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REVIEW

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The cardio-pulmonary axis: A review of bidirectional crosstalk in critical care

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ABSTRACT

Background and aims: The cardiopulmonary axis describes the critical, bidirectional relationship between the heart and lungs, where dysfunction in one organ rapidly precipitates failure in the other. This crosstalk is a major determinant of morbidity and mortality in the ICU. This review aims to synthesize evidence on the mechanisms, diagnostics, and therapies governing this axis.

Data sources: A literature search was conducted using PubMed, Google Scholar, and Scopus databases.

Study selection: We selected systematic reviews, meta-analyses, and landmark clinical trials published from 2000 to 2024, focusing on cardiopulmonary interactions in critical care, including ARDS, mechanical ventilation, and COVID-19.

Data synthesis: Pathological crosstalk is driven by mechanical interdependence (e.g., ventricular interdependence, effects of PEEP) and molecular mechanisms (inflammatory mediators, RAAS, microRNAs). This manifests in high-mortality syndromes like acute cor pulmonale in ARDS and COPD/HF overlap. Advanced diagnostics, particularly RV-centric echocardiography (e.g., TAPSE, RV/LV ratio) and biomarkers (BNP, troponins), are crucial for early detection and guiding integrated therapies like lung-protective ventilation and conservative fluid management.

Conclusion: Effective management of the cardiopulmonary axis requires an integrated, multi-system approach. Future research should focus on targeted molecular therapies and the unique challenges in pediatric populations to improve critical care outcomes.

KEY WORDS

Critical care medicine; Acute respiratory distress syndrome; Cardiopulmonary crosstalk; Mechanical ventilation; Right ventricular dysfunction

ARTICLE HISTORY

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Introduction

The human body is a symphony of interconnected systems, and nowhere is this more evident than in the intimate and life-sustaining partnership between the heart and the lungs. Encased together within the thoracic cavity, their functions are inextricably linked, forming the cardio-pulmonary axis. This axis is responsible for the vital processes of oxygen uptake, carbon dioxide elimination, and the circulation of oxygenated blood to the body's tissues. In a state of health, this relationship is a model of efficiency and coordination. However, in the setting of critical illness, this delicate interplay can become a source of profound instability, initiating a vicious cycle of organ dysfunction that is a daily challenge for intensivists [1,2]. The management of a critically ill patient, particularly one with respiratory failure, is a constant balancing act, where interventions aimed at supporting one organ can have unintended and often detrimental effects on the other.

Acute Respiratory Distress Syndrome (ARDS), a devastating form of hypoxemic respiratory failure, serves as the archetypal example of pathological heart-lung crosstalk. The primary lung injury, characterized by diffuse alveolar damage and inflammation, triggers a cascade of events that reverberate throughout the cardiovascular system [3,4]. The mechanical ventilation required to support these patients, while life-saving, imposes its own set of physiological stresses. The application of positive pressure ventilation (PPV), a cornerstone of ARDS management , fundamentally alters the pressure dynamics within the thorax, impacting venous return, cardiac filling, and ventricular function in ways that can compromise hemodynamic stability [5,6]. The resulting pulmonary hypertension, right ventricular dysfunction, and systemic inflammation create a complex clinical picture that demands a deep and nuanced understanding of the underlying physiology.

This review article aims to provide a comprehensive overview of the cardio-pulmonary axis in the context of critical care. We will begin by revisiting the fundamental physiological principles that govern heart-lung interactions, laying the groundwork for understanding the pathological changes that occur in disease. We will then explore the specific pathophysiological mechanisms of bidirectional crosstalk in ARDS, including the impact of mechanical ventilation, the role of inflammatory mediators, and the utility of biomarkers in assessing cardiac strain and injury. Recognizing the profound impact of the recent pandemic, we will dedicate a section to the unique features of cardio-pulmonary interactions in COVID-19. Finally, we will synthesize the current evidence for clinical management strategies, offering a practical framework for navigating the complex hemodynamic challenges posed by the critically ill patient with respiratory failure. Through this comprehensive exploration, we hope to illuminate the intricate dance between the heart and lungs, providing clinicians with the insights needed to improve outcomes for this vulnerable patient population.

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The Physiological Basis of Heart-Lung Interactions

The mechanical coupling of the heart and lungs within the thoracic cavity forms the basis of their intimate physiological relationship. Every breath and every heartbeat influences the function of the other, primarily through changes in Intrathoracic Pressure (ITP), lung volume, and autonomic tone. Understanding these fundamental interactions is crucial for interpreting the hemodynamic changes observed in critically ill patients, particularly those on mechanical ventilation.

The impact of intrathoracic pressure

The heart can be conceptualized as a pressure chamber existing within another pressure chamber, the thorax. As such, fluctuations in ITP directly influence the transmural pressures of the cardiac chambers and great vessels, thereby affecting cardiac filling and ejection. The effects of ITP changes are best understood by contrasting spontaneous and PPV.

