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'The Right Ventricle in Acute Respiratory Distress Syndrome'

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Abbreviations:

ACP = acute cor pulmonale; ARDS = acute respiratory distress syndrome; ASE = American Society of Echocardiography; CI = confidence interval; CMV = conventional mechanical ventilation; CO_2 = carbon dioxide; CRRT = continuous renal replacement therapy; CT = computed tomography; CRRT = continuous renal replacement therapy; CVP = central venous pressure; DTI = doppler tissue imaging; E/E' = the ratio of early tricuspid inflow to annular diastolic velocity; EF = ejection fraction; ET-1 = endothelin 1; $ECCO_2R$ = extracorporeal CO_2 removal; FAC = fractional area change; F_iO_2 = fraction of inspired oxygen; 5HT = 5-hydroxytryptamine; HFOV = high frequency oscillatory ventilation; ICU = intensive care unit; LPV = lung protective ventilation; LVEDA = left ventricular end-diastolic area; MAP = mean arterial pressure; mPAOP = mean pulmonary artery occlusion pressure; MPI = myocardial performance index; MRI = magnetic resonance imaging; PAC = pulmonary artery catheter; P_aCO_2 = partial pressure of arterial carbon dioxide; P_aO_2 = partial pressure of arterial oxygen; PAOP = pulmonary

artery occlusion pressure; sPAP = systolic pulmonary artery pressure; PBW = predicted body weight; PCWP = pulmonary capillary wedge pressure; PDE = phosphodiesterase; PEEP = positive end-expiratory pressure; PLR = passive leg raise; PPV = pulse pressure variation; PVR = pulmonary vascular resistance; PVRi = pulmonary vascular resistance index; RCT= randomized controlled trial; RIMP = right ventricular index of myocardial performance; RV = right ventricle; RVD = right ventricular dysfunction; RVEDA = right ventricular end-diastolic area; RVFAC = right ventricular fractional area change; RVEF = right ventricular ejection fraction; RVTDI = right ventricular tissue Doppler imaging; sPAP = systolic pulmonary arterial pressure; SpO_2 = oxygen saturation; SVI = stroke volume index; TAPSE = tricuspid annular plane systolic excursion; TEE = transesophageal echocardiography; TPG = transpulmonary gradient; 3D = three dimensional; TTE = transthoracic echocardiography; VAECMO = veno-arterial extracorporeal membrane oxygenation; VVECMO = veno-venous extracorporeal membrane oxygenation;

ABSTRACT

Acute respiratory distress syndrome is associated with poor clinical outcomes with a pooled mortality rate of approximately 40% despite best standards of care. Current therapeutic strategies are based upon improving oxygenation and pulmonary compliance while minimizing ventilator induced lung injury. It has been demonstrated that relative hypoxemia can be well tolerated and improvements in oxygenation do not necessarily translate into survival benefit. Cardiac failure, in particular right ventricular dysfunction, is commonly encountered in moderate to severe acute respiratory distress syndrome and is reported to be one of the major determinants of mortality. The prevalence rate of echocardiographically evident right ventricular dysfunction in acute respiratory distress syndrome varies across studies ranging from 22% to 50%. Although there is no definitive causal relationship between right ventricular dysfunction and mortality, severe right ventricular dysfunction is associated with increased mortality. Factors that can adversely affect right ventricular function include hypoxic pulmonary vasoconstriction, hypercapnia, and invasive ventilation with high driving pressure. It might be expected that early diagnosis of right ventricular dysfunction would be of benefit however, echocardiography markers (qualitative and quantitative) used to prospectively evaluate the right ventricle in acute respiratory distress syndrome have not been tested in adequately powered studies. In this review we examine the prognostic implications and pathophysiology of right ventricular dysfunction in acute respiratory distress syndrome and discuss available diagnostic modalities and treatment options. We aim to identify gaps in knowledge and directions for future research that could potentially improve clinical outcomes in this patient population.

