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ABOUT COVER

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MINIREVIEWS

Acute cor pulmonale in patients with acute respiratory distress syndrome: A comprehensive review

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Abstract

Acute respiratory distress syndrome (ARDS)-related acute cor pulmonale (ACP) is found in 8%-50% of all patients with ARDS, and is associated with adverse hemodynamic and survival outcomes. ARDS-related ACP is an echocardiographic diagnosis marked by combined right ventricular dilatation and septal dyskinesia, which connote simultaneous diastolic (volume) and systolic (pressure) overload respectively. Risk factors include pneumonia, hypercapnia, hypoxemia, high airway pressures and concomitant pulmonary disease. Current evidence suggests that ARDS-related ACP is amenable to multimodal treatments including ventilator adjustment (aiming for arterial partial pressure of carbon dioxide < 60 mmHg, plateau pressure < 27 cmH_2O, driving pressure < 17 cmH_2O), prone positioning, fluid balance optimization and pharmacotherapy. Further research is required to elucidate the optimal frequency and duration of routine bedside echocardiography screening for ARDS-related ACP, to more clearly delineate the diagnostic role of transthoracic echocardiography relative to transesophageal echocardiography, and to validate current and novel therapies.

Key Words: Coronavirus; Critical care; Echocardiography; Hypertension; Pulmonary; Respiratory distress syndrome; Adult; Ventricular dysfunction; Right

Core Tip: Acute respiratory distress syndrome (ARDS)-related acute cor pulmonale (ACP) is associated with adverse hemodynamic and survival outcomes. It is an echocardiographic diagnosis marked by combined right ventricular dilatation and septal dyskinesia. Checking for ARDS-related ACP should be done in patients with ≥ 2 of 4 risk factors: Pneumonia, arterial partial pressure of oxygen-to-inspired oxygen fraction ratio < 150 mmHg, arterial partial pressure of carbon dioxide ≥ 48 mmHg, and

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driving pressure ≥ 18 cmH_2O. Treatments include ventilator adjustment (aiming for arterial partial pressure of carbon dioxide < 60 mmHg, plateau pressure < 27 cmH_2O, driving pressure < 17 cmH_2O), prone positioning, fluid balance optimization and pharmacotherapy.

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INTRODUCTION

For patients with acute respiratory distress syndrome (ARDS), concurrent acute cor pulmonale (ARDS-related ACP) is associated with adverse hemodynamic effects–and when severe–with a near doubling of mortality risk[1-4]. ARDS-related ACP is an echocardiographic diagnosis, which involves a dilated right ventricle with both systolic and diastolic dysfunction. As can be surmised, the greater the right ventricular dilatation, the more severe is the ACP, and the higher the risk of mortality.

The prevalence of ARDS-related ACP ranges from 8%-50% in various studies (Table 1)[1,2,4-10]. Given the current pandemic, special mention must be made about coronavirus disease 2019 (COVID-19). The first report of ACP in COVID-19 described five critically ill patients, with intracardiac thrombus being visualized on echocardiography in two patients[11]. Overall, it remains unknown if the prevalence of ACP differs significantly between COVID-19 and non-COVID-19 ARDS, though pulmonary embolism or pulmonary vascular thrombosis may predispose the former to ACP regardless of ARDS.

PATHOPHYSIOLOGY AND RISK FACTORS FOR ARDS-RELATED ACP

ARDS-related ACP occurs when right ventricular afterload increases acutely, leading to right ventricular systolic and diastolic dysfunction. Given the relatively stiff pericardial envelope, right ventricular diastolic dysfunction leads to right ventricular dilatation and leftward septal displacement, restricting the left ventricle (*i.e.*, ventricular interdependence). Consequently, ARDS-related ACP has been associated with adverse hemodynamic outcomes associated with both right and left ventricular dysfunction: Decreased stroke index, impairment of left ventricular diastolic function and compensatory tachycardia[5].