During spontaneous inspiration, the contraction of the diaphragm and intercostal muscles generates a negative ITP. This drop in pressure has two main effects on the heart. First, it decreases the pressure in the right atrium, which increases the pressure gradient for venous return from the systemic circulation, thereby augmenting right ventricular preload [7,8]. Second, the negative ITP increases the pressure gradient that the Left Ventricle (LV) must overcome to eject blood into the systemic circulation. This is because the aorta is also subjected to the negative ITP, effectively increasing the afterload on the LV [9]. Thus, spontaneous inspiration can be seen as a form of exercise for the LV, increasing its workload. In contrast, PPV, a mainstay of respiratory support in the ICU, reverses these pressure dynamics. During a positive-pressure breath, ITP increases. This has the opposite effect on cardiac function compared to spontaneous breathing. The increased ITP raises right atrial pressure, which reduces the pressure gradient for venous return and consequently decreases RV preload [10]. Simultaneously, the increased ITP reduces the transmural pressure of the LV during systole, effectively decreasing LV afterload [11]. The net effect of PPV on cardiac output is a balance between the reduction in preload and the reduction in afterload. In most cases, particularly in hypovolemic patients, the preload-reducing effect predominates, leading to a decrease in cardiac output (Table 1) [12].

Table 1. Physiological effectsof mechanical ventilation on cardiopulmonary hemodynamics.

Parameter	Effect of PPV	Physiological consequence
ITP	Increases	Reduces transmural cardiac pressures
Venous Return	Decreases	Reduced RV preload due to increased right atrial pressure
RV Afterload	Increases	Increased PVR from alveolar distention and hypoxic vasoconstriction
RV Ejection	Decreases	Reduced stroke volume due to increased afterload and decreased preload
IVS	Shifts leftward	Diastolic dysfunction and reduced LV filling (ventricular interdependence)
LV Preload	Decreases	Reduced RV output and leftward septal shift
LV Afterload	Decreases	Reduced transmural LV systolic pressure
Cardiac Output	Decreases	Net effect of reduced preload and afterload, typically dominated by preload reduction

The role of lung volume

Changes in lung volume, independent of ITP, also play a significant role in heart-lung interactions. As the lungs inflate, the pulmonary vessels are stretched and compressed. This has a biphasic effect on Pulmonary Vascular Resistance (PVR). At very low lung volumes, PVR is high due to the collapse of extra-alveolar vessels. As lung volume increases towards Functional Residual Capacity (FRC), these vessels are pulled open, and PVR decreases.

However, as lung volume continues to increase beyond FRC, the alveolar capillaries are compressed, leading to a progressive increase in PVR [13]. This increase in PVR imposes a greater afterload on the right ventricle (RV), which can lead to RV dysfunction, particularly in the setting of pre-existing pulmonary hypertension or ARDS.

Furthermore, the physical expansion of the lungs within the fixed space of the thoracic cavity can directly compress the heart, a phenomenon known as cardiac tamponade physiology. This is particularly relevant in patients with severe hyperinflation or those receiving high levels of Positive End-Expiratory Pressure (PEEP). The compression of the heart can impair diastolic filling of both ventricles, further contributing to a reduction in cardiac output.

Ventricular interdependence

The RV and LV are not independent chambers; they are structurally linked by the Interventricular Septum (IVS) and enclosed within the common pericardium. This relationship, known as ventricular interdependence, means that changes in the size or pressure of one ventricle can affect the function of the other. In the context of heart-lung interactions, this is most evident in the effects of increased RV afterload. When PVR is elevated, the RV must generate higher pressures to eject blood. This can lead to RV dilation and a shift of the IVS towards the LV. This septal shift has two important consequences: it impairs LV diastolic filling by reducing the compliance of the LV, and it can also directly obstruct the LV outflow tract, further compromising cardiac output [14] (Figure 1). This phenomenon is a key mechanism of hemodynamic instability in patients with severe ARDS and pulmonary hypertension.

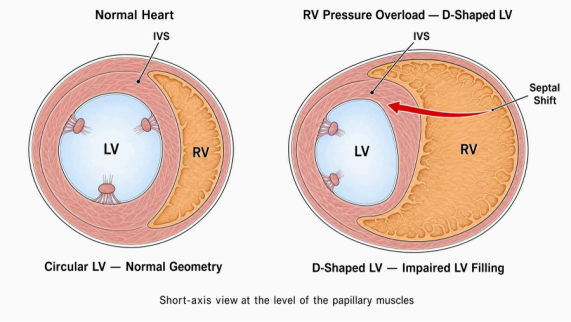

Figure 1. Echocardiographic short-axis view comparing normal ventricular geometry with RV pressure overload-induced d-shaped LV. Left panel: In the normal heart, the left ventricle (LV) maintains a circular cross-sectional geometry at the level of the papillary muscles, with the RV forming its

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characteristic crescent shape along the right border. The IVS curves naturally toward the RV. Right panel: In the setting of RV pressure overload(as seen in ARDS-associated pulmonary hypertension), the RV dilates and generates elevated pressures that force the IVS to bow leftward (septal shift, red arrow), compressing the LV into a characteristic D-shape. This geometric distortion impairs LV diastolic filling and reduces cardiac output through the mechanism of ventricular interdependence. IVS = interventricular septum; LV = left ventricle; RV = right ventricle.

