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Review

Sepsis-Induced Cardiomyopathy and Acute Respiratory Distress Syndrome

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ABSTRACT: Sepsis remains the leading cause of acute respiratory distress syndrome (ARDS) and cardiovascular dysfunction in the ICU. Sepsis-induced cardiomyopathy (SCM) and sepsis-associated ARDS frequently coexist and share overlapping mechanisms, including cytokine-driven injury, endothelial disruption, microvascular dysfunction, and mitochondrial abnormalities. Despite their clinical relevance, these entities are often evaluated in isolation, overlooking the integrated heart-lung interactions that characterize severe sepsis and ARDS. This narrative review synthesizes current evidence on the shared pathophysiology and diagnostic approach to cardiomyopathy and lung injury in sepsis-associated ARDS, emphasizing the physiologic links that unify these syndromes. We review the immunologic, endothelial, and metabolic mechanisms that drive concurrent myocardial depression and alveolocapillary injury, with particular attention to microcirculatory failure, autonomic dysregulation, and mechanical ventilation-associated cardiopulmonary interactions. We then review diagnostic tools, including echocardiography, lung ultrasound, CT imaging, biomarkers, and advanced hemodynamic monitoring, and highlight the impact of integrated assessment on accurate phenotyping and management. Cardiomyopathy and ARDS in sepsis arise from common pathophysiologic drivers and should be understood as a unified cardiopulmonary phenotype rather than isolated organ failures. Early multimodal detection is critical for optimizing management strategies and improving outcomes.

Keywords: ARDS; Septic shock; Cardiogenic shock; Cardiopulmonary disease

1. Introduction

Sepsis is the leading global cause of acute respiratory distress syndrome (ARDS) [1–3], accounting for 35–45% of ARDS presentations and associated with more severe hypoxemia [3]. Septic cardiomyopathy (SCM) is highly prevalent but frequently under-recognized. Reversible myocardial depression occurs in approximately 40–60% of patients with septic shock [4,5]. Early descriptions by Parker et al. identified rapid onset, global ventricular dysfunction which resolved within 7–10 days [6]. Studies using modern

echocardiography confirm this phenotype and highlight significant right ventricular (RV) dysfunction as a common subphenotype, especially in the presence of ARDS [7,8].

The overlap between ARDS and SCM is substantial. Patients with sepsis-associated ARDS have higher rates of RV dysfunction and myocardial strain due to increased pulmonary vascular resistance (PVR), mechanical ventilation effects, and systemic inflammation [7–9]. These epidemiologic patterns underscore the need to conceptualize SCM and ARDS as interconnected manifestations of a shared cardiopulmonary pathobiology rather than isolated organ failures.

Most reviews address ARDS and SCM separately, even though these conditions frequently coexist and arise from overlapping molecular and physiologic mechanisms [5,6,10–14]. Treating ARDS as a pulmonary disorder and SCM as a cardiac complication fails to account for the substantial heart-lung interaction seen in septic shock, where pulmonary vascular dysfunction, hypoxemia, mechanical ventilation, and inflammatory signaling directly influence myocardial performance [7,8].

Recent insights highlight shared pathways, such as cytokine-driven endothelial injury, glycocalyx shedding, mitochondrial dysfunction, microcirculatory collapse, and dysregulated autonomic signaling [5,6,10–14]. These mechanisms simultaneously impair oxygen delivery, cardiac output, alveolar stability, and ventilation-perfusion matching. Understanding these common pathways is essential for accurate diagnosis and optimization of therapy.

Diagnostic strategies for sepsis associated cardiopulmonary dysfunction are rapidly evolving. Echocardiography, lung ultrasound, computerized tomography (CT) phenotyping, and biomarker assays provide critical complementary information while emerging modalities, including cardiac magnetic resonance imaging (CMR), electrical impedance tomography, and machine learning-enhanced ultrasound, offer unprecedented insights into regional physiology [6,15–19]. However, no existing review integrates these diagnostic approaches into a unified framework.

This narrative review aims to use the existing literature to introduce a conceptual framework that (1) synthesizes the shared pathophysiology linking cardiomyopathy and ARDS in sepsis, and (2) provides a comprehensive, multimodal diagnostic and management strategy for evaluating these intertwined syndromes.

2. Definitions

SCM is defined in this review as an acute, reversible myocardial dysfunction occurring during sepsis or septic shock, typically presenting with global systolic impairment, reduced myocardial strain, and frequent right ventricular involvement [4,5].

Sepsis-associated ARDS is defined according to the Berlin criteria, which require the presence of bilateral pulmonary opacities within one week of an infectious insult and hypoxemia not fully explained by cardiac failure or fluid overload [1]. ARDS is further graded based on PaO_2/FiO_2 thresholds, reflecting the severity of gas exchange impairment [1,3]. In sepsis, ARDS typically reflects a diffuse alveolocapillary injury pattern with inflammatory exudation, surfactant dysfunction, and pulmonary vascular remodeling [2].

2.1. Scope of Review

This narrative review focuses on the shared pathobiology and diagnostic evaluation of cardiomyopathy and lung injury in the setting of sepsis-associated ARDS. The scope is intentionally integrative, emphasizing the mechanisms and diagnostic tools that unify these two organ dysfunctions rather than treating them as isolated syndromes.

Specifically, this review will address:

1. Overlapping mechanisms of injury, synthesizing data on cytokine-mediated myocardial depression, endothelial and glycocalyx injury, mitochondrial dysfunction, microcirculatory failure, and autonomic

dysregulation. These mechanisms are implicated in both SCM and ARDS [5,6,10–14,16]. These pathways form the conceptual foundation for understanding the sepsis induced cardiopulmonary axis.
2. Heart-lung interactions in sepsis. Ventilatory mechanics, PVR, and RV function tightly interact in sepsis [7,8]. The review highlights the physiologic bidirectionality linking the heart and lungs, including the impact of positive pressure ventilation on hemodynamics and oxygen delivery.
3. Multimodal diagnostics. We describe the evidence supporting echocardiography, lung ultrasound (LUS), CT morphology, biomarkers, and hemodynamic monitoring as essential components of diagnostic evaluation [6,15,20–23]. Emerging modalities are reviewed for their potential to refine phenotyping [16–19].
4. Conceptual reframing of sepsis-induced cardiopulmonary failure. The review suggests that SCM and ARDS can be viewed as a unique unified pathophysiologic condition rather than discrete complications. Understanding this integrated framework may inform future research and therapeutic strategies that target shared injury pathways.

The review does not address the following: non-septic causes of ARDS (e.g., trauma, transfusion), chronic cardiomyopathies, heart failure due to acute coronary syndrome or primary structural heart disease, and detailed management strategies (e.g., fluid resuscitation, ventilator settings) except as specific to this phenotype, and pediatric-specific data.

2.2. Search Strategy

A comprehensive literature search was performed using the electronic databases PubMed and Embase. Keywords included “ARDS”, “acute respiratory distress syndrome”, “septic cardiomyopathy”, “septic shock”, “cardiogenic shock”, “cardiopulmonary disease” and “hemodynamic management” were used. Boolean operators (“AND”, “OR”) were used to refine the search. Selected articles were primarily published from January 2000–December 2025, with preference for articles published after January 2010.