KEY WORDS: acute respiratory distress syndrome, right ventricular dysfunction, cor-pulmonale, critical care echocardiography

Acute respiratory distress syndrome (ARDS) is characterized by the acute development of hypoxemia and bilateral lung infiltrates. [1] Five decades after it was first described and despite lung protective mechanical ventilation strategies[2, 3] and other therapeutic advances such as prone positioning, fluid restrictive therapy and neuromuscular blockade,[4-6] ARDS is still associated with substantial morbidity and mortality. In a systematic review and meta-analysis that included 89 ARDS studies (53 observational, 36 randomized controlled trials), Phua et al found that the overall pooled weighted mortality was 44.3% (95% confidence interval [CI], 41.8-46.9). [7] In a recent randomized controlled trial (RCT) comparing conservative (SpO_2 88–92%) versus a liberal oxygenation target (≥96%), there were no significant differences in organ dysfunction or mortality between the two groups. These results suggest that patients can survive short periods of relative hypoxemia without significant adverse effect and that hypoxemia may not be the leading cause of mortality in ARDS. [8] On the other hand, hemodynamic instability in the context of ARDS appears to be strongly associated with mortality.[9] One potential mechanism is the dysfunction of the right ventricle (RV) and pulmonary vasculature which is often underappreciated in ARDS.[10] As a result the RV fails to deliver adequate cardiac output to the left sided circulation thus resulting in systemic hypoperfusion and multiple organ dysfunction. [11]

The aim of the current review is to discuss the epidemiology of RV dysfunction (RVD) in ARDS and its effect on clinical outcomes, examine the current state of knowledge in the pathophysiology of RV dysfunction, identify gaps and explore the use of novel imaging markers, preventive and therapeutic strategies. Unanswered questions such as effectiveness of 'low lung-stress' ventilation, timing of proning and whether RVD alone should be an indication for proning, the role of extracorporeal life support and natural history of RVD in ARDS survivors will be discussed.

DEFINITIONS

There is a variety of definitions for RV dysfunction (RVD) and failure (RVF) in the literature with the terms being used interchangeably at times. According to the American Society of Echocardiography (ASE) RVD is present when the parameters to quantify RV function are less than the lower value of the normal range: tricuspid annular plane systolic excursion (TAPSE) < 17mm, pulsed Doppler S wave < 9.5cm/sec, RV fractional area change (RVFAC) < 35%, RV ejection fraction (RVEF) < 45%. RVFAC has been used to grade the degree of RVD as mild (25-35%), moderate (18-25%) and severe (<18%).[12, 13] RVF is defined as the inability of the RV to provide adequate blood flow through the pulmonary circulation at normal central venous pressure (CVP).[11] Acute cor pulmonale (ACP) refers to acute dilatation and/or dysfunction of the RV in the context of acute lung disease (eg ARDS) and associated pulmonary vascular dysfunction.[14] ACP is a form of RVD due to acute increase in RV afterload that may lead to RVF and it is defined echocardiographically as septal dyskinesia with a ratio of right ventricular end-diastolic area (RVEDA): left ventricular end-diastolic area (LVEDA) greater than 0.6 (greater than 1 for severe dilatation). In the RV-focused view, RV diameter greater than 41mm at the base and greater than 35mm at midlevel indicates chamber dilatation.[12, 13] In this review we have chosen to use the term 'RVD' instead of 'ACP' as it provides a broader overview of RV pathology in acute pulmonary disease. Assessment of the RV by echocardiography is discussed further in the 'diagnosis' section of this review.

EPIDEMIOLOGY & PROGNOSIS

The reported incidence of RVD in ARDS varies across studies (22% to 50% (Table 1).[15-24]) Although there is no robust evidence to support a definitive causal relationship between RVD and mortality in ARDS, it has been shown that RVD has a negative impact on the ARDS course and that severe RVD is associated with increased mortality even during lung protective mechanical ventilation.

In a prospective multicentre study (n= 200), Lhéritier et al [19] showed that ARDS patients with RVD (assessed by transthoracic (TTE) or transesophageal echocardiography (TEE) and defined as ACP), received prone mechanical ventilation and vasoactive therapy more frequently, and required higher dose of inhaled nitric oxide (NO) as a rescue therapy, than those without RVD. The incidence of RVD in this study was 22.5% (95% CI 19.9-28.9%). In a prospective observational study [20] which enrolled 226 patients with moderate to severe ARDS (Berlin definition) [25] RVD was detected in 22% and was found to be an independent predictor of 28-day mortality ($p<0.01$). A secondary analysis [22] of the Fluid and Catheter Treatment Trial (FACTT) examined the association between pulmonary vascular dysfunction, (defined as elevated transpulmonary gradient (TPG) or increased pulmonary vascular resistance index (PVRi) assessed by pulmonary artery catheter (PAC)) and outcomes in ARDS patients. Increased baseline TPG was associated with higher 60-day mortality (30 vs 19%; $p<0.02$) and PVRi was statistically higher in non-survivors (326 [209–518] versus 299 [199–416]; $p = 0.01$). Of note, the median PVRi was highest [304.6 (204.3–430.9)] early in the course of ARDS (Day 0 and Day 1).