Normal right ventricular function depends on maintaining a low pulmonary vascular resistance. Any factor that increases pulmonary vascular resistance thus promotes ARDS-related ACP. ARDS itself, particularly when driven by pneumonia, can lead to endothelial dysfunction, microthrombi formation, vascular remodelling and occlusion of the pulmonary arterial bed. Among patients with ARDS, having more severe lung disease as measured by pulmonary dead space monitoring, may predict the risk of ACP[12]. Concomitant diseases that cause pulmonary vascular dysfunction can aggravate ARDS-related ACP. An example would be sickle cell disease, which can be complicated by pulmonary vasoconstriction (from hemolysis and nitric oxide scavenging) and vaso-occlusion (from fat embolism and *in situ* thrombosis)[10].

A potentially modifiable risk factor for ARDS-related ACP is hypercapnia[5], which causes pulmonary vasoconstriction, particularly when the arterial partial pressure of carbon dioxide exceeds 60 mmHg[7]. Hypercapnia can be particularly common in ARDS due to underlying ventilation-perfusion mismatch and the use of permissive hypercapnia. Another potential risk factor is hypoxemia, which causes hypoxic pulmonary vasoconstriction, though this is less well-demonstrated in clinical studies than for hypercapnia. Furthermore, positive pressure ventilation, high plateau pressure (especially if it exceeds 27 cmH_2O[4]), high driving pressure, and the use of positive end-expiratory pressure can increase pulmonary vascular resistance. Whether ACP predisposes ARDS patients to further harm by the high airway pressures in high-frequency oscillatory ventilation remains uncertain[3,13].

A combination of four risk factors have been used to risk stratify patients for ARDS-

Table 1 Definitions and prevalence of acute respiratory distress syndrome -related acute cor pulmonale

Ref.	Definition	Test	Prevalence
Vieillard-Baron *et al*[5] (2001)	Ratio of right ventricular end-diastolic area to left ventricular end-diastolic area in the long axis > 0.6 associated with septal dyskinesia in the short axis	TEE	19/75 (25%)
Jardin *et al*[4] (2007)	Ratio of right ventricular end-diastolic area to left ventricular end-diastolic area in the long axis > 0.6 associated with septal dyskinesia in the short axis	TEE	101/352 (29%)
Vieillard-Baron *et al*[6] (2007)	Ratio of right ventricular end-diastolic area to left ventricular end-diastolic area in the long axis > 0.6 associated with septal dyskinesia in the short axis	TEE	21/42 (50%)
Fichet *et al*[9] (2012)	Right ventricular dilatation was defined by a right ventricular end-diastolic area to left ventricular end-diastolic area ratio > 0.6 and reported as severe when ratio was ≥ 1 (apical four-chamber view). ACP was defined by right ventricular dilatation associated with septal dyskinesia observed in the short-axis view	TTE	ACP: 4/50 (8%); Severe ACP: 4/50 (8%)
Boissier *et al*[2] (2013)	Ratio of right ventricular end-diastolic area to left ventricular end-diastolic area in the long axis > 0.6 associated with septal dyskinesia in the short axis	TEE	49/226 (22%)
Lhéritier *et al*[7] (2013)	Association of right ventricular dilatation inthe long-axis view of the heart (ratio of right ventricular end-diastolic area to left ventricular end-diastolic area > 0.6) and a visually identified systolic paradoxical ventricular septal motion in the short-axis view of the heart	TEE	45/200 (23%)
Mekontso-Dessap *et al*[14] (2015)	Septal dyskinesia (in the short axis) with a dilated right ventricle (end-diastolic right/left ventricle area ratio > 0.6 in the long axis). Severe ACP defined as septal dyskinesia (in the short axis) with a dilated right ventricle (end-diastolic right/left ventricle area ratio ≥ 1 in the long axis)	TEE	ACP: 164/752 (22%); Severe ACP: 54/752 (7%)
Legras *et al*[8] (2015)	Association of right ventricular dilatation inthe long-axis view of the heart (ratio of right ventricular end-diastolic area to left ventricular end-diastolic area > 0.6) and a visually identified systolic paradoxical ventricular septal motion in the short-axis view of the heart	TEE	36/195 (18%)
Cecchini *et al*[10] (2016)	Dilated right ventricle (end-diastolic right ventricle/left ventricle area ratio > 0.6) associated with septal dyskinesia on the short-axis view	TEE or TTE	88/362 (24%)
See *et al*[1] (2017)	Severe ACP defined as right-to-left ventricular size (area) ratio ≥ 1 in end diastole at the papillary muscle level and interventricular septal straightening/paradoxical motion using the parasternal short axis view. NB. Apical four-chamber view was used as a secondary safeguard against false ACP determination, which did not occur	TTE	Only severe ACP reported: 66/234 (28%)