3. Pathophysiology

SCM is pathophysiologically distinct from atherosclerotic ischemia. Rather than resulting from obstructive coronary disease, myocardial dysfunction in sepsis reflects cytokine-mediated depression, mitochondrial injury, and microcirculatory dysregulation, producing a reversible pattern of global rather than regional contractile impairment [5,6,10,16].

A full biochemical review of sepsis-associated ARDS and SCM is beyond the scope of this article. However, these conditions arise from intertwined inflammatory, endothelial, and metabolic disturbances that simultaneously affect the heart and lungs. Cytokine-mediated microvascular dysfunction and mitochondrial injury create a unified cardiopulmonary phenotype that evolves with the host response to sepsis [4,5,24,25]. Sepsis induces a hyperinflammatory response characterized by elevated TNF-α, IL-1β, IL-6, IFN-γ, and chemokines that directly impair cardiomyocyte contractility through impaired calcium cycling, reduced β-adrenergic signaling, and nitric oxide (NO) mediated myofilament desensitization [5,10]. These same cytokines drive ARDS by disrupting epithelial tight junctions, promoting neutrophil recruitment, and producing diffuse alveolar damage (DAD) [2]. Neutrophil extracellular traps, elastases, and reactive oxygen species further damage the alveolocapillary barrier [2,26].

Endothelial dysfunction is central to both cardiac and pulmonary injury. Glycocalyx degradation by way of syndecan-1 shedding increases vascular permeability, promoting myocardial interstitial edema and alveolar flooding [11,12]. Injury to the endothelial barrier promotes microthrombosis and loss of vascular regulation, which impairs both coronary and pulmonary perfusion [13,14].

Cardiomyocytes in sepsis exhibit reduced oxidative phosphorylation and impaired ATP generation, reflecting mitochondrial bioenergetic failure rather than ischemic necrosis [4]. These changes produce the reversible myocardial depression first described by Parker et al. [6]. In the lung, mitochondrial damage in

type II pneumocytes reduces surfactant production and impairs alveolar fluid clearance, worsening alveolar collapse and lung compliance [27].

Sepsis produces profound microvascular heterogeneity due to endothelial swelling, leukocyte sequestration, microthrombosis, and impaired autoregulation [13,16]. These abnormalities worsen myocardial contractility and increase pulmonary dead space and pulmonary hypertension [7].

Sepsis is also associated with an adrenergic imbalance characterized by β-receptor desensitization, catecholamine hyporesponsiveness, and increased catecholamine demand [5]. Catecholamines (endogenous and exogenous) increase myocardial oxygen consumption and may worsen RV strain in ARDS [7]. Simultaneously, dysregulation of nitric oxide and endothelin-1 contributes to vasoplegia and impaired coronary perfusion [24].

Direct cellular injury represents the downstream expression of the inflammatory and endothelial mechanisms described earlier. In the myocardium, cytokine-mediated membrane permeability, oxidative stress, and microvascular dysregulation lead to troponin release and reversible myocyte dysfunction, without the necrosis typical of ischemic injury [20]. These inflammatory effects, together with mitochondrial impairment, produce the global, reversible depression characteristic of SCM [5,6,10].

In the lung, diffuse alveolocapillary injury arises from cytokine signaling, endothelial barrier disruption, and neutrophil-derived oxidants, resulting in alveolar epithelial injury, hyaline membrane formation, and impaired surfactant production [2,21,22,27]. Cellular injury in both the heart and lung reflects the final common pathway of systemic inflammation, endothelial dysfunction, and mitochondrial injury, linking the earlier mechanistic steps to the structural manifestations of SCM and ARDS.

Treatment strategies in sepsis-associated ARDS may exacerbate these underlying factors. In patients who require invasive mechanical ventilation (IMV), the use of a higher positive end-expiratory pressure (PEEP) strategy, often favored in ARDS, may contribute to increased RV afterload in and may produce a septal shift with reduced left ventricular (LV) filling and consequent reduction in stroke volume [7]. Lung hyperinflation elevates PVR and decreases venous return, contributing to the RV failure sometimes seen in ARDS [7,8]. Allowing for permissive hypercapnia and acidosis can directly impair right ventricular (RV) contractility and increase PVR, thereby increasing RV afterload [7,8]. Vasopressors with predominant α-adrenergic activity, such as phenylephrine, may increase PVR and further exacerbate RV afterload [28]. Although early fluid resuscitation is recommended by sepsis management guidelines [24], liberal fluid administration may worsen ventricular performance and tissue perfusion in patients with impaired myocardial contractility [4,7].

SCM and ARDS result from overlapping pathways. Cytokine mediated injury, endothelial disruption, mitochondrial dysfunction, microcirculatory collapse, and maladaptive heart-lung interactions result in a unified cardiopulmonary phenotype of sepsis. A summary of these pathways can be found in Figure 1.

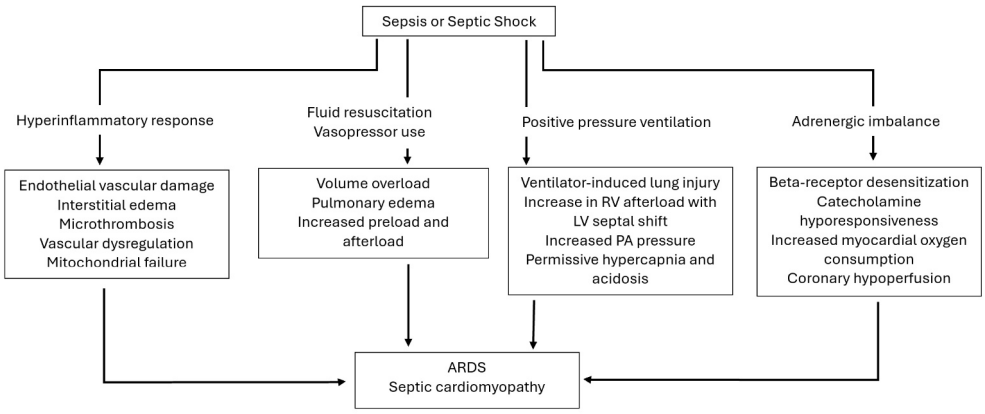

Figure 1. Broad overview of the common pathophysiologic drivers of ARDS and septic cardiomyopathy. RV, right ventricle; LV, left ventricle; ARDS, acute respiratory distress syndrome. Shared pathophysiologic causes leading to an inflammatory

response affecting cardiac function, whereas therapeutic strategies for ARDS, sepsis, and shock can potentially impact cardiopulmonary interactions.

4. Detection and Diagnostics

The diagnostic approach to SCM and sepsis-associated ARDS requires multimodal integration: clinical evaluation, echocardiography, lung imaging, biomarkers, and hemodynamic monitoring. Because SCM and ARDS frequently coexist, careful evaluation is required to differentiate intrinsic myocardial dysfunction from pulmonary vascular strain and distributive physiology.

4.1. Clinical Features and Bedside Phenotyping

Septic shock is a distributive state characterized by low systemic vascular resistance (SVR) and a compensatory high cardiac output [4]. When SCM develops, this expected high-output state is lost, and patients exhibit signs of inadequate myocardial contractility in addition to vasodilation [5]. Thus, clinical features that suggest SCM reflect the development of a mixed septic and cardiogenic shock state. These patients have hypotension disproportionate to the degree of vasoplegia, a narrow pulse pressure, tachycardia with an inappropriately low stroke volume, and persistent shock despite adequate fluids and vasopressors [5]. In distributive shock, the expected cardiac response is hyperdynamic; therefore, the presence of apparently ‘normal ’cardiac function in septic shock may reflect an inappropriately blunted response and underlying myocardial insufficiency [4–6].