Pathophysiology of Cardiopulmonary Crosstalk in ARDS

In ARDS, the physiological heart-lung interactions described above are amplified and distorted, creating a volatile and often precarious hemodynamic state. The underlying lung injury, combined with the iatrogenic effects of mechanical ventilation, initiates a vicious cycle of inflammation, pulmonary hypertension, and cardiac dysfunction that is a major determinant of outcome (Figure 2) [15].

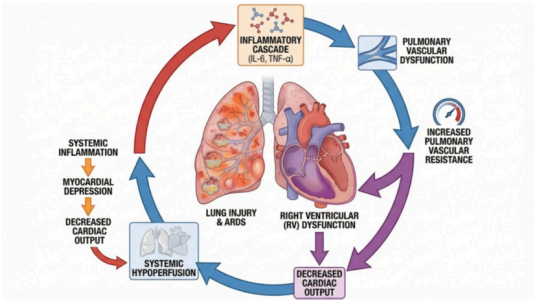

Figure 2. The vicious cycle of cardiopulmonary crosstalk in ARDS. This diagram illustrates the deleterious feedback loop initiated by acute lung injury. Lung injury triggers an inflammatory cascade, leading to pulmonary vascular dysfunction and increased PVR. This elevates the right ventricular afterload, causing RV dysfunction and reduced cardiac output. The ensuing systemic hypoperfusion and inflammation further exacerbate the initial lung injury, perpetuating the cycle.

The hallmark of ARDS is diffuse alveolar damage, leading to increased permeability of the alveolar-capillary barrier, interstitial and alveolar edema, and the release of a torrent of inflammatory mediators [16]. This inflammatory storm, coupled with the mechanical stresses of ventilation, drives the development of pulmonary hypertension, a central feature of ARDS-related cardiopulmonary crosstalk.

Several mechanisms contribute to the increase in PVR in ARDS:

Hypoxic Pulmonary Vasoconstriction (HPV)

In healthy lungs, HPV is a protective mechanism that diverts blood flow away from poorly ventilated alveoli to better-ventilated areas, thus optimizing ventilation-perfusion (V/Q) matching. In ARDS, however, this mechanism becomes dysregulated and contributes to a global increase in PVR [17].

Vascular compression

The edematous and consolidated lung tissue, along with the positive pressure from mechanical ventilation, physically compresses the pulmonary microvasculature, increasing resistance to blood flow [18].

Endothelial dysfunction and microthrombosis

The inflammatory process in ARDS causes widespread endothelial injury, leading to a pro-coagulant state and the formation of microthrombi within the pulmonary circulation. This further obstructs blood flow and increases PVR [19].

Inflammatory mediators

Cytokines such as TNF-α and interleukins can directly cause pulmonary vasoconstriction and contribute to vascular remodelling [20].

The sustained increase in PVR imposes a significant afterload on the RV. The RV, with its thin wall and crescent shape, is poorly adapted to handle high-pressure loads. The acute increase in afterload can lead to RV dilation, contractile dysfunction, and eventually, overt RV failure, a condition known as acute cor pulmonale. Clinically, standard left ventricular metrics like Ejection Fraction (EF) are often misleading in this setting; instead, diagnosis relies on specific RV-centric echocardiographic parameters such as a reduced Tricuspid Annular Plane Systolic Excursion (TAPSE < 17 mm) and an elevated RV/LV end-diastolic area ratio (> 0.6), which directly quantify the harmful hemodynamic crosstalk. As the RV fails, it is unable to effectively pump blood through the pulmonary circulation, leading to a decrease in LV preload and a subsequent fall in cardiac output and systemic blood pressure. The dilation of the RV also leads to a leftward shift of the IVS, further impairing LV filling and function through the mechanism of ventricular interdependence [21]. This cascade of events, from lung injury to RV failure and systemic circulatory collapse, represents the most severe manifestation of adverse heart-lung crosstalk in ARDS.

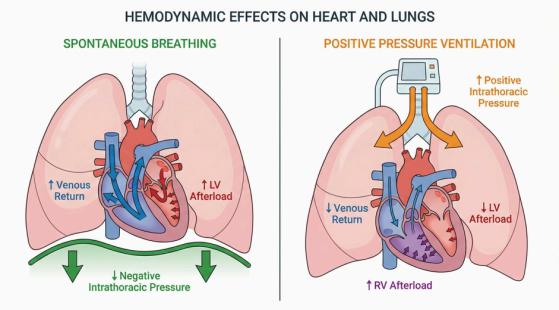

Figure 3. Effects of spontaneous vs. PPV on cardiopulmonary hemodynamics. This figure contrasts the hemodynamic effects of spontaneous breathing and PPV. Spontaneous breathing (left) generates negative ITP, increasing venous return and LV afterload. PPV (right) increases ITP, which decreases venous return and LV afterload but increases RV afterload.