ACP: Acute cor pulmonale; ARDS: Acute respiratory distress syndrome; TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography.

related ACP: Pneumonia as a cause of ARDS, an arterial partial pressure of oxygen-to-inspired oxygen fraction (P/F) ratio < 150 mmHg, an arterial partial pressure of carbon dioxide 48 mmHg or greater, and a driving pressure 18 cmH2O or greater[14]. When two or more risk factors were present, the prevalence of ARDS-related ACP exceeded 20%, which led the authors to encourage routine echocardiography screening for such patients. Conversely, when fewer than two risk factors were present, the prevalence of ARDS-related ACP was 10% or less, and echocardiography can be done on demand.

DIAGNOSIS AND DEFINITION OF ARDS-RELATED ACP

The hallmark of ARDS-related ACP would be combined right ventricular dilatation and septal dyskinesia, which connote simultaneous diastolic (volume) and systolic (pressure) overload respectively. Without septal dyskinesia, the singular finding of right ventricular dilatation does not mean ACP. Serum-based biomarkers like cardiac troponin and pressure-based thresholds obtained *via* invasive pulmonary artery catheterization have not been useful for determining ACP[14], though B-type natriuretic peptide may be useful for risk stratification in the absence of left ventricular dysfunction[15].

In patients with ARDS, the presence of a dilated right ventricle does not automatically mean ARDS-related ACP. Two important differential diagnoses need to be considered: Pulmonary embolism and chronic right ventricular dilatation. Confident exclusion of pulmonary embolism requires either a low risk-adjusted d-dimer or a negative high-sensitivity test like computed tomography pulmonary angiography. Chronic right ventricular dilatation can be recognized by a right ventricular free wall diastolic thickness exceeding 9 mm (normal thickness < 5 mm)[16], which occurs *via* right ventricular remodelling. Such remodelling occurs in the context of gradual, rather than acute, elevation of pulmonary vascular resistance and development of pulmonary arterial hypertension *e.g.*, in patients with severe chronic

obstructive pulmonary disease and obesity-hypoventilation syndrome.

After excluding pulmonary embolism and chronic right ventricular dilatation, identification of ARDS-related ACP is by bedside ultrasound. The reference standard comprises transesophageal long axis and transgastric short axis views obtained by transesophageal echocardiography, with mean interobserver and intraobserver variability both under 10%[16]. ACP and severe ACP are defined as a ratio of right ventricular end-diastolic area to left ventricular end-diastolic area in the long axis being > 0.6 and ≥ 1 respectively, in combination with septal dyskinesia[14] (Table 1). An absolute threshold of right ventricular area to diagnose dilatation in ACP does not exist. To identify septal dyskinesia, short axis views are required to demonstrate a leftward shift of the septum in diastole. To determine right ventricular dilatation, comparative assessment of right and left ventricular areas in the long axis view can be achieved by standard measurements[16]. If one wishes to look for severe ACP, then eyeballing may suffice[1,17], and can be done in the short axis view[18]. Nonetheless, comparison of right and left ventricular areas could be of limited value if the left ventricle is chronically dilated due to valvular disease or cardiomyopathy[16].