In contrast to classic distributive shock, which is typically characterized by low SVR and warm extremities, patients with a substantial cardiogenic component may present with cooler extremities, reflecting reduced cardiac output and relatively increased SVR [4–6]. Although no lab test is specific for SCM, patients may have an elevated B-type natriuretic peptide (BNP) and low mixed venous oxygen saturation (MvO2); in contrast, patients with isolated septic shock tend to have MvO2 > 70% [4–6,29,30].

In sepsis-associated ARDS, patients develop progressive hypoxemia despite supplemental oxygen, diffuse infiltrates, decreased lung compliance, and increasing ventilatory requirements [2]. These features overlap with those seen in cardiogenic pulmonary edema, and in patients with suspected myocardial dysfunction, it is therefore essential to determine whether pulmonary findings are a cause or consequence of cardiomyopathy [1,5,7]. Bedside tools to aid in this differentiation are described below. Anecdotally, patients with isolated cardiogenic pulmonary edema tend to have greater improvement in oxygenation with the institution of positive-pressure ventilation and diuresis, compared with patients with ARDS.

4.2. Echocardiography

Echocardiography is the cornerstone of diagnosing SCM and typically reveals a pattern of global, rather than regional, LV hypokinesis, distinguishing it from ischemic cardiomyopathy [6]. Although a reduced ejection fraction (EF) may be present, EF can appear deceptively normal in states of profound vasoplegia, making it an unreliable standalone measure of systolic function. Global longitudinal strain (GLS) offers greater sensitivity for detecting early myocardial impairment and often identifies dysfunction even when EF is preserved [17]. Diastolic abnormalities are frequently observed in septic cardiomyopathy and contribute to reduced cardiac output by impairing ventricular filling. Echocardiographic markers include elevated E/e′ ratios, abnormal transmitral inflow patterns, and tissue Doppler indices consistent with increased filling pressures and impaired relaxation [4]. These findings are particularly relevant in septic shock, where tachycardia and altered loading conditions amplify the hemodynamic consequences of diastolic dysfunction [4]. The pattern first described by Parker et al., characterized by reversible biventricular depression, remains consistent with findings from modern strain-based studies that confirm the dynamic and reversible nature of septic myocardial dysfunction [6].

The RV is particularly vulnerable in ARDS and septic shock due to elevated PVR, hypoxic pulmonary vasoconstriction, mechanical ventilation effects (PEEP), and pulmonary microvascular obstruction [7,16]. Key echocardiographic findings of RV dysfunction include RV dilation, reduced tricuspid annular plane systolic excursion (TAPSE) and S′, decreased fractional area change, and septal flattening ("D-sign"), reflecting pressure overload and impaired RV–pulmonary arterial (PA) coupling [8]. In addition to these cardiac findings, systemic venous congestion can be assessed at the bedside using venous Doppler ultrasound. Abnormal flow patterns in the hepatic, portal, and intrarenal veins, summarized by the venous excess ultrasound (VEXUS) score, reflect elevated right-sided filling pressures and impaired venous return and have been associated with organ congestion and adverse outcomes [31]. Collectively, these echocardiographic and venous ultrasound markers highlight the central role of RV dysfunction and venous congestion in ARDS, a relationship emphasized by Vieillard-Baron [32] and Petit [8], who identified RV failure as a major determinant of mortality.

4.3. Lung Ultrasound (LUS)

LUS provides characteristic findings in sepsis-associated ARDS, including heterogeneous B-line patterns, subpleural consolidations, dynamic air bronchograms, pleural line thickening or irregularity, and non-dependent spared areas, with progressive loss of aeration on serial examinations [9,33]. Importantly, this heterogeneous and regional distribution distinguishes ARDS from cardiogenic pulmonary edema, which typically shows bilateral, symmetric, gravity-dependent B-lines, a smooth pleural line, and minimal consolidations [33]. LUS has been established as a rapid, bedside modality for detecting acute lung injury and for differentiating ARDS from cardiogenic edema based on these sonographic patterns [33]. Additional tools have included LUS reaeration score, which quantifies aeration changes in response to PEEP adjustments and provides practical guidance for titrating ventilatory support [9]. More recently, Costamagna [15] showed that LUS can reliably distinguish focal versus non-focal ARDS phenotypes, an important observation, given that recruitability and optimal ventilator strategies differ significantly between these morphologic patterns.

4.4. Chest CT

CT remains the gold standard for structural lung assessment and ARDS phenotyping. In early (exudative) ARDS, CT typically demonstrates bilateral ground-glass opacities, often with dependent consolidations, impaired aeration with relative ventral sparing, air bronchograms, and regions of mosaic attenuation, reflecting alveolar flooding, inflammatory infiltrates, and surfactant dysfunction [2]. As ARDS evolves into the fibroproliferative and late phases, CT findings increasingly include traction bronchiectasis, architectural distortion, reduced lung compliance, and, in some cases, reticular changes consistent with fibrotic remodeling [2]. Differentiating early from late CT patterns is clinically relevant, as early disease may retain greater recruitability, whereas late-stage changes reflect irreversible structural injury with important implications for ventilatory strategy and prognosis. Focal and nonfocal ARDS can be distinguished on CT based on the distribution and morphology of lung injury, a distinction with important prognostic and management implications [15]. Focal ARDS is characterized by localized consolidations, often involving dependent or lobar regions with relatively preserved aeration elsewhere, whereas nonfocal ARDS demonstrates diffuse, bilateral loss of aeration and widespread ground-glass opacities [15]. These morphologic patterns are clinically relevant because nonfocal ARDS is generally associated with lower lung compliance, reduced recruitability, and worse outcomes, while focal ARDS may tolerate lower PEEP strategies and targeted recruitment approaches [15].

In contrast, cardiogenic pulmonary edema typically exhibits symmetric, gravity-dependent ground-glass opacities, interlobular septal thickening, pleural effusions, and perihilar predominance without the

regional heterogeneity or spared areas characteristic of ARDS [2]. Differentiating these CT patterns is essential, as misclassification may lead to inappropriate ventilatory strategies or fluid management, particularly in patients with concomitant myocardial dysfunction. Equally important is consideration of other etiologies of parenchymal pulmonary disease, such as acute eosinophilic pneumonia, as well as underlying interstitial lung disease exacerbations.

RV strain can be identified on CT by RV dilation, interventricular septal flattening, and PA enlargement, as well as reflux of intravenous contrast into the inferior vena cava and hepatic veins, reflecting elevated right-sided pressures and pulmonary vascular load [3,7,8]. These findings correlate strongly with RV dysfunction on echocardiography and are associated with increased mortality [7,8].

4.5. Biomarkers

Cardiac biomarkers complement imaging for phenotyping and prognostication. Commonly used markers in sepsis-induced cardiomyopathy include troponin and BNP/NT-proBNP. Troponin is elevated in approximately 40–70% of patients with septic shock and typically reflects inflammatory membrane injury and microvascular dysfunction rather than plaque rupture. Importantly, troponin elevations in sepsis are generally modest compared with the marked elevations seen in acute coronary syndromes, and often lack a dynamic rise-and-fall pattern or regional wall motion abnormalities consistent with ischemia [20].