Mechanical ventilation, while essential for survival in ARDS, can exacerbate these pathological interactions. High tidal volumes and plateau pressures can cause Ventilator-Induced Lung Injury (VILI), further fuelling the inflammatory response and worsening pulmonary hypertension. High levels of PEEP, while necessary to recruit collapsed alveoli and improve oxygenation, can over-distend compliant lung regions, increasing PVR and impeding venous return [22]. Therefore, the management of mechanical ventilation in ARDS is a delicate balancing act, requiring a strategy that optimizes gas exchange while minimizing the detrimental hemodynamic consequences (Figure 3).

Molecular Mechanisms and Biomarkers of Cardiopulmonary Crosstalk

The bidirectional communication between the heart and lungs is not solely a mechanical phenomenon. A complex network of molecular signals, including inflammatory mediators, hormones, and cellular components, orchestrates a systemic response that profoundly influences the function of both organs. In critical

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illness, this molecular crosstalk is amplified, contributing significantly to the pathogenesis of organ dysfunction.

The inflammatory cascade

At the heart of pathological cardiopulmonary crosstalk lies a dysregulated inflammatory response. In ARDS, the initial lung injury triggers the release of a flood of pro-inflammatory cytokines and chemokines, such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1β (IL-1β), and Interleukin-6 (IL-6), from activated alveolar macrophages and epithelial cells [23,24]. These mediators spill over into the systemic circulation, leading to a Systemic Inflammatory Response Syndrome (SIRS). This systemic inflammation has direct and indirect effects on the cardiovascular system.

Many of these cytokines, particularly TNF-α, are known to be potent myocardial depressants, directly impairing myocyte contractility and contributing to the cardiac dysfunction often seen in sepsis and ARDS [25]. They also induce widespread endothelial activation and dysfunction, leading to increased vascular permeability, vasodilation, and a pro-thrombotic state. This endothelial injury is not confined to the lungs; it is a systemic process that can impair coronary blood flow and contribute to myocardial ischemia.

Damage-Associated Molecular Patterns (DAMPs), such as High-Mobility Group Box 1 (HMGB1) and mitochondrial DNA, are released from injured lung cells and further amplify the inflammatory cascade, perpetuating the cycle of lung and cardiac injury [26]. This molecular storm creates a hostile environment for the heart, simultaneously increasing its metabolic demand while impairing its contractile function.

Biomarkers of cardiac strain and injury

The clinical assessment of cardiac function in the complex hemodynamic environment of the ICU can be challenging. In recent years, cardiac biomarkers have emerged as valuable tools for detecting and quantifying cardiac stress and injury in critically ill patients. However, the practical utility of these biomarkers depends heavily on their clinical availability. To guide clinical practice, we propose a tiered approach to biomarker utilization, distinguishing between universally available standard-of-care markers (Tier 1) and highly predictive but investigational markers (Tier 2) [27-29].

Table 2. Classification and clinical characteristics of Tier 1 and Tier 2 biomarkers in critical care.

Tier	Biomarker	Clinical Availability	Clinical Application	Status
Tier 1 (Standard of Care)	B-type Natriuretic Peptide (BNP) N-terminal pro-BNP (NT-proBNP)	Universally available in US clinical centers	Routine ICU monitoring: prognostic marker for cardiac stress	Established
Tier 1 (Standard of Care)	Cardiac Troponins (cTnT, cTnI)	Universally available in US clinical centers	Routine ICU monitoring; marker of myocardial injury	Established
Tier 2 (Investigational)	sRAGE (soluble Receptor for AGE)	Limited availability; research settings only; no standardized commercial assays	Marker of alveolar epithelial injury; correlates with ARDS severity and mortality	Research only
Tier 2 (Investigational)	Angiopoietin-2 (Ang-2)	Limited availability; research settings	Marker of endothelial activation;	Investigational

Tier 1 (Standard of Care) - Natriuretic Peptides and Troponins: Natriuretic Peptides (BNP and NT-proBNP): As universally available Tier 1 biomarkers, B-type natriuretic peptide (BNP) and its N-terminal pro-hormone (NT-proBNP) are routinely utilized in US clinical centers. They are released from the ventricles in response to myocardial stretch and pressure overload (Table 2).

Cardiac Troponins (cTnT and cTnI)

Cardiac troponins T and I are highly specific markers of myocyte necrosis. Their presence in the blood of a critically ill patient without overt acute coronary syndrome is indicative of non-ischemic myocardial injury. In patients with ARDS, elevated troponin levels can result from a variety of insults, including severe hypoxemia, systemic inflammation, catecholamine-induced cardiotoxicity, and RV strain-induced ischemia [30]. The detection of elevated troponins is a powerful predictor of adverse outcomes, including increased mortality and prolonged duration of mechanical ventilation [31].