As an alternative to transesophageal echocardiography, basic critical care echocardiography identification of ARDS-related severe ACP, *via* the transthoracic parasternal short axis view, can be achieved by trainees who have undergone as few as 30 practice scans[17]. Training requires few resources and can be facilitated by dyad (training in pairs) rather than individual training[18]. The transthoracic parasternal short axis view was chosen as the main view to assess the relative sizes of the right and left ventricles and to assess for septal straightening/paradoxical motion, as this view had a fixed landmark (papillary muscles) and was not prone to foreshortening or rotational error[1]. For severe ACP, since identification relies on a ratio of 1 between the right and left ventricle sizes, rapid visual comparison was possible without routine manual tracing of the endocardial borders. Meanwhile, the apical four-chamber view was used only as a secondary safeguard against false ACP determination, as it is prone to foreshortening or rotational error, and would lead to under-recognition of ACP.

For the identification of non-severe ACP, the sensitivity and specificity of transthoracic echocardiography were found to be 66% and 99% respectively, compared to transesophageal echocardiography[7]. The relatively low sensitivity of transthoracic echocardiography was ascribed to technical limitations for obtaining adequate images in critically ill patients with ARDS, and thus caution is needed when using transthoracic echocardiography to rule out ACP. Conversely, if image acquisition can be achieved (*e.g.* in non-obese patients), the very high specificity of transthoracic echocardiography means that it remains useful to rule in ACP.

MANAGEMENT OF ARDS-RELATED ACP

Fortunately, ARDS-related ACP is reversible and once reversed, ARDS-related ACP does not seem to elevate mortality risk[5]. While few randomized clinical trials for ARDS-related ACP therapy are available, several observational studies exist to guide clinical management (Table 2). Foremost in the treatment of ARDS-related ACP would be to minimize positive pressure. This can be achieved *via* reduction of tidal volume, reduction of positive end-expiratory pressure, or both. However, trade-offs exist. When tidal volume is too low despite increased respiratory rate, hypercapnia ensues, increasing pulmonary vasoconstriction. Avoiding an arterial partial pressure of carbon dioxide exceeding 60 mmHg[19] or 48 mmHg[20] have been proposed. Additionally, positive end-expiratory pressure should not be lowered if de-aeration and hypoxemia occurs.

Without resorting to extracorporeal membrane oxygenation or carbon dioxide removal, prone positioning can improve both hypercapnia and lung aeration of the dorsal segments. This can allow tidal volumes and positive end-expiratory pressure to be kept lower than what would have been possible in the supine position. In turn, prone positioning would mitigate ARDS-related ACP. Direct visualization of this effect was recently demonstrated in a patient with COVID-19 ARDS using real-time 3D transesophageal echocardiography[21]. During prone positioning, right ventricular end-diastolic volume decreased and paradoxical septal motion disappeared. And on reversion to supine positioning, acute cor pulmonale recurred.

Besides ventilatory strategies and prone positioning, fluid management should also be optimized to avoid hypervolemia, which would exacerbate right ventricular volume overload. Volume expansion should be stopped once ACP is recognized[22]. Pharmacologic therapy, based on physiology and yet to be widely demonstrated for

Table 2 Management options for acute respiratory distress syndrome-related acute cor pulmonale

Management option	Details	Best supporting evidence
Ventilator adjustment	Limit end-inspiratory plateau pressure to 30 cmH_2O. Target a tidal volume of 6-9 mL/kg. Positive end-expiratory pressure selected to improve oxygenation without requiring specific hemodynamic support, except for blood volume expansion	Observational study[5]
	Aim for partial pressure of carbon dioxide < 60 mmHg	Observational study[7]
	Aim for partial pressure of carbon dioxide < 48 mmHg	Observational study[14]
	Aim for plateau pressure < 27 cmH_2O	Observational study[4]
	Aim for driving pressure < 17 cmH_2O	Observational study[2]
Prone positioning	Ventilation in the prone position, especially for patients with refractory severe hypoxemia (P/F ratio < 100 mmHg)	Observational study[5,6,29]
Fluid balance optimization	Stop volume expansion	Expert opinion[22]
	Consider diuresis or fluid removal using hemofiltration	Expert opinion[28]
Pharmacotherapy	Pulmonary vasodilation using inhaled nitric oxide	Expert opinion[16]
	Pulmonary vasodilation using levosimendan	Pilot trial[23]
	Vasopressors to restore systemic blood pressure and to avoid right ventricular ischemia	Expert opinion[28]

ACP: Acute cor pulmonale; ARDS: Acute respiratory distress syndrome; P/F = Arterial partial pressure of oxygen/inspired oxygen fraction.