4.6. Hemodynamic Monitoring

Advanced hemodynamic monitoring may be helpful when shock is mixed or when echocardiographic findings are equivocal. PA catheterization (PAC) is useful for distinguishing cardiogenic *vs*. non-cardiogenic pulmonary edema and for quantifying PVR, RV afterload, and mixed venous oxygen saturation. Historically, PAC was frequently used for hemodynamic monitoring in septic shock, and PAC-derived parameters were incorporated into early goal-directed therapy protocols and used as clinical trial endpoints [34]. More recent large-scale randomized trials demonstrated that protocolized resuscitation strategies do not improve outcomes compared with usual care, leading to a shift away from rigid hemodynamic targets in septic shock management [35–37]. After the ESCAPE and PAC-MAN trials demonstrated no mortality benefit and potential harm associated with routine PAC use, including increased complications without improved outcomes, PAC-guided management fell out of favor in both cardiogenic and septic shock [38,39]. However, in selected patients and in experienced hands, PAC can provide a wealth of information. In patients with SCM, PAC measurements may demonstrate reduced cardiac output with elevated PA pressures, while patients with concomitant LV dysfunction often exhibit marked elevation of pulmonary capillary wedge pressure, reflecting impaired forward flow and elevated filling pressures [4,6,7]. Sampling of mixed-venous blood gases from a PA catheter can help characterize shock physiology. Patients with isolated distributive septic shock typically demonstrate preserved or elevated MvO_2 (>70%), reflecting high cardiac output and impaired oxygen extraction, whereas patients with significant myocardial depression or inadequate compensatory response often exhibit reduced MvO_2 (<70%) [4,6,34]. These data can be used to make decisions on vasopressors, inotropes, and fluid management.

Minimally invasive hemodynamic monitoring tools are increasingly used in critically ill patients. For example, the Pulse index Continuous Cardiac Output (PiCCO) system uses transpulmonary thermodilution to estimate cardiac output and derive additional parameters, including extravascular lung water (EVLW), which quantifies pulmonary edema, and global end-diastolic volume (GEDV), a volumetric surrogate of cardiac preload [23]. These measurements can aid in differentiating cardiogenic from non-cardiogenic pulmonary edema and in guiding fluid and ventilatory management. Other minimally invasive monitoring systems, such as FloTrac, NICOM, and bioreactance methods, have been evaluated in shock. However, a recent systematic review noted that most cardiac output monitors demonstrate poor agreement with

reference methods and that their true clinical utility remains unclear, particularly regarding precision and trending under dynamic conditions [40].

4.7. Emerging Diagnostic Modalities

Emerging diagnostic modalities offer additional insight into the cardiopulmonary dysfunction seen in sepsis. Cardiac MRI (CMR) can identify non-ischemic inflammatory injury, including myocardial edema and elevated T1/T2 relaxation times, which help confirm myocarditis-like patterns characteristic of SCM [19]. Electrical impedance tomography (EIT) provides real-time, regional assessments of ventilation, allowing clinicians to evaluate PEEP responsiveness, detect overdistension, and assess recruitment heterogeneity at the bedside [17]. Advances in machine learning-enhanced LUS further improve diagnostic reproducibility by using deep-learning algorithms to classify ARDS phenotypes and detect pathologic LUS patterns [18]. Additionally, sublingual microcirculatory imaging can reveal reductions in perfused vessel density and increased flow heterogeneity, physiologic abnormalities that correlate with organ failure and mortality in sepsis [16]. Collectively, these modalities complement traditional imaging and hemodynamic assessment by providing higher-resolution physiologic data relevant to both SCM and sepsis-associated ARDS.

Several biomarkers of pulmonary injury have been investigated in sepsis-associated ARDS, including receptor for advanced glycation end products (RAGE), surfactant protein-D (SP-D), and angiopoietin-2 (Ang-2). RAGE reflects type I pneumocyte injury and is associated with ARDS severity and mortality [21]. SP-D is a type II pneumocyte injury marker predictive of ARDS development and outcomes [22], while Ang-2 reflects endothelial activation and permeability and correlates with mortality and ARDS severity [11]. These biomarkers are not routinely used in clinical practice, but provide important mechanistic insight and may inform future diagnostic or prognostic strategies.

4.8. Integrated Diagnostic Approach

A structured diagnostic strategy synthesizes the following:

1. Clinical phenotype—shock type, hypoxemia severity
2. Bedside ultrasonography—LV/RV function + LUS findings + markers of systemic venous congestion (e.g., by VEXUS)
3. Biomarkers—troponin, BNP
4. Hemodynamic monitoring—cardiac output, PA pressure, pulmonary capillary wedge pressure
5. CT phenotyping—distinguish focal versus nonfocal ARDS morphology, evaluation for non-ARDS causes of bilateral pulmonary infiltrates, and diagnostic differentiation from cardiogenic pulmonary edema
6. Assessment of heart-lung interaction—RV strain, TAPSE/PASP ratio
7. Serial re-evaluation

5. Interventions and Therapeutic Strategies

A framework for visualizing therapeutic strategies by ARDS phenotype with SCM can be found in Table 1. This framework uses the practical patient presentation of hypoxia and bilateral pulmonary infiltrates, along with clinical tools, to provide a phenotypic characterization of the patient. Fundamentally, it is key to distinguish ARDS from cardiogenic pulmonary edema and, thereafter, determine the ARDS phenotype in relation to SCM. As Table 1 suggests, this is not always clear, and diagnostic features of ARDS and pulmonary edema due to cardiomyopathy frequently overlap. It is also important, in this framework, to consider more rare causes of ARDS, non-ARDS causes of bilateral pulmonary infiltrates, coexisting valvular disease, and the possibility of coexisting thromboembolic disease.

Table 1. A basic framework for conceptualizing the treatment approach to the patient with bilateral pulmonary infiltrates and hypoxia, highlighting shared attributes and differences. ARDS, acute respiratory distress syndrome; SCM, septic cardiomyopathy; RV, right ventricle; LVEF, left ventricular ejection fraction; CT, computerized tomography; IVC, inferior vena cava; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; PRN, as-needed; MvO_2, mixed venous oxygen saturation; VEXUS, venous excess ultrasound; VAV, veno-arterio-venous; VV, veno-venous; VA, veno-arterial; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