Mekontso Desapp and colleagues [17] undertook a large prospective observational study (n=752) in which patients with moderate to severe ARDS receiving the least damaging mechanical ventilation (low tidal volume and plateau pressure < 30 mmHg) were assessed using TEE. 22% of the cohort (95% CI 19-25%) had RVD (defined as ACP) and 7.2% of patients had severe RV dilatation (RVEDA/LVEDA>1). Hospital mortality did not differ between patients with or without RVD but was significantly higher in patients with severely dilated RV [31/54 (57 %) vs. 291/698 (42 %); $p = 0.03$] which was also found to be an independent predictor of mortality. This could be explained by the fact that this subset of patients had established RVF which was unresponsive to therapeutic interventions aimed at decreasing RV afterload and 'protecting' the RV.[17] On the other hand, patients with mildly dilated RV and septal dyskinesia included in the RVD group may have had preserved RV systolic function and this might explain the insignificant difference in mortality between the patients with or without RVD as defined by the authors. Patients enrolled had only a single TEE study during the first three days of ARDS diagnosis and therefore the natural history of RVD in ARDS remains unknown.[17]

Those studies assessing RV function in ARDS have not examined the impact of temporal changes in RV function on mortality, the natural history of RV function in survivors, nor the reversibility of RVD with progression of ARDS (Table 1). Whether patients with ARDS develop RV diastolic dysfunction, that might affect clinically important outcomes, also remains unknown. In most studies, RVD is defined as RV dilatation with or without septal dyskinesia. The clinical significance of isolated RV dilatation as a 'red flag' and its impact on mortality remain unclear. Only two studies used an ASE criterion (TAPSE) to define RVD (Table 1). [15, 16] There is a need for a consensual definition that reflects the pathophysiology of RVD in the context of ARDS and positive pressure ventilation. This will enable intensive care specialists to identify patients at risk of RVF and implement strategies that may protect the RV.

PATHOPHYSIOLOGY

The RV is responsible for maintaining adequate pulmonary perfusion pressure in order to deliver desaturated mixed venous blood to the respiratory membrane and low systemic venous pressure to prevent organ congestion. The RV is sensitive to changes in afterload because it is anatomically adapted for the generation of low-pressure perfusion.[11, 26]

Why is the RV failing in ARDS?

RVD is not always associated with an increase in PVR and pulmonary arterial hypertension; it can also be secondary to primary contractile impairment.[11] As a result, low cardiac output (CO) with low mean arterial pressure (MAP) can occur. This can develop into in a vicious cycle, leading to a progressive downward spiral and cardiogenic shock.[11, 26]

Mekontso Desapp et al,[17] reported four parameters (one clinical and three physiological) that were identified as statistically significant predictors of RVD in ARDS: 1) lower respiratory tract infection as a cause of pulmonary ARDS, 2) partial pressure of arterial oxygen : fraction of inspired oxygen (P_aO_2:F_iO_2) ratio < 150 mmHg, 3) $P_aCO_2 \geq$ 48 mmHg and 4) driving pressure (plateau pressure – total positive end expiratory pressure) $\geq$ 18 cmH_2O. These variables had a statistically significant correlation with RVD. Patients with an RVD score greater than or equal to 2 had a higher incidence of RVD (19%, 34% and 74% for risk scores of 2, 3 and 4 respectively). The authors recommend that echocardiography should be routinely performed in all ARDS patients with a score $\geq$ 2. There is lack of data that illustrate sequential relation of any of the above four parameters and severity of RVD. Although the RVD risk score has not yet been validated, it may provide a framework whereby researchers could test the hypothesis that early echocardiography and early implementation of RV protective measures and modification of the above physiological parameters might prevent RV failure and reduce mortality in patients with ARDS. [17]

Pulmonary Vascular Tone

Elevated pulmonary vascular tone in ARDS could be due to a variety of causes including an imbalance between vasoconstrictors and vasodialators, endothelial injury, arteriolar hypoxic pulmonary vasoconstriction, hypercapnia, acidemia, in situ thrombosis, and muscularization of non-muscularized arteries (pulmonary vascular remodeling).[27-29] Raised PVR may lead to acute distension of the thin-walled and 'afterload-sensitive' RV resulting in increased oxygen demand, decreased right coronary artery perfusion-pressure with reduced oxygen delivery, and tricuspid annular dilatation worsening tricuspid regurgitation and exacerbating volume overload. In addition RV dilatation can cause shifting of the interventricular septum toward the left impeding left ventricular diastolic filling and reducing left ventricular stroke volume, potentially leading to systemic hypotension. This phenomenon is known as 'ventricular interdependence'.[26, 30] It has been shown that pulmonary hypertension may cause RV diastolic dysfunction

which is related to impaired RV mechanical compliance and elevated RV afterload and does improve by reducing the afterload. RV diastolic dysfunction and diastolic ventricular interaction again has not been systematically studied in the context of ARDS.[31]