The inflammatory cascade

Tier 2 (Investigational) - Biomarkers of lung injury

Biomarkers that reflect the extent of lung epithelial and endothelial injury provide profound insights into the severity of the inflammatory process and the risk of subsequent cardiac complications. However, it is crucial to acknowledge that these are currently research tools with limited practical implications for daily ICU management, as they are not routinely available at most clinical centers in the US.

Soluble Receptor for Advanced Glycation End products (sRAGE)

SRAGE is a highly predictive marker of alveolar epithelial type I cell injury. While elevated plasma levels of sRAGE strongly correlate with the severity of lung injury and mortality in ARDS [32], testing is largely confined to research settings due to a lack of standardized commercial assays.

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Angiopoietin-2 (Ang-2)

Ang-2 is a marker of endothelial activation and injury. It promotes vascular permeability and is associated with the development of pulmonary edema and ARDS severity [33]. Similar to sRAGE, Ang-2 remains an investigational tool pending broader clinical validation and availability.

While Tier 1 biomarkers like BNP and troponin remain the cornerstone of current clinical assessment, the future integration of Tier 2 markers (sRAGE, Ang-2) holds promise. Once these novel markers transition from the research laboratory to routine clinical availability, clinicians will be able to gain a more comprehensive picture of the patient's pathophysiological state and better risk-stratify patients for adverse cardiopulmonary events (Table 3).

Table 3. Key Inflammatory mediators and biomarkers in cardiopulmonary crosstalk.

Mediator/Biomarker	Role in pathophysiology	Clinical significance
IL-6	Pro-inflammatory cytokine, mediates systemic inflammation	Associated with ARDS severity, mortality, and cardiac dysfunction
(TNF-α)	Key inflammatory cytokine, induces endothelial activation	Contributes to lung injury, capillary leak, and myocardial depression
Brain Natriuretic Peptide (BNP) / NT-proBNP	Released in response to ventricular stretch and pressure overload	Marker of RV dysfunction and strain, predicts mortality in ARDS
Troponins (cTnT,cTnI)	Released from injured cardiomyocytes	Indicates myocardial injury, associated with worse outcomes in ARDS and COVID-19
sRAGE (Soluble Receptor for Advanced GlycationEnd products)	Marker of alveolar epithelial type I cell injury	Correlates with the extentof lung injury and mortality in ARDS
Ang-2	Marker of endothelial activation and injury	Associated with increased vascular permeability and ARDS severity
C-Reactive Protein(CRP)	Acute-phase reactant, marker of systemic inflammation	General marker of inflammation, elevated levels correlate with disease severity
D-dimer	Fibrin degradation product, marker of coagulation activation	Elevated levels suggest thromboembolic complications and are associated with mortality in COVID-19ARDS

The Cardio-pulmonary Axis in COVID-19

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has brought the critical importance of the cardio-pulmonary axis into sharp focus. While COVID-19 is primarily a respiratory illness, it is now clear that it is also a profound systemic disease with significant cardiovascular manifestations. The interplay between the lungs and the heart in severe COVID-19 is particularly complex and often devastating.

COVID-19 ARDS shares many features with traditional ARDS, but it also has distinct characteristics that amplify the pathological crosstalk (Table 4). A key feature of severe COVID-19 is a profound endotheliitis and microvascular thrombosis [34]. The virus can directly infect endothelial cells via the ACE2 receptor, leading to widespread endothelial dysfunction, inflammation, and a pro-coagulant state. This results in the formation of microthrombi throughout the pulmonary circulation, contributing to a marked increase in PVR and a high incidence of pulmonary hypertension [35]. This thrombotic diathesis is a major driver of the severe right ventricular dysfunction observed in many critically ill COVID-19 patients (Figure 4).

Table 4. ARDS phenotypes and their cardiac implications.

ARDS phenotype	Key characteristics	Cardiac implications
Hypoinflammatory (Phenotype 1)	Lower plasma biomarkers of inflammation (e.g., IL-6, sTNFR-1)	Lower incidence of shock and organ dysfunction, potentially better cardiac tolerance to therapies
Hyperinflammatory (Phenotype 2)	Higher plasma biomarkers of inflammation, more severe shock, metabolic acidosis	Higher risk of cardiac dysfunction, myocardial injury, and catecholamine-resistant vasodilation
Direct (Pulmonary) ARDS	Injury confined primarily to the lungs (e.g., pneumonia, aspiration)	More severe hypoxemia and higher PVR, leading to a greater risk of acute cor pulmonale and RV failure
Indirect (Extrapulmonary) ARDS	Systemic inflammatory response (e.g., sepsis, pancreatitis)	Systemic inflammation and endothelial dysfunction contribute significantly to myocardial depression and vasoplegia
COVID-19 ARDS	Endotheliitis, microthrombosis, profound inflammatory response	High incidence of RV dysfunction, pulmonary hypertension, thromboembolic events, and direct viral or inflammatory myocardial injury