Data	Findings	Sepsis-Related ARDS + SCM with Biventricular Failure	Sepsis-Related ARDS + SCM with RV Failure	Sepsis-Related ARDS with Appropriate Cardiac Response	Pulmonary Edema Due to Primary Cardiomyopathy without ARDS
Physical exam	Cool extremities, bradycardia	+ or −	+ or −	−	+
	Warm extremities, tachycardia	+ or −	+ or −	+	−
Echocardiogram	LVEF reduction	+	−	−	+
	RV dilation/dysfunction	+	+	−	+
	Wall motion abnormalities	+ or −	−	−	+ or −
CT of the lungs	Dependent consolidations	+	+	+	−
	Diffuse groundglass opacities	+	+	+	+
	Interlobular septal thickening	+	−	−	+
	RV dilation/IVC reflux	+ or −	+	−	+ or −
Hemodynamics	High PA pressure	+	+	−	+
	Low cardiac output	+	+	−	+
	High PAWP	+	−	−	+
Mixed venous oxygen saturation	≤70%	+ or −	+ or −	−	+
	>70%	+ or −	+ or −	+	−
		Norepinephrine + PRN vasopressin Early addition of dobutamine/milrinone or epinephrine, target MvO_2 VEXUS → diurese if congested Lung protective ventilation Prone positioning Consider early steroids Treat primary cause of ARDS Consider VAV ECMO in refractory cases	Norepinephrine + early vasopressin Early addition of dobutamine/milrinone or epinephrine, target MvO_2 Inhaled nitric oxide/epoprostenol Lung protective ventilation but avoid permissive hypercapnia and acidosis Prone positioning Consider early steroids Treat primary cause of ARDS Consider VV/VAV ECMO in refractory cases	Norepinephrine + PRN vasopressin VEXUS → diurese if congested Lung protective ventilation Prone positioning Consider early steroids Treat primary cause of ARDS Consider VV ECMO in refractory cases	Norepinephrine Early addition of dobutamine/milrinone or epinephrine, target MvO_2 VEXUS → diurese if congested Treat primary cause of cardiomyopathy Consider IABP, Impella, or VA ECMO in refractory cases

5.1. Hemodynamic Management

5.1.1. Intravascular Volume Management

Early fluid resuscitation to maintain cardiac output and tissue perfusion remains a cornerstone of sepsis management [41,42]. However, in patients with SCM or ARDS, there is a delicate balance between

restoring systemic perfusion and avoiding iatrogenic pulmonary edema. The amount of fluid infused during early periods of hospitalization may be associated with the development of lung injury and ARDS, with positive fluid balance a poor prognostic factor [43]. A retrospective cohort study of 598 patients with sepsis and acute decompensated heart failure found that, compared to the guideline-recommended 30 mL/kg crystalloid administration [42], resuscitation volumes of 10–15 mL/kg may have a lower risk of in-hospital mortality; however, that study focused on those with existing heart failure versus cardiomyopathy induced by sepsis [44].

There is also emerging evidence via the ANDROMEDA-SHOCK 2 trial, which utilized a personalized resuscitation algorithm based around capillary refill time (CRT)—highlighting the use of dynamic measures of fluid responsiveness to guide individualized fluid resuscitation, rather than a "one-size-fits-all" approach [45]. These approaches aim to prevent excessive RV preload, which can worsen right-heart failure, impair LV filling, and exacerbate oxygenation deficits in ARDS [23,46]. Here, echocardiography plays a key role in measuring parameters such as inferior vena cava (IVC) distensibility to predict fluid responsiveness, or in identifying significant RV failure, which may skew other measures of responsiveness, such as pulse-pressure variation (PPV) and stroke volume variation (SVV) [23,47]. Studies have shown that dynamic echocardiographic indices, such as respiratory variation in superior vena cava diameter or change in aortic velocity-time integral, have good predictive value for fluid responsiveness in ARDS [48]. Given the known risks of lung injury with over-administration of fluids, regular monitoring of these dynamic measurements should be done to accurately guide fluid therapy [49].

Finding the balance between fluid resuscitation and vascular decongestion in patients with mixed septic and cardiogenic shock, as often seen with SCM, can be a significant therapeutic challenge [50]. Currently, there is a need for more robust data on the use of resuscitation measures such as CRT in patients with SCM and SCM-ARDS overlap. American College of Cardiology guidelines emphasize that patients with signs of venous congestion on echocardiogram or invasive monitoring should be treated with loop diuretics, with the addition of thiazide diuretics or renal replacement therapy if needed [51]. The aforementioned VEXUS bedside ultrasound protocol uses IVC diameter and Doppler flow patterns of hepatic, portal, and renal veins to grade overall systemic venous congestion on a scale of zero to three. This has a good association with mean PA and right atrial pressures as measured by PAC, and a good association between weight change and congestion in patients with heart failure undergoing diuresis [52]. Recent studies show no significant association between VEXUS assessments and AKI occurrence [53,54], and this tool is currently being studied for its use in patients with septic shock [55].

5.1.2. Vasopressors

Norepinephrine. Norepinephrine (NE) remains the first-line hemodynamic agent for undifferentiated shock, with both vasopressor and inotropic properties [42,49]. However, increasing SVR may lead to increased LV afterload, which should be considered in patients with SCM or ARDS. Small cohort studies of patients with septic shock found that patients with normal LV function prior to administration of NE developed global LV hypokinesia within 24 to 48 h, thought to be related to an increase in afterload unmasking underlying myocardial dysfunction [56]. Increasing afterload may impose additional LV stress and worsen RV dysfunction, which can be compounded by hypoxic pulmonary vasoconstriction seen with ARDS [57]. There are, however, studies that show NE may augment RV myocardial oxygen delivery without meaningfully altering PA pressures or PVR [58,59]. With this in mind, NE should still be used as the first-choice vasopressor, but additional vasopressor/inotrope combinations can be considered based on clinical exam, echocardiography, and other parameters of perfusion [42]. Recent studies also underscore NE's potential to modulate microcirculatory flow, which may influence myocardial and pulmonary perfusion simultaneously, although this has mainly been studied in the setting of anesthesia-related hypotension or endotoxic shock [60].

Epinephrine. Epinephrine is a vasopressor with more potent inotropic properties, with lower doses functioning primarily on beta-1 adrenergic receptors [42]. In experimental rat models of septic shock with severe myocardial dysfunction, both epinephrine and NE improved mean arterial pressure and cardiac output, and preload-recruitable stroke work. Notably, epinephrine was associated with increased heart rate, myocardial oxygen consumption, and arrhythmia incidence [61]. A separate randomized controlled trial (RCT) and network meta-analysis comparing either NE plus dobutamine versus epinephrine alone in patients with persistent hypoperfusion despite adequate volume status showed no significant difference in mortality between the two approaches [62,63].

Vasopressin. Vasopressin is a secondary option that may have an additional potential benefit of reducing PA pressure. Recent studies in neonates show improvements in pulmonary hemodynamics with vasopressin. One study of newborns with refractory acute pulmonary hypertension showed decreased oxygen requirements and improved oxygenation index after administration of vasopressin [64]. A different observational study of mechanically ventilated infants found that vasopressin significantly decreased echocardiographic indices of pulmonary hypertension, such as tricuspid regurgitation velocities, and improved biventricular output [65]. However, these studies primarily focused on infant patients; there is less data on vasopressin-induced reductions in PA pressures in adult patients, and thus we use caution when extrapolating from neonatal studies. Recent adult data from a single-center randomized crossover trial with 153 cardiac surgery patients ultimately showed no significant difference in the ratio of mean PA pressure to systemic arterial pressure when comparing vasopressin to norepinephrine [66]. At higher doses, however, vasopressin may increase PA and coronary artery vasoconstriction [67].

Phenylephrine. Phenylephrine is generally not a favorable choice in SCM with ARDS, given its primarily alpha-1 adrenergic vasoconstrictor properties, which elevate SVR and could increase myocardial workload and decrease LV output [68]. Additionally, phenylephrine has been shown to cause unopposed pulmonary vasoconstriction and increased PVR [69–71], which could make this unsuitable for ARDS patients who have RV dysfunction. However, phenylephrine may be a useful adjunct in patients who have arrhythmias, particularly atrial fibrillation with rapid ventricular response, related to either epinephrine or NE, as it does not stimulate beta-1 receptors and thus will not accelerate arrhythmias. This is relevant as patients with SCM are highly dependent on adequate atrial filling and emptying to provide ventricular preload.

Angiotensin II. While not yet studied in SCM specifically, angiotensin II has been shown to be effective in raising blood pressure in those with vasodilatory shock refractory to other conventional vasopressors [72,73]. Animal models of septic shock found that angiotensin II was associated with less myocardial oxygen consumption and expression of myocardial inflammatory markers compared to norepinephrine [74], which could suggest benefits with SCM. Additionally, a post-hoc analysis of ARDS patients suggested that angiotensin II improved P/F ratios and oxygenation indices compared to placebo [75].

5.1.3. Inotropes

Dobutamine. For patients with impaired contractility secondary to sepsis, inotropes are used to improve cardiac output, with the beta-1 receptor agonist dobutamine one of the more well-studied options. Both experimental models [76,77] and clinical studies have shown improvement in cardiac output, splanchnic perfusion, and tissue oxygenation in patients with septic shock [78]. However, it is important to note that dobutamine is also a peripheral vasodilator, and Surviving Sepsis guidelines explicitly warn that dobutamine infusions may cause vasodilation in distributive shock and lower MAP further [42]. Dobutamine in conjunction with NE can mitigate these issues, and there is data showing that the addition of dobutamine with reduced doses of NE is associated with improved LV hypokinesia and hemodynamics [56]. Despite promising results regarding its physiological effects, the effects of dobutamine on actual patient outcomes remain unclear. In fact, some studies suggest an association with increased mortality, or at least its use as an independent predictor of 90-day mortality [79]. The efficacy of dobutamine in SCM

specifically is even less clear; there is currently an ongoing RCT assessing its use in patients with sepsis-induced LV failure [80].

Milrinone. Milrinone is a phosphodiesterase III inhibitor that prevents the breakdown of cAMP and cGMP in myocardial and vascular musculature, respectively, giving it both inotropic and vasodilatory properties [81]. An RCT compared milrinone to placebo in the treatment of adults with non-hypotensive septic shock with adequate fluid resuscitation, but with signs of poor tissue perfusion (defined as elevated lactate or decreased urine output) or echocardiogram evidence of LV dysfunction, and showed that milrinone had a significantly improved cardiac output and greater percentage change in cardiac index. However, 28-day mortality was identical between the two groups [82]. Another recent propensity-matched retrospective study of patients with sepsis-induced myocardial injury showed that milrinone treatment significantly improved 365-day survival of 66.7% from 59.7% [83]. Compared with dobutamine, recent evidence shows that, although there is no mortality difference between the two, patients treated with milrinone required longer inotropic support, longer hospital stays, and more antiarrhythmic agents [84].

Levosimendan. Levosimendan is a myofilament calcium-sensitizer with inotropic properties, as well as anti-inflammatory and antioxidant characteristics [85]. This mechanism of action is largely separate from beta adrenergic activity and theoretically results in a more favorable inotropic effect by increasing the sensitivity of myocytes to already existing stores of calcium, avoiding the risk of arrhythmia seen with adrenergic modulators [86–88]. However, the LeoPARDS large-scale RCT found no significant reduction in organ failure or mortality in patients with septic shock treated with levosimendan when compared to placebo in addition to standard care [89], and further subgroup analysis showed no association with lower mortality in patients specified to have evidence of cardiac dysfunction via cardiac biomarkers [90]. Despite the lack of evidence supporting mortality benefits, levosimendan has been associated with lowering of serum lactate, increased cardiac contractility, and augmented cardiac index and LV EF [91,92]. Some studies comparing levosimendan to dobutamine suggested a benefit to the former in patients with myocardial dysfunction, with improvement in cardiac index, lactate levels, and biomarkers of myocardial injury, although there were no significant differences in mortality or ICU length of stay between the two interventions [93,94]. The role of levosimendan in sepsis complicated by ARDS remains uncertain, and it is currently not approved by the Food and Drug Administration (FDA) for use in the United States.

5.1.4. Beta-Adrenergic Blockers

Modulation of heart rate with short-acting beta-blockers has gained increased interest as a strategy to prevent tachyarrhythmias and reduce the harmful effects of catecholamines in sepsis and ARDS. These agents may improve ventricular efficiency and reduce oxygen consumption without compromising perfusion when carefully titrated.

Esmolol. In one RCT assessing esmolol use in SCM with elevated heart rates (HR), all patients achieved their target HR of less than 100 beats/minute without a significant reduction in LV contractility, while also improving short-term mortality [95]. Two meta-analyses also concluded that esmolol had a significant decrease in 28-day mortality and improved levels of cardiac troponin. However, the effects of esmolol on oxygen metabolism are less clear. One analysis showed a significant increase in central venous oxygen saturation ($ScvO_2$), with shortened duration of mechanical ventilation and ICU length of stay, whereas another overall found no difference in ICU length of stay, $ScvO_2$, or PO_2/FiO_2 ratio [96,97].

Landiolol. Landiolol is a short-acting beta-blocker that, while currently FDA-approved only for the treatment of supraventricular tachycardia in the U.S., has also been studied for use in sepsis with mixed results. One study showed effectiveness in HR reduction without increasing pressor requirements in patients with septic shock and ongoing tachycardia, but there were no significant differences in adverse effects and 28-day mortality compared to standard of care [98]. Infusions of landiolol have not been shown to reduce organ failure within septic shock patients, giving evidence that landiolol should not be used for the

management of tachyarrhythmias in septic shock. Furthermore, it is speculated that patients with SCM may require elevated heart rates to maintain adequate cardiac output, thus rendering beta-blocker usage a controversial topic in the realm of sepsis management [99].

Ivabradine. Ivabradine, a selective sinoatrial node inhibitor, is an alternative to beta-blockers that theoretically offers rate control and reduced myocardial oxygen demand without negative inotropic effects, making it a potentially safer option in patients with impaired myocardial function [100]. The MODIFY trial looked at 70 patients with multiple organ dysfunction syndrome due to cardiac or septic shock, and treatment with ivabradine for 96 h showed improvements of cardiac performance markers such as cardiac index [101]. Another RCT supported the findings of improved cardiac function, although, as with studies of beta-blockers, there was no difference in 30-day mortality [102]. Overall, ivabradine shows promise as a rate-stabilizing agent in patients with septic shock, although it is important to note that its use in patients specifically with cardiomyopathy or ARDS is not as well-documented. Overall, inotropes 'combined impact on both cardiac function and pulmonary physiology remains an area of active inquiry.

5.1.5. Pulmonary Vasodilators

Inhaled nitric oxide (iNO) can selectively reduce PVR and improve RV afterload, which may be beneficial for ARDS patients with RV failure. It has been well established that iNO reduces PA pressures and PVR [103]. While past trials have not shown consistent mortality benefit with iNO [104,105], a more recent study of patients with severe ARDS with RV dysfunction showed that iNO may improve mortality and reduce the need for renal replacement therapy, although it did not affect the length of stay in the ICU or hospital [106]. Despite these promising results in ARDS, the use of iNO in patients with SCM is less understood and may even be contraindicated, as the synthesis of nitric oxide via the IL-1 inflammatory pathway is implicated in the reduction of myocardial contractility in sepsis [86], and theoretically may lead to pulmonary edema due to volume equilibration in the PA and pulmonary venous compartments as pressure between them approximate [107]. Inhaled prostacyclins, such as epoprostenol, have shown similar benefits in reducing PA pressure and possible improvements in RV function, although, like iNO, their effects on SCM are not well-studied [108–110].

5.2. Ventilation Strategies

5.2.1. Cardiopulmonary Effects with Mechanical Ventilation

Mechanical ventilation (MV) is a mainstay of the management of ARDS. However, it can substantially affect cardiac preload and afterload—an important consideration in patients with SCM, particularly in those who may already experience RV strain due to hypoxic pulmonary vasoconstriction [57]. Elevated intrathoracic pressures can reduce venous return and further impair RV output, although this effect can be mitigated with lung-protective tidal volumes, which are now commonly used in ARDS protocols [111,112].

Positive end-respiratory pressure (PEEP) settings can affect cardiac output as well. Higher PEEP increases intrathoracic pressures and inversely affects venous return, which can exacerbate RV strain [113]. Higher PEEP may simultaneously decrease LV preload and afterload due to baroreceptor response to aortic compression, which may actually benefit patients with left-sided heart failure, although overall effects of PEEP on hemodynamics will vary based on each patients 'preload dependence, LV function, and severity of RV failure [51]. Excessively low PEEP, however, can worsen hypoxemia and result in microvascular injury, further exacerbating underlying heart and lung injury [114,115]. Thus, it is crucial to understand the patient-specific balance of PEEP tolerance, especially in patients with combined ARDS and SCM. There are emerging strategies tailored to protect right heart function, including more careful titration of PEEP, lowering plateau pressures, and avoiding hypercapnia [116,117].

5.2.2. Prone Positioning

Proning is a cornerstone in the management of ARDS, shown in the PROSEVA trial to improve oxygenation and mortality in ARDS [118]. Prone positioning may also reduce RV afterload. A study using transesophageal echocardiography before and after proning sessions found an association between reductions in plateau pressures and PaO2, and improvements in septal dyskinesia and RV end-diastolic area/LV end-diastolic area ratios [119]. The mechanisms of this effect include improvement of lung compliance, leading to decreased plateau and driving pressures. Additionally, homogenization of atelectatic lung allows expansion of pulmonary vessels and improved oxygenation, thereby decreasing pulmonary vasoconstriction that may contribute to RV failure. Lastly, proning can increase intra-abdominal pressure, which may augment venous return and cardiac preload [119–121]. Unfortunately, there has been little exploration regarding actual cardiovascular outcomes from early prone positioning, although the PROSEVA trial showed fewer cardiac arrests and more cardiac failure-free days at 28 days in its prone ventilation arm [118,122].

5.3. Extracorporeal Membrane Oxygenation (ECMO)

ECMO Modalities

Venoarterial (VA)-ECMO is a form of extracorporeal circulation support that allows oxygenated blood to cycle throughout the body while bypassing the heart completely [123]. Studies have shown that, for cardiogenic shock due to SCM, VA-ECMO can be used to provide full cardiac support. In one study of fourteen patients with refractory septic shock—defined as LVEF < 25%, cardiac index < 2.2 L/min/m2, persistent hypotension, extensive skin mottling, or elevated lactate levels despite high-dose catecholamines—the median LVEF had significantly improved to 60% after discontinuation of ECMO. It is speculated that this apparent reversal of cardiomyopathy is due to ECMO giving the failing heart more time to recover [124]. A separate retrospective study of 82 patients with refractory shock found the use of VA-ECMO led to improved 90-day survival, rapid reduction in pressor requirements, and enhanced lactate clearance. These results were achieved even with VA-ECMO patients having worse cardiac index, LVEF, and organ failure in comparison to control groups [125].

Venovenous (VV)-ECMO has been used in severe cases of ARDS and may benefit by reducing cardiac dysfunction without the need for VA-ECMO. VV-ECMO allows for control of oxygenation and carbon dioxide levels, which are two drivers for increased PVR, thereby reducing RV afterload [126]. VV-ECMO can reduce plateau pressures and driving pressures during mechanical ventilation, which could benefit right heart function [8]. A large randomized clinical trial of VV-ECMO did not meet its statistically significant primary endpoint of 60-day mortality but demonstrated a substantial benefit in patients with severe ARDS as compared with usual care [127].

Alternatively, veno-arteriovenous (VAV)-ECMO offers hybrid support for combined respiratory and cardiac failure, often used in patients who are already on VA or VV-ECMO [128]. One retrospective study assessed outcomes of severe ARDS patients on VV-ECMO who needed additional VAV ECMO support. These patients had an ICU survival rate of 52%, with long-term outcomes of survival and organ functional status comparable to patients who underwent more classical VA or VV-ECMO [129]. The use of VAV-ECMO is an area of further study with potential benefit in combined heart and lung injury, although overall the choice between ECMO modalities largely depends on the predominant physiologic derangements.

Percutaneous LV assist devices (LVAD) such as microaxial flow pumps or “Impella” devices have been approved for use in patients with cardiogenic shock secondary to acute myocardial infarction, postcardiotomy care, or acute left heart failure; however, SCM is not among these indications [130]. The recent DanGer Shock trial showed lower all-cause 180-day mortality among patients treated with Impella versus standard care, but looked at patients with post-STEMI cardiogenic shock [131]. Ultimately, the

literature supports the use of VA-ECMO as the preferred device for temporary circulatory support in patients with SCM [132,133].

Intra-aortic balloon pumps (IABP) have also historically been used for cardiogenic shock secondary to myocardial infarction, although the IABP-SHOCK II trial showed no significant reduction in 30-day mortality, and a more recent meta-analysis of 12 RCTs confirmed the lack of improvement [134,135].

5.4. Anti-Inflammatory Therapies

5.4.1. Corticosteroids and Mineralocorticoids

Steroids are an important consideration in the management of septic shock and ARDS, given their ability to modulate systemic inflammation, stabilize endothelial barriers, and improve shock reversal [136]. Recent guidelines underscore steroids 'role in reducing mortality, ICU and hospital length-of-stay, and mechanical ventilation days [136]. A 2018 RCT showed that a combination of hydrocortisone and fludrocortisone demonstrated accelerated weaning from vasopressor therapy and a reduction in 90-day mortality for patients in septic shock [137]. More recent trials also suggest that combinations of hydrocortisone and fludrocortisone are superior to hydrocortisone alone [138]. However, while broader sepsis literature demonstrates clear benefits to steroid use, there is a lack of trials focusing on patients with SCM specifically. One prospective study investigating steroids 'effects on echocardiographic data in early septic shock showed significant improvements in arterial pressure, heart rate, LV afterload, and multiple parameters of LV contractility, including GLS and the valve peak systolic wave, providing insights into how they can benefit cardiac function in patients with SCM [139].