ARDS-related ACP, would be to use pulmonary vasodilators like inhaled nitric oxide[16] and levosimendan[23].

FUTURE DIRECTIONS

Future directions arising from animal experiments

Mechanical ventilation may contribute to the development of ACP *via* excessive pressure swings. In an experiment involving adult male Sprague-Dawley rats, Katira *et al*[24] induced acute right ventricular dilatation and ACP when the rats were exposed to high peak inspiratory airway pressure (45 cmH_2O) and zero positive end-expiratory pressure. In contrast, rats avoided ACP when they received the same peak inspiratory airway pressure and 10 cmH_2O of positive end-expiratory pressure. The postulated mechanism of ACP in this murine model is unclear, but it appears that positive end-expiratory pressure may mitigate repetitive lung strain, cyclic interruption/exaggeration of pulmonary blood flow and microvascular injury. Further work will be needed confirm this mechanism and to optimize the use of positive end-expiratory pressure for ACP management in humans.

Besides ventilator adjustments, animal data suggest that pharmacotherapy with Tris (hydroxymethyl) aminomethane (THAM), a pure proton acceptor, may be helpful to reduce ACP incidence or severity. When repeated lung lavage was used to create lung injury in piglets, administration of THAM buffered respiratory acidosis without generating carbon dioxide, and dampened the effect of arterial hypercarbia on pulmonary vasconstriction, compared to control animals which did not receive THAM[25]. Translational research would be needed to establish the same benefit in human patients at risk of ARDS-related ACP.

Further directions for clinical studies

Even though risk profiling of ARDS patients for ACP and bedside echocardiography are readily available, continuous monitoring for ACP can now only be achieved with single-use transesophageal echocardiography probes. It is unlikely that the latter can be justified for all patients with ARDS, and therefore, an optimal frequency and duration of routine bedside echocardiography screening for ARDS-related ACP needs to be defined[1]. Compared to transesophageal echocardiography, while transthoracic

echocardiography has limited sensitivity for ACP in general, studying the comparative accuracy and reliability for severe ACP would be interesting. Such comparison would also be clinically relevant given the wider availability and utilization of bedside transthoracic echocardiography compared to transesophageal echocardiography among intensivists.

Given the consistent evidence of ARDS-related ACP as an independent and modifiable risk factor for mortality from observational studies, future work should involve studies–including randomized trials if possible–to prevent the onset of ARDS-related ACP and to validate existing strategies to treat ARDS-related ACP. A promising novel therapy for ARDS-related ACP is veno-venous extracorporeal carbon dioxide removal, which corrects hypercapnia, allows low tidal volume ventilation and which appears to improve right ventricular function in a porcine model[26]. Beyond this proof-of-concept, human studies would be necessary as clinical effectiveness of extracorporeal therapy cannot be assured. For instance, among three patients with ARDS on veno-venous extracorporeal membrane oxygenation, ACP still developed. Pathophysiological mechanisms proposed included thromboembolic burden to the pulmonary vasculature, hypoxemia, acidosis, pathologic progression of ARDS, and chronic nonphysiologic flow to the right heart[27]. Finally, mechanical circulatory support devices like right ventricular assist devices and veno-arterial extracorporeal membrane oxygenation would help to unload the right ventricle[28]. Studies specific to ARDS-related ACP would be needed to delineate the appropriate use, timing and cost-effectiveness of these devices.

CONCLUSION

ARDS-related ACP is a prevalent and clinically important condition that leads to adverse hemodynamic and survival outcomes. Current evidence suggests that it is amenable to multimodal treatments including ventilator adjustment, prone positioning, fluid balance optimization and pharmacotherapy. However, more work is required to elucidate the optimal frequency and duration of routine bedside echocardiography screening for ARDS-related ACP, and to more clearly delineate the diagnostic role of transthoracic echocardiography. Prospective validation of current and novel therapies for ARDS-related ACP are awaited, especially *via* randomized controlled clinical trials.

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