The role of Carbon Dioxide (CO_2)

Contributors to acute hypercapnia in ARDS include physiological factors such as increased alveolar dead space causing ventilation-perfusion mismatch and clinical factors such as low tidal volume/high respiratory rate ventilatory strategy in order to reduce the risk of ventilator induced lung injury. The role of acute hypercapnic acidemia in the pathophysiology of ARDS is not fully understood. Despite its potentially beneficial anti-inflammatory effect on pulmonary cytokines [32, 33] hypercapnia could also exacerbate hypoxic pulmonary vasoconstriction or induce direct vasoconstriction of the pulmonary vasculature by increasing extracellular Ca^{++} influx. [34, 35] Pulmonary vasoconstriction induces an increase in arterial elastance of the pulmonary vascular system (Ea), whereas the RV system is characterized by the RV elastance (Ees). The ratio Ees/Ea reflects the mechano-energetic aspects of RV-pulmonary vascular coupling which is of paramount importance for cardiovascular performance as it determines RV systolic pressure and RV stroke volume. When Ees/Ea is >1 the system is coupled providing adequate RV performance, stroke work and right coronary blood flow. Hypercapnia-induced increase in RV afterload results in increased Ea and RVD may develop due to uncoupling between the RV and pulmonary circulation.[36, 37] Experimental studies have shown that the buffering of respiratory acidosis is associated with worsening of ARDS.[38] This observation suggests that some of the beneficial anti-inflammatory effects of respiratory acidosis are likely to be due to the acidemia rather than hypercapnia alone.[38] A secondary analysis of the ARDSnet trial data[3] showed that hypercapnic acidemia in ARDS patients who were mechanically ventilated with high tidal volumes (12ml/kg predicted body weight) was associated with reduced 28-day mortality. However, the authors did not examine the effect of hypercapnic acidemia on outcomes at various time-points or over

time and due to its observational nature this study could not prove a cause-effect relationship between hypercapnic acidemia and mortality benefit. [39]

It has been demonstrated that patients with severe ARDS, and hypercapnic acidemia induced by low tidal volume ventilation and high positive-end expiratory pressure (PEEP) at a constant plateau pressure, are likely to develop RVD.[40] Vieillard-Baron and colleagues found that the partial pressure of arterial carbon dioxide (P_aCO_2) is an independent predictor of RVD in patients with ARDS receiving protective ventilation ($p<0.0001$).[24] In another study which included 200 patients with moderate to severe ARDS, P_aCO_2 > 60mmHg was strongly associated with RVD [odds ratio (OR) 3.70; 95 % CI 1.32–10.38; p = 0.01]. [19]

Positive Pressure Ventilation

Patients with ARDS typically have considerably reduced functional residual capacity (FRC) and overall lung compliance and a need for an elevated airway pressure to adequately maintain alveolar recruitment. This approach may have deleterious hemodynamic consequences.[41] Positive pressure mechanical ventilation causes an increase in transpulmonary pressure (difference between alveolar and pleural pressure) which worsens non-physiological lung 'stress' and strain (ratio between tidal volume and functional residual capacity).[42] PEEP, tidal volume and lung compliance are the main determinants of lung stress caused by positive pressure invasive ventilation which highlights the need for optimal mechanical ventilation strategies. When transpulmonary pressure exceeds pulmonary venous pressure, it acts as a back-pressure for pulmonary venous return and may increase the RV afterload.[43, 44]

Increased PVR occurs at the extremes of lung volume. At low volumes it is caused by the elastic recoil forces of the lung parenchyma causing extra-alveolar vessel and terminal airway collapse leading to alveolar hypoxia and hypoxic pulmonary vasoconstriction. At

high lung volumes increased PVR may occur due to collapse of the alveolar vessels consequent to the tension of the alveolar wall. When PVR is graphically plotted against lung volume, a U-shaped relation is observed with the lowest PVR occurring at the FRC. [45]

In ARDS, the distribution of intrapulmonary gas is heterogeneous with collapsed alveoli coexisting with normally aerated lung areas.[46] High PEEP levels can cause hyperinflation of the normally aerated alveoli and intra-alveolar vessel compression leading to high PVR and increased RV afterload.[47] The effect of PEEP on the RV outflow impedance in the context of ARDS has been evaluated by pulmonary artery flow velocity using TEE. High PEEP ($13\pm4 cmH_2O$) was associated with a significant reduction in RV stroke index [47] High plateau pressure (> 27 cmH_2O) has been associated with a high incidence of RVD (up to 60%) and high mortality rates (up to 42%) in ARDS [48]. Driving pressure (as a surrogate of lung stress) has recently been found to be a ventilation variable that is strongly associated with survival and RVD risk.[17, 49]

This suggests that it is the stress and strain on the lung that poses risks of abnormal RV physiology. Unfortunately, there is lack of prospective data on whether a 'low pressure' ventilatory approach is 'RV-protective'. Also, it remains unknown as to how much the chest wall contributes to the calculated airway pressures and whether this needs to be taken into account when attempting to risk stratify patients for RVD in ARDS.

Sepsis

In sepsis-related ARDS (pulmonary or extra-pulmonary), RVD can be an early phenomenon and appears to be associated with increased circulating levels of endothelin-1 (ET-1). [50] High ET-1 levels in sepsis are inversely correlated to RV function. A proposed mechanism for RVD in sepsis is increased PVR due to endothelial dysfunction and altered vaso-reactivity, despite systemic vasodilatation. (SVR). [26, 50, 51]

DIAGNOSIS OF ACUTE RIGHT VENTRICULAR DYSFUNCTION

1. Hemodynamic Monitoring

Standard hemodynamic monitoring can provide direct and indirect evidence suggesting the development of acute RVD. It is important to identify and diagnose patients with RVD early, so that interventions aimed at reducing the sequelae may be initiated.

Arterial line monitoring can detect the development of pulse pressure variation (PPV) and allows real-time blood pressure monitoring. PPV refers to dynamic changes of arterial pulse pressure (systolic blood pressure – diastolic blood pressure) induced by mechanical ventilation which can be derived from the arterial pressure waveform analysis and is thought to predict fluid responsiveness. In the context of low tidal volumes and a low pulmonary compliance state such as ARDS, the presence of PPV may signify either volume responsiveness or elevated RV afterload.[52-54] Of note, for the assessment of PPV to be valid the patient must not be spontaneously breathing, and must be receiving an appropriate controlled tidal volume and be in a regular heart rhythm. If the patient is deemed to be potentially volume responsive, a volume challenge may be given that will both confirm hypovolemia and subsequently improve RV outflow. If the PPV is due to elevated RV afterload (and not secondary to reduced RV preload), a fluid challenge will not reduce the PPV and may in fact worsen RV outflow. In such cases PPV cannot be used as a reliable predictor of fluid responsiveness. However, in patients with elevated PPV who are 'fluid-unresponsive' RVD due to elevated RV afterload should be suspected and investigated promptly with echocardiography.[55]

CVP monitoring directly measures right atrial (RA) pressure and although it is considered a poor predictor of fluid responsiveness it could be useful when values are particularly low or high (patients with very low CVP are likely to be 'fluid-responsive' and those with very high CVP are likely to be 'non-responders'). A rapid increase in CVP following a fluid challenge could serve as an indicator of impending RVD or RVF when fluid resuscitation exceeds the normal RV unstressed volume operation range.[56, 57]

2. Pulmonary Artery Catheter (PAC)

The traditional method of diagnosing RVD was to use a PAC. Given the potential risks of placement and development of less invasive methods of investigating cardiac function, the use of a PAC is now much less common. [57]

If a PAC is placed, then the usual findings suggestive of RVD include an elevated CVP (greater than 20mmHg), a CVP greater than pulmonary artery occlusion pressure, and a low cardiac index (< 2.0 L/min/m^2) and mixed-venous oxygen saturation (SvO_2 < 55%). The pulmonary vascular resistance is usually elevated in ARDS. [22] In addition, a PAC can be used to estimate the trans-pulmonary gradient (mean PA pressure – pulmonary artery occlusion pressure) which is also a marker of pulmonary vascular dysfunction which better estimates the resistance of the pulmonary vasculature in ARDS where West zones 1 and 2 can be abnormally extended due to increased transpulmonary pressure.[22]

The challenges of using the PAC include the risks of insertion and measurement of the wedge pressure. Its advantages, once placed, are the ease and rapidity of performing repeated measurements, particularly if many interventions to the patient's physiology are made. However, use of PAC in ARDS should probably be reserved for those patients with echocardiographic evidence of severe RVD at risk of RVF or patients with established RVF to guide inodilator and/or pulmonary vasodilator therapy and monitor the effