmonary capillary interface (ie, interstitial lung disease); and hypoventilation secondary to reduced minute ventilation from central neurologic conditions (ie, sedation, central apnea in cardiac arrest survivors) or peripheral neuromuscular disorders (ie, cervical spine injuries, diaphragmatic weakness). Finally, of particular importance in a cardiac population is decreased mixed venous oxygen content (ie, low cardiac output due to pump failure). In low cardiac output states, low mixed venous hemoglobin saturation can cause severe hypoxemia if even a small degree of V/Q mismatch or shunt simultaneously coexists (**Central Illustration**).

AN OVERVIEW OF AHRF AND INVASIVE MECHANICAL VENTILATION IN thE CICUs

A familiar cause of AHRF in the CICUs is cardiogenic pulmonary edema.[2] This occurs when a rise in LV end-diastolic and left atrial pressures produce increased hydrostatic pressures in the pulmonary capillaries. Elevated hydrostatic pressures overwhelm the active lymphatic resorption of fluids leading to alveolar edema and impaired gas exchange.[4] Importantly, multiple processes may coexist. For example, in cardiogenic shock (CS), there is often an accompanying systemic inflammatory cascade due to upregulation of inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, tissue necrosis factor-α, and the complement system.[5-7] In some patients, this inflammatory cascade may increase permeability of the pulmonary vascular membrane, leading to noncardiogenic pulmonary edema. Mechanical circulatory support strategies that increase end-diastolic pressure may also promote these mechanisms.[8] The downstream effect of both high filling pressures and capillary leak in CS may result in worsening hypoxemia leading to further myocardial ischemia, tissue hypoxia, and progressive multiorgan failure.

A proportion of patients with AHRF admitted to CICUs are managed with either high flow nasal cannula or other forms of noninvasive positive pressure ventilation (PPV). High flow nasal cannula uses heated and humidified flow rates of up to 60 L/minute, providing a more reliable FiO_2 and minimal positive end expiratory pressure (PEEP). Other forms of noninvasive PPV include bilevel positive airway pressure which can support both hypoxia and hypercarbia. The most common indication for invasive mechanical ventilation (IMV) in CICUs remains AHRF. However, IMV may also be required for airway protection postcardiac arrest and to facilitate invasive procedures. When contemplating initiation of IMV, it is crucial to consider the hemodynamic effects of induction, intubation, and PPV, as discussed below and additionally reviewed elsewhere.[9]

HIGHLIGHTS

- Acute hypoxemic respiratory failure is common in contemporary cardiac intensive care units.
- When initiating invasive mechanical ventilation, it is crucial to consider the hemodynamic effects of both positive pressure ventilation and the impact of analgesic and sedation strategies.
- Adjunctive treatments for refractory hypoxemia in patients with cardiac critical illness remain understudied.

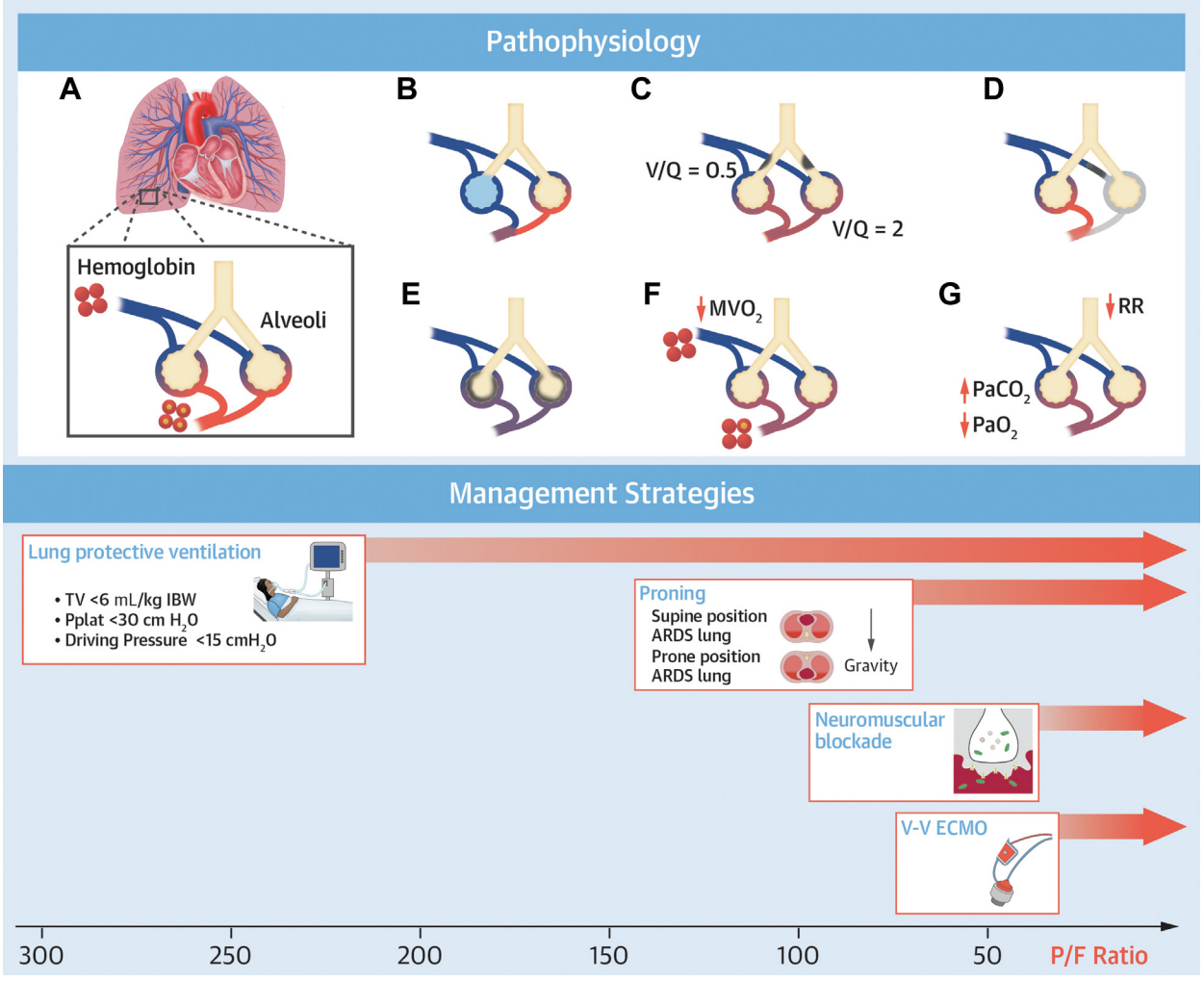
HEART-LUNG INTERACTIONS AND THE IMPACTS OF SEDATION DURING IMV

On initiating IMV, the heart-lung unit undergoes several important changes related to the shift to PPV. The hemodynamic effects of IMV are mediated through a reduction in respiratory muscle effort, lung and chest wall inflation, and via the switch from negative to positive pleural pressures. Importantly, these hemodynamic changes have differential effects on the right and left sides of the heart (**Figure 1**).

RV preload is equal to cardiac venous return. Venous return is principally determined by the difference between mean systemic filling pressures and right atrial pressure.[10] Initiation of IMV increases intrathoracic pressure and subsequently right atrial pressure, decreasing the gradient between mean systemic filling pressures and the right atrium, and impairing venous return.[11] During spontaneous respiration, pleural pressures become more negative during inspiration, and transmural cardiac pressures drop, increasing the gradient between the mean systemic filling pressures and the right atrium. In contrast, during IMV, each breath is accompanied by increased intrathoracic pressure without variation in right atrial pressures.[12,13]

IMV has significant effects on RV afterload, classically described as a U-shaped curve mediated through changes in lung volume and pulmonary vascular

CENTRAL ILLUSTRATION **Hypoxemic Respiratory Failure in Critically Ill Cardiac Patients**

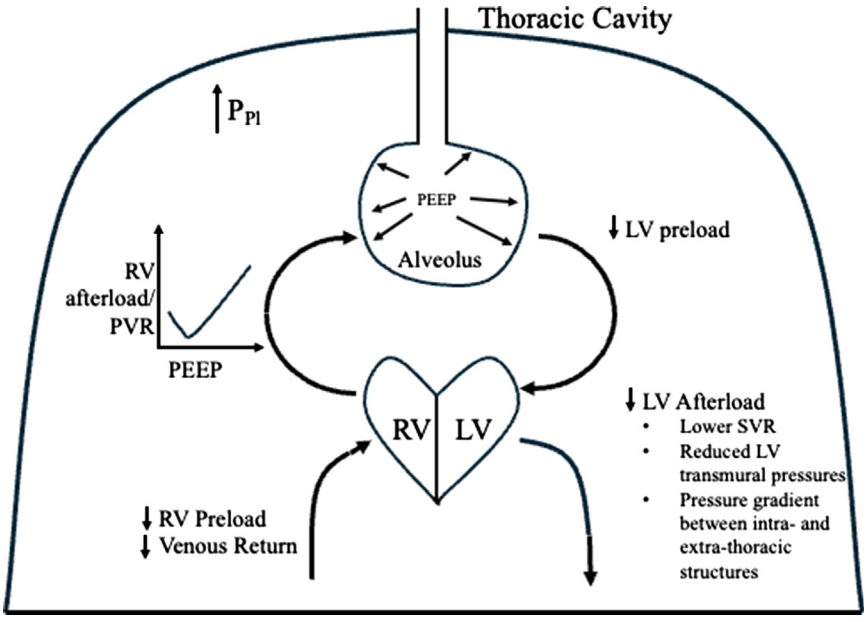


Sterling LH, et al. JACC Adv. 2025;■(■):101616.

The figure highlights pathophysiological mechanisms of hypoxemia. (A) A heart-lung unit with normal blood flows through a nondiseased lung. (B) An example of intraparenchymal shunt with zero ventilation to a perfused portion of lung, (C) V/Q mismatch, (D) an example of dead space ventilation, where a fully ventilated alveolus has zero perfusion, (E) diffusion impairment, (F) low mixed venous oxygen saturation seen in situations such as cardiogenic shock, and (G) hypoventilation. V/Q = ventilation/perfusion.

resistance. PEEP may reduce atelectasis and, for a subset of patients, decrease RV afterload. However, in most cases, IMV increases RV afterload. The combination of decreased RV preload and increased RV afterload culminates in decreased right-sided cardiac output. Ultimately, the cautious use of PEEP with RV dysfunction is more nuanced than a simplistic minimization or worse yet, avoidance. Common scenarios where PEEP titration must be undertaken cautiously include the patient struggling with refractory hypoxemia or acidosis as both produce synergistic pulmonary vasoconstriction increasing RV afterload, and those with noncompliant lung parenchyma without a PPV-responsive condition, that is, interstitial lung disease. In this latter scenario, small changes in alveolar pressure produce marked rises in RV afterload. Finally, in patients with systemic hypotension, high PEEP raises central venous pressures, lowers RV perfusion pressure and may exacerbate RV ischemia. Conversely, patients with preserved RV function and adequate preload are less sensitive to the effects of PEEP and more liberal titration can be

FIGURE 1 Effects of Positive Pressure Ventilation on Preload and Afterload



Differential effects of positive pressure ventilation on left and right ventricular preload and afterload. LV = left ventricle; PEEP = positive end expiratory pressure; P_{Pl} = pleural pressures; PVR = pulmonary vascular resistance; RV = right ventricle; SVR = systemic vascular resistance.

undertaken to unload both the respiratory muscles and LV.[9]

In the absence of intracardiac shunts, LV preload is determined by cardiac output from the RV. Given the hemodynamic impact of IMV on the RV, there is often decreased LV preload during IMV. During spontaneous respiration, decreases in pleural pressures increase LV afterload.[14] However, PEEP during IMV decreases LV afterload through multiple mechanisms. First, PEEP increases pressure on the LV and thoracic aorta causing a pressure gradient between intrathoracic structures and the systemic circulation, promoting forward flow.[15] Second, increased intrathoracic pressures activate aortic baroreceptors, lowering systemic vascular resistance.[11] Finally, positive pleural pressures decrease transmural LV pressure and reduce LV wall tension. In patients with LV dysfunction, IMV may have numerous beneficial effects on LV performance by reducing preload and afterload, mimicking the effects of diuretics and afterload reducing agents. Conversely, in rare situations, IMV may not only induce neurohormonal activation and volume retention, but the necessity of sedation may necessitate vasopressors which could increase the risk of arrhythmias and myocardial ischemia.[16] Ultimately, the effects of IMV on hemodynamics will depend on the sum of the effects on RV and LV preload and afterload, as well as the systemic effects of PPV and will vary from patient to patient.

The optimal timing for endotracheal intubation and initiation of IMV in AHRF is unknown with no randomized controlled trial data to guide decision-making (**Table 1**).[17] Even less evidence is available to guide this decision in the CICUs.[9] Timing of intubation is thus highly individualized. However, the available data suggest that once the decision has been made to initiative IMV, delays are associated with increased mortality.[18,19] There is a risk of peri-intubation hypotension and cardiac arrest with the attenuation in sympathetic tone inherent to all induction agents—a prominent concern in the patient with low cardiac output reliant on systemic vascular resistance to maintain systemic perfusion. This is compounded by the potential cardiodepressant effects of induction medications. Propofol was recently compared vs etomidate as an induction agent for patients requiring IMV in context of acute myocardial infarction: propofol was associated with reduced in-hospital mortality.[20] However, these data remain retrospective and at high risk for unmeasured confounding. In absence of prospective, randomized data, it may be most appropriate to use agents one is most

TABLE 1 Clinical Pearls for the Clinician Managing Hypoxemic Respiratory Failure in Critically Ill Cardiac Patients

What is the optimal timing for intubation?	• Optimal timing for endotracheal intubation and in AHRF is unknown and highly individualized. • Once the decision has been made to initiative IMV, delays are associated with increased mortality
What are the hemodynamic considerations during induction and initiation of IMV	• All induction agents attenuate sympathetic tone and may cause peri-intubation hypotension. • Patients who are preload dependent, particularly those with RV dysfunction or pulmonary hypertension, should be placed on the lowest effective PEEP to maintain adequate oxygenation and prevent lung derecruitment • LV preload and afterload will be reduced with positive pressure ventilation
How should my patient with AHRF be assessed for extubation?	• Extubation readiness includes resolution of the condition requiring intubation, absence of significant tracheal secretions, adequate cough reflex and mentation, and stable cardiovascular and respiratory status. • Standardized breathing trial reduce total mechanical ventilation days and identify objective and subjective indices of failure • Weaning-induced pulmonary edema is a common cause of weaning failure and volume status should be optimized prior to extubation.

AHRF = acute hypoxemic respiratory failure; IMV = invasive mechanical ventilation; LV = left ventricle; PEEP = positive end expiratory pressure; RV = right ventricle.

familiar with, with the smallest cardiodepressant effects and at lowest possible doses.[21] Additionally, important strategies in those with RV preload dependent states include avoidance of intubation if feasible, and if not, to maintain spontaneous respiration during induction, maintain mean arterial pressure above pulmonary artery pressure, and optimize preload.

Most patients require sedation during IMV. Guidelines recommend intravenous opioid analgesics and sedatives at lowest possible effective doses, with titration based on established sedation scores, like the Richmond Agitation-Sedation Score.[22] Opioids have minimal effect on cardiac output and may reduce myocardial oxygen demand.[23] Opioid-sparing strategies may also be considered, including regional blocks for rib fractures post cardiac arrest, or ketamine or lidocaine infusions. There is a paucity of evidence for the optimal sedative medication for intubated patients with cardiac critical illness. Recommended first-line sedatives in a general ICU population include propofol, short-acting benzodiazepines, and dexmedetomidine.[22] A full overview of all available sedative medications and their relative utility in various clinical scenarios encountered in the CICUs is outside the scope of this article but has been the focus of prior expert reviews.[24] Ultimately the sedation strategy for patients requiring IMV in the CICUs should be individualized considering hemodynamics, baseline cardiac function, anticipated duration of IMV, and target level of sedation.

OPTIMIZING VENTILATORY SETTINGS IN THE CICUs

There is sparse evidence to inform optimal ventilator settings in the CICUs. Best practices are drawn from the general ICU literature, and in cases of severe hypoxemia, from patients with acute respiratory distress syndrome (ARDS). In general, the various modes of IMV involve setting the fraction of inspired oxygen, level of PEEP, mandatory or patient-initiated ventilation (referred to as controlled or support modes) and choice of tidal volumes or peak pressures as a target for ventilation.[25]

Mechanistically, the focus during initial resuscitation is to offload the respiratory muscles with controlled modes of ventilation with a transition to an assisted mode when patients can tolerate the workload of spontaneous respiration. Achieving lung protective settings with low tidal volume ventilation (LTVV) and noninjurious ventilator settings is also commonly emphasized. LTVV minimizes alveolar overdistension and ventilator-induced lung injury and reduces mortality in ARDS.[26-28] The role of LTVV in AHRF not due to ARDS is less clear. A trial of 961 intubated patients without ARDS found that LTVV was not superior to intermediate tidal volume ventilation.[29] In contrast, a meta-analysis of multiple interventional and observational studies suggested benefit of LTVV in non-ARDS respiratory failure, though mortality benefit was only seen among observational studies.[30] The evidence for a LTVV strategy in the CICUs remains limited. In a cohort of 51 ventilated patients with heart failure or cardiac arrest in a tertiary care CICU, the median initial tidal volume was 9.3 mL/kg. All-cause mortality was 23% in patients who received a tidal volume below the median value and 36% in those who received a tidal volume above the median value.[31] Similarly, in an analysis of the Extracorporeal Life Support Organization registry, intubated patients with CS supported on venoarterial extracorporeal membrane

oxygenation (ECMO) managed with a LTVV strategy had lower in-hospital mortality.[32] Unfortunately, tidal volumes and driving pressure could only be inferred from the reported PEEP and peak inspiratory pressures, highlighting the need for high-quality observational data in a CICU population.

Pathophysiologically, volutrauma, atelectotrauma, and barotrauma all increase concentrations of inflammatory cytokines and may perpetuate ongoing multi-organ failure.[27] The inflammatory cascade of CS is profound and a growing area of exploration in CS management. Optimization of tidal volumes to minimize secondary sources of inflammation may provide an additional avenue for therapeutic benefit. Conversely, permissive hypercapnia from LTVV can cause acidosis, a myocardial depressant, so acid-base status should be monitored. Currently, LTVV is recommended for intubated patients with CS mostly based on expert opinion[33] with no randomized trial data yet showing benefit.

Lung protective ventilation aims to minimize the risk of ventilator-associated lung and diaphragm injury. Another major cause of ventilator-associated lung injury remains patient-ventilator dyssynchrony. Asynchrony can occur at each stage of breath triggering, delivery, and termination. Patient ventilation dyssycnhrony is associated with worse clinical outcomes and in some cases contributes to ongoing lung injury.[34] Strategies to minimize dyssychrony include changing ventilation parameters to match patient demand, optimizing sedation and occasionally, paralysis. A full overview of all patient-ventilator dyssycnhrony has been well covered in prior reviews.[35]

Another mainstay of lung protective ventilation involves administration of PEEP to optimize and sustain alveolar recruitment. Selection of PEEP should consider underlying cardiovascular pathology, hemodynamics, and time point in disease course. Patients who are preload dependent, particularly those with RV dysfunction or pulmonary hypertension, should be placed on the lowest effective PEEP to maintain adequate oxygenation and prevent lung derecruitment. In contrast, for patients who are predominantly afterload sensitive, most commonly those with LV dysfunction, higher PEEPs may have beneficial effects. In a mechanistic study, application of higher PEEPs (from 3 to 20 cm H20) improved mitral annular dimensions and reduced LV end systolic volumes. High PEEP strategies may thus be particularly beneficial in patients with LV dysfunction and significant mitral regurgitation.[36]

Beyond the use of LTVV and higher PEEP, several alternative ventilation strategies are under investigation for treatment of AHRF. The first involves targeting a low respiratory system driving pressure. Driving pressure is defined as the difference between plateau pressure and PEEP. In a post hoc analysis of several randomized trials of patients with ARDS, reduction in driving pressure was the best predictor of survival, even beyond achievement of LTVV and noninjurious PEEP.[37] Several ongoing randomized trials are examining the efficacy of lower driving pressures in ARDS and non-ARDS forms of AHRF.[38,39] Second, several trials have examined an "open lung" ventilation strategy in patients with ARDS. No standardized definition exists for "open lung" ventilation, but it usually involves serial recruitment maneuvers or the use of inverse ratio ventilation. While there has been considerable interest in recruitment maneuvers, when compared against conventional LTVV in ARDS, there is no mortality benefit or improvement in ICU length of stay.[30]

REFRACTORY HYPOXEMIA IN CARDIAC CRITICAL ILLNESS

Despite optimization, a subset of patients in the CICUs will develop refractory hypoxemia; defined as a PaO_2 ≤60 mm Hg or a PaO_2 to fraction of inspiratory oxygen ≤100 with FiO_2 ≥0.8 and either PEEP >15 cm H20 or plateau pressures >30 cm H_2O for >12 hours despite LTVV.[40] Management of refractory hypoxemia may involve adjunctive treatment strategies including prone positioning, neuromuscular blockade, inhaled pulmonary vasodilators (eg, nitric oxide or epoprostenol), inverse I/E ventilation, and ECMO. There is a knowledge gap in the use of adjunctive treatments for refractory AHRF in CICU patients. Below is summarized the most common adjunctive treatments of refractory hypoxemia and the evidence for their use in patients with significant cardiac disease.

PRONE POSITIONING. Prone positioning for at least 16 hours daily reduces mortality in patients with moderate to severe ARDS.[27] Prone positioning can improve RV hemodynamics and may be helpful in context of acute cor pulmonale from AHRF. The hemodynamic effects on the LV are less clear. Improvement in RV hemodynamics increase LV preload and rises in pulmonary capillary wedge pressures have been reported with prone positioning.[41] Additionally, ventricular arrhythmias remain a significant concern in patients admitted to CICUs. Even under optimal conditions, supination to facilitate chest compressions may take up to 3 minutes.[42] The use of prone positioning in the CICUs or patients with LV predominant CS should therefore be undertaken

on a case-by-case basis, accounting for the potentially deleterious hemodynamic effects of higher LV filling pressures and arrhythmic risk.

NEUROMUSCULAR BLOCKADE. Neuromuscular blockade in patients with severe ARDS is theorized to improve outcomes by relaxation of expiratory muscle effort, reducing patient-ventilator dyssynchrony, lowering work of breathing and potential anti-inflammatory mechanisms.[43] However, paralysis is associated with several important adverse effects including myopathy, polyneuropathy, pressure ulcers, deep venous thrombosis, and corneal abrasions.[44] Guidelines conditionally recommend neuromuscular blockade in early severe ARDS. While ACURASYS (the Neuromuscular blockers in early acute respiratory distress syndrome) trial demonstrated improved 90-day survival, ROSE (the Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome) trial failed to show benefit when using a lighter sedation strategy, which is more reflective of contemporary practice.[45-47] Practically, use of neuromuscular blockade is reserved for patients who remain dyssynchronous with the ventilator despite adequate sedation or with severe hypoxemia. Neuromuscular blocking agents are unlikely to cause direct hemodynamic effects but may reduce myocardial oxygen demand. In the comatose patient following cardiac arrest, prior exposure to neuromuscular blockade may represent an important confounder. Residual paralysis should be excluded prior to formal neuroprognostication.

INHALED NITRIC OXIDE AND PULMONARY VASODILATORS. Inhaled nitric oxide (iNO) may improve V/Q mismatch via local pulmonary vasodilation in well-ventilated alveoli. While iNO often improves oxygenation, there is no established reduction in mortality and concerning associations with renal impairment when used for longer durations.[48] In patients with CS with predominantly RV failure, iNO may have a role to temporarily reduce pulmonary vascular resistance and augment cardiac index.[49] In patients with severe LV dysfunction, augmentation of right-sided cardiac output may increase LV preload.[50] While a potential tool in managing patients with RV dysfunction or severe AHRF, the decision to use iNO in the CICUs should be individualized.

EXTRACORPOREAL MEMBRANE OXYGENATION. V-V ECMO reduces mortality in severe ARDS[51,52] and may indirectly improve RV hemodynamics by allowing for ultra-lung protective ventilation and improvement in hypoxic vasoconstriction.[53] A subset of patients will have marked hemodynamic improvement with V-V ECMO if their RV dysfunction improves with optimization of oxygenation and ventilation. If V-V ECMO fails to improve RV hemodynamics other options include switching to venoarterial ECMO or addition of right-sided circulatory support. However, if ECMO is being considered in context of LV predominant CS and refractory hypoxemia, V-A configurations are more appropriate. Notably, the routine use of V-A ECMO in acute myocardial infarction-associated CS does not improve outcomes and is associated with vascular complications.[54]

WEANING FROM INVASIVE MECHANICAL VENTILATION

Ideally, patients improve to the point of being ready for liberation from IMV.[55] An assessment of extubation readiness includes resolution of the condition requiring intubation, absence of significant tracheal secretions, adequate cough reflex and mentation, and stable cardiovascular and respiratory status. Thereafter, a spontaneous breathing trial (SBT) should be performed[56] to assess for objective and subjective indices of failure.

The weaning process constitutes up to 50% of ventilator days and 26% to 42% of patients fail their first wean attempt.[57] Importantly, weaning-induced alveolar edema is a common cause of failed SBTs.[58] Ensuring optimization of filling pressures, commonly through diuresis or cautious fluid loading in preload dependent states, is therefore crucial. Other important causes of failed SBTs include excessive respiratory load, neuromuscular dysfunction, critical illness neuromuscular abnormalities, neuropsychological factors, and metabolic/endocrine disorders.[59] Standardized ventilator liberation protocols reduce mechanical ventilation days, ICU length of stay, and the risk of prolonged IMV.[60]

CONCLUSIONS

This review provides an overview of the epidemiology and management of AHRF and refractory hypoxemia in the CICUs. Several research gaps remain. First, a better understanding of optimal induction and sedation strategies in the decompensated cardiac patient is required. Second, the current use of lung protective ventilation in the CICUs and the ideal ventilatory strategy for AHRF in the CICUs remains unknown. Finally, the approach to refractory hypoxemia in the CICU patient who is failing despite lung protective strategies remains understudied.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Fan has received personal fees from ALung Technologies, Aerogen, Baxter, GE Healthcare, Inspira, and Vasomune, outside of the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS **cardiac intensive care, heart-lung interactions, invasive mechanical ventilation**