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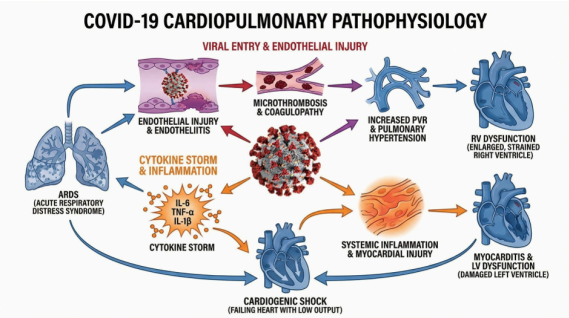

Figure 4. Cardiopulmonary Pathophysiology in Severe COVID-19. This illustration details the unique mechanisms of cardiopulmonary injury in COVID-19. Viral entry leads to both direct endothelial injury, causing microthrombosis and pulmonary hypertension, and a cytokine storm, causing systemic inflammation and myocardial injury. These pathways converge to cause severe RV and LV dysfunction, leading to cardiogenic shock.

Furthermore, the inflammatory response in severe COVID-19 is often characterized by a cytokine storm, a massive and uncontrolled release of pro-inflammatory mediators that far exceeds what is typically seen in other forms of ARDS [36]. This hyperinflammation has profound systemic effects, including:

Direct myocardial injury

The cytokine storm can lead to myocarditis, a direct inflammation of the heart muscle, impairing its contractile function [37].

Stress cardiomyopathy (Takotsubo cardiomyopathy)

The profound physiological stress and high levels of circulating catecholamines can trigger a stress-induced cardiomyopathy, leading to acute LV dysfunction.

Arrhythmias

The inflammatory milieu, electrolyte disturbances, and hypoxemia create a pro-arrhythmic environment, with a high incidence of atrial and ventricular arrhythmias.

Clinical Management of Cardiopulmonary Crosstalk

Managing the critically ill patient with ARDS requires a nuanced approach that acknowledges and addresses the delicate interplay between the heart and the lungs. The goal is to support gas exchange and maintain organ perfusion while minimizing iatrogenic injury. This involves a bundle of care that includes lung-protective ventilation, judicious fluid management, and targeted therapies to support cardiovascular function.

Mechanical ventilation strategies

The cornerstone of ARDS management is Lung-Protective Ventilation (LPV). The primary goal of LPV is to mitigate VILI by minimizing the mechanical stress and strain on the injured lungs. The landmark ARMA trial demonstrated that a Low Tidal Volume (LTV) strategy of 6 mL/kg of predicted body weight, compared to a traditional 12 mL/kg, significantly reduced mortality [39]. This strategy minimizes alveolar overdistension and reduces the release of inflammatory mediators, thereby lessening the systemic inflammatory response and its impact on the heart.

Maintaining a Plateau Pressure (Pplat) below 30 cmH2O is another key component of LPV. Pplat reflects the pressure in the alveoli at the end of inspiration and is a surrogate for alveolar stress. More recently, the concept of driving pressure (Pplat - PEEP) has emerged as a powerful predictor of outcome in ARDS [40]. Driving pressure represents the cyclic strain applied to the lungs with each breath. Minimizing driving pressure, ideally keeping it below 15 cmH_2O, has been associated with improved survival and is now a key target in ventilator management [41].

PEEP is applied to prevent alveolar collapse at the end of expiration, improve oxygenation, and reduce the shear stress associated with cyclic opening and closing of alveoli. However, the application of PEEP must be carefully balanced against its potential hemodynamic consequences. High levels of PEEP can increase ITP, impede venous return, and increase RV afterload [42]. The optimal PEEP strategy remains a subject of debate, but an individualized approach that considers the patient's lung mechanics and hemodynamic status is essential. Incremental PEEP trials while monitoring cardiac output and driving pressure can help identify the PEEP level that provides the best balance of recruitment and hemodynamic stability.

Fluid management

Fluid management in ARDS is a classic example of the heart-lung balancing act. While adequate fluid resuscitation is necessary to maintain cardiac output and organ perfusion, excessive fluid administration can worsen pulmonary edema, impair gas exchange, and increase the risk of RV failure. The FACTT trial provided crucial evidence in this domain, comparing a conservative versus a liberal fluid management strategy in patients with ARDS. The conservative strategy, which aimed for a lower central venous pressure and used diuretics to achieve a negative fluid balance, did not improve the primary outcome of 60-day mortality but resulted in significant improvements in lung function, a shorter duration of mechanical ventilation, and fewer ICU days, without an increase in non-pulmonary organ failure [43].