5.4.2. Immunomodulators

Agents targeting cytokine pathways, such as IL-6 inhibitors and TNF-alpha blockers, and JAK inhibitors, are being investigated for their use in acutely severe inflammatory states. Their effects on both cardiac contractility and pulmonary endothelial activity remain under active study. Increased levels of IL-6, TNF-alpha, and IL-1-beta have been recorded in patients with SCM, which may indicate these cytokines as crucial targets for diagnostics and treatment for SCM [140]. While not specifically studied for use in SCM, the IL-6 receptor antagonist tocilizumab has been shown to decrease systemic inflammation and myocardial injury in patients surviving out-of-hospital cardiac arrest, indicating potential for treatment in other cardiac-related dysfunctions [141]. Lastly, a study of mice with induced SCM investigated the use of 1-deoxynojirimycin (DNJ), a modulator of the JAK2/STAT6 pathway, and results suggest attenuation of myocardial injury, decreased oxidative damage, and inflammation [142].

6. Knowledge Gaps and Future Directions

6.1. Integrated Cardio-Pulmonary Phenotyping

There is growing recognition that current diagnostic and therapeutic strategies inadequately capture the intertwined nature of myocardial and pulmonary injury in sepsis. By stratifying broad groups of SCM or ARDS patients into more specific phenotypes, one can possibly guide more personalized therapies and identify high-risk groups. One study used transesophageal echocardiography (TEE) to split septic shock patients into five distinct clusters based on cardiac function, which included groups with LV dysfunction, hyperkinetic function, RV failure, and persistent hypovolemia. Each cluster exhibited significant variance in mortality outcomes, with those with LV failure and RV failure having the highest mortality rates [143]. A different study used transthoracic echocardiography (TTE) and stratified patients into five groups based on LV EF and found that the extremes of LVEF (<25% and >70%) were linked with significantly higher

in-hospital mortality [144]. These studies show distinct outcome differences among clusters of patients with septic shock, and it is possible that similar findings may be seen in SCM and ARDS.

Phenotyping is a highly variable field of study, with multiple studies using different methods to stratify their patients. A meta-analysis revealed many clustering variables that appeared to predict treatment response, including echocardiographic measurements, inflammatory and coagulation markers, and various transcriptomic and genomic expression profiles [145]. While this shows potential in the utility of phenotyping, it also illustrates that current approaches are extremely heterogeneous and require further validation, with the hope of developing a more authenticated method of clustering that would allow for individualized therapies.

6.2. Therapies Targeting Organ Cross-Talk

Interventions that interrupt harmful signaling between the heart and lungs are an emerging area of interest. Neutrophil elastase inhibitors, such as sivelestat, have shown promise in mitigating alveolar damage and may also protect cardiac tissue from inflammatory proteolytic injury. Multiple animal and molecular studies have detailed sivelestat's ability to reduce apoptosis, inhibit the release of inflammatory factors, and downregulate inflammation-related protein expression in damaged myocardium [146,147]. A randomized trial of 97 patients with both ARDS and SCM compared treatment with sivelestat against controls, and showed significantly lower levels of IL-6, IL-8, and INF-alpha levels. More importantly, stroke volume, E/A values, and TAPSE measurements were significantly higher in the sivelestat group, implying that sivelestat could be efficacious for treating SCM [148]. Another retrospective study investigated sivelestat in patients with ARDS, showing a significant reduction in 30-day mortality and cytokine levels without a significant increase in side effects [149]. Whether these therapies improve outcomes in combined cardiopulmonary dysfunction remains to be tested, but these findings suggest neutrophil elastase inhibitors could be compelling future therapies for those with SCM and ARDS.

6.3. Artificial Intelligence and Multi-Parametric Monitoring

The use of artificial intelligence (AI) in the management of ARDS and SCM is rapidly evolving. Machine learning applied to hemodynamics, ventilator waveforms, echocardiographic data, and biomarkers may enable earlier identification of patients developing dual organ injury. Machine learning models have been used to rapidly cluster sepsis-associated ARDS patients, determine clinical outcomes and treatment responses within those clusters, such as mortality rate, lactic acid levels, and ICU length-of-stay, and identify risk factors. They have also been used to explore mortality rates among different PEEP levels within these specific clusters, showcasing the potential utility of real-time AI tools to support individualized titration of ventilation parameters [150–152]. Machine learning has also been used to generate models for predicting fluid responsiveness in septic shock by analyzing TTE parameters, with similar predictive value to more established methods such as passive leg raising, again showing promise in AI as a tool for more personalized titration of fluids [153]. Lastly, studies have used machine learning models to phenotype and predict mortality in patients requiring VA-ECMO, with good accuracy and reliability. While these studies were not tailored towards patients with ARDS or SCM specifically, they illustrate the importance of the evolving field of AI as a future tool for targeted ECMO intervention [154,155].

There is a lack of published research into the use of AI in the diagnosis, treatment, and clinical outcomes of SCM. Machine learning has been used to identify biomarkers, regulatory molecules, and genes associated with SCM, which may provide insights into future therapies [156–158], but AI models assessing clinical parameters require further research. Machine learning models may become a key tool in the diagnosis of sepsis-related sequelae; however, the dependability and practicality of AI in the clinical setting is an area of ongoing study [159].

6.4. Underrepresentation of RV Dysfunction

Right-heart failure is underrecognized in ARDS trials and registries. One scoping review of 51 studies on ARDS interventions found that only 27% of studies aimed to modify RV function, and only 5.9% were randomized controlled trials [160]. Further reviews have emphasized that, despite RV injury being a critical consideration in ARDS, there are limited large-scale trials to properly evaluate effective treatment strategies [57,161].

Notably, VA-ECMO has not been systematically studied for isolated RV failure in ARDS, leaving a significant evidence gap. VA-ECMO has generally been reserved for cases with concomitant LV failure or shock, and there are no large-scale trials evaluating its use in isolated RV failure, with most data from small, retrospective studies [162,163]. RV-protective strategies require more rigorous evaluation in both clinical trials and translational models.

6.5. Temporal Evolution of Dual-Organ Injury

The trajectories of SCM and ARDS differ markedly, yet their time courses overlap in clinically important ways. Understanding the temporal sequence of inflammation, microvascular injury, and functional decline could inform optimal timing of therapies such as prone positioning, β-blockade, or ECMO. The dynamic interplay and timing of these processes remain poorly understood. For example, although emerging evidence indicates that inflammation, microvascular injury, and myocardial edema are key players in SCM, the temporal relationships among them are not fully characterized [164]. Furthermore, although advances in molecular and imaging techniques have occurred, the sequence of events from the initial inflammatory insult to microvascular injury to functional decline remains unclear [165,166]. The literature underscores a critical gap in understanding the temporal evolution of inflammation and injury within SCM and ARDS, and how this may be a barrier to the development of effective, early interventions.

7. Conclusions

ARDS due to sepsis remains a heterogeneous condition; when SCM complicates ARDS, it can pose additional diagnostic and treatment challenges. Characterizing the specific cardiopulmonary interaction of SCM and ARDS allows for nuanced phenotyping and patient-oriented treatment strategies. A significant amount of research remains in the field of ARDS subphenotyping and treatment options.

Author Contributions

B.O. and G.E. conducted the literature review and wrote the initial manuscript and provided revisions. Y.M. conceived of the review, oversaw manuscript writing and contributed to revisions.

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