These findings support the use of a conservative fluid strategy once the initial phase of shock has resolved. The assessment of fluid responsiveness is key to guiding fluid administration. Static measures such as central venous pressure have been shown to be poor predictors of fluid responsiveness. Dynamic parameters that utilize the hemodynamic changes induced by mechanical ventilation, such as Pulse Pressure Variation (PPV) and Stroke Volume Variation (SVV), are more accurate in predicting which patients will increase their cardiac output in response to a fluid bolus [44,45]. These tools allow for a more targeted and rational approach to fluid therapy, avoiding unnecessary and potentially harmful fluid administration.

Prone positioning

Prone positioning has become a standard of care for patients with moderate to severe ARDS. By turning the patient onto their stomach, prone positioning improves V/Q matching by recruiting dorsal lung regions that are collapsed in the supine position and redirecting blood flow to better-ventilated areas [46]. The landmark PROSEVA trial showed that early and prolonged application of prone positioning (at least 16 hours per day) significantly reduced mortality in patients with severe ARDS [47].

Beyond its effects on oxygenation and lung mechanics, prone positioning also has favorable hemodynamic effects. It can reduce RV afterload by decreasing PVR and unloading the RV. The gravitational shift of the heart and mediastinum can also improve cardiac function [48]. While the transition to the prone position requires a coordinated effort and careful monitoring, its

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proven mortality benefit and positive hemodynamic profile make it an essential intervention in the management of severe ARDS.

Pharmacological interventions and advanced therapies

In patients with severe ARDS and refractory hypoxemia or RV failure, a number of pharmacological and advanced therapies may be considered.

Pulmonary vasodilators

Inhaled pulmonary vasodilators, such as inhaled Nitric Oxide (iNO) or prostacyclins, can be used to selectively reduce PVR and improve RV function without causing systemic hypotension [49]. By improving V/Q matching, they can also lead to a transient improvement in oxygenation. However, their routine use has not been shown to improve mortality in ARDS [50].

Neuromuscular blockade

The use of Neuromuscular Blocking Agents (NMBAs) in early, severe ARDS has been shown in some studies to improve oxygenation and reduce mortality by facilitating patient-ventilator synchrony and reducing oxygen consumption [51]. However, a more recent large trial (the ROSE trial) did not confirm a mortality benefit and highlighted the potential for increased muscle weakness [52]. The use of NMBAs remains a topic of debate and should be considered on a case-by-case basis.

Extracorporeal Membrane Oxygenation (ECMO)

For patients with life-threatening refractory hypoxemia despite optimal ventilator management and prone positioning, veno-venous ECMO (VV-ECMO) can be a life-saving rescue therapy. VV-ECMO provides gas exchange, allowing for ultra-protective lung ventilation with minimal tidal volumes and pressures, thereby reducing VILI [53]. While the CESAR and EOLIA trials have provided evidence supporting its use, ECMO is a complex and resource-intensive therapy with its own set of risks, and patient selection is critical (Table 5) [54,55].

Table 5. Clinical management strategies and cardiopulmonary considerations in ARDS.

Management Strategy	Objective	Cardiopulmonary Considerations
Low Tidal Volume Ventilation (LTVV)	Minimize VILI	Reduces ITP swings, decreases RV afterload, and minimizes hemodynamic impact
PEEP Titration	Recruit alveoli, improve oxygenation	Must be balanced to avoid overdistention, which can increase PVR and compromise RV function
Conservative Fluid Management	Prevent fluid overload and pulmonary edema	Improves lung function and shortens ventilation duration without increasing shock or renal failure
Prone Positioning	Improve V/Q matching, recruit dorsal lung regions	Can improve RV function by reducing afterload, but requires careful hemodynamic monitoring
Pulmonary Vasodilator Therapy	Selectively reduce PVR	Improves RV function and oxygenation by decreasing RV afterload without causing systemic hypotension
Neuromuscular Blockade	Facilitate lung-protective ventilation, reduce dyssynchrony	Can improve gas exchange and reduce lung stress, but may cause muscle weakness and requires deep sedation
Weaning and Spontaneous Breathing Trials (SBTs)	Liberate patient from mechanical ventilation	Acts as a cardiac stress test; failure can be due to weaning-induced cardiac failure from increased preload and afterload

Weaning from Mechanical Ventilation: The Ultimate Cardiopulmonary Stress Test

Liberation from mechanical ventilation is a major milestone in the recovery of a critically ill patient, but the process itself can impose a significant stress on the cardiopulmonary system. The transition from passive PPV to spontaneous breathing represents a dramatic shift in physiology, effectively acting as a cardiac stress test [56].

During a SBT, the patient must assume the work of breathing. This leads to more negative swings in ITP, which, as previously discussed, simultaneously increases venous return (RV preload) and LV afterload [57]. The increased work of breathing also increases myocardial oxygen demand. For a patient with underlying cardiac dysfunction, this combination of increased preload, increased afterload, and increased oxygen demand can be overwhelming, leading to the development of weaning-induced cardiac failure or weaning-induced pulmonary edema [58].

Failure to wean from mechanical ventilation is a common problem in the ICU, and cardiac dysfunction is a frequently under-recognized cause. Patients who fail an SBT may exhibit signs of respiratory distress, such as tachypnea and accessory muscle use, but the underlying problem may be cardiac in origin.

The use of targeted bedside echocardiography specifically assessing dynamic changes in RV function (e.g., TAPSE, RV fractional area change) and LV filling pressures alongside biomarkers like BNP during an SBT can help identify patients with weaning-induced cardiac failure [59]. Management of these patients involves optimizing their cardiac function with diuretics, vasodilators, or targeted vasoactive support before re-attempting a weaning trial (Figure 5). When selecting vasoactive agents, the specific cardiopulmonary profile of the drug must be considered.

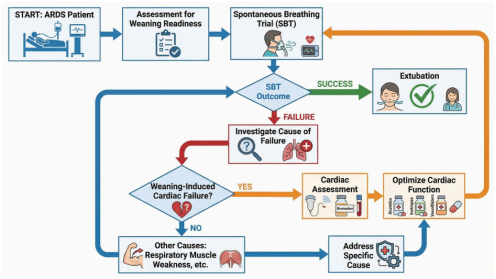

Figure 5. Algorithm for managing weaning failure. This flowchart provides a clinical pathway for managing weaning failure. After a failed SBT, the first step is to investigate the cause, with a key decision point being the presence of weaning-induced cardiac failure. If cardiac failure is identified, a cardiac assessment is performed, and function is optimized before re-attempting an SBT. If other causes are identified, they are addressed specifically.

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For instance, while norepinephrine is the standard first-line agent in shock, the landmark VASST trial demonstrated that low-dose vasopressin may offer a survival benefit in less severe shock states [60]. Furthermore, recent evidence suggests that vasopressin leads to a lower PVR compared to norepinephrine in vasoplegic patients [61]. In the context of ARDS and weaning-induced cardiac failure, where RV afterload is a primary concern, this differential effect on PVR makes vasopressin an attractive option to support systemic perfusion without exacerbating right-sided heart strain.

Conclusion

The cardio-pulmonary axis is a complex and dynamic system that lies at the very center of critical care medicine. The bidirectional crosstalk between the heart and the lungs is a powerful force that can either sustain life or drive a patient towards multi-organ failure. In ARDS, this relationship is pushed to its limits, as lung injury, inflammation, and the interventions required for support conspire to create a hostile hemodynamic environment. A deep understanding of the physiological principles of heart-lung interaction, the pathophysiological derangements in disease, and the molecular mediators of this crosstalk is essential for any clinician managing these complex patients.

The past few decades have seen significant advances in our understanding and management of ARDS. The principles of lung-protective ventilation, conservative fluid management, and prone positioning have become pillars of care, all of which are rooted in an appreciation for their impact on the cardiopulmonary system. The COVID-19 pandemic has further highlighted the critical importance of this axis, revealing the devastating consequences of endothelial injury and uncontrolled inflammation on both the heart and the lungs.

As we move forward, the challenge lies in translating our growing understanding into more personalized and targeted therapies. The use of biomarkers to phenotype patients, the development of novel therapies that target the molecular drivers of injury, and the refinement of our supportive care strategies will all be crucial. Ultimately, the successful management of the critically ill patient requires a holistic approach that recognizes the heart and lungs not as separate entities, but as the two intimately connected partners they are, working in concert at the core of the cardio-pulmonary axis.

Ethical and Compliance Statements

Strengths

- This review provides a comprehensive and up-to-date overview of the Cardio-Pulmonary Axis, integrating molecular, clinical, and therapeutic perspectives.
- The inclusion of dedicated sections on pediatric crosstalk and the impact of COVID-19 addresses highly relevant and contemporary aspects of critical care.
- The use of multiple figures and tables enhances the clarity and accessibility of complex information.

Limitations

- As a narrative review, this study is based on published literature and may be subject to publication bias.
- The broad scope of the review may limit the depth of discussion on any single topic.

Highlights

- Comprehensive review of bidirectional heart-lung crosstalk in critical care.
- Focuses on mechanical, molecular, and neurohormonal mechanisms
- Explores clinical syndromes, advanced diagnostics, and therapeutic strategies
- Includes new insights on pediatric aspects and COVID-19 impact

Institutional Review Board Statement

Not applicable. This study is a reviewof existing literature and did not require ethical approval.

Patient Consent for Publication

Not applicable. No patient data is Included in this article.

Clinical Trial Registry Number

Not applicable. This is not a clinical trial.

Availability of Data and Materials

Data sharing is not applicable to this article as no new data were created or analyzed in this article.

Author Contributions

Gaurav Narain Gupta: Conceptualization, Study Design, Supervision, Critical review, Final approval.

Munish Narain Gupta: Data curation, Critical review, Manuscript drafting (sections). Sweta Gupta: Data analysis, Critical review, Manuscript drafting (sections).

All authors review and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflictsof interest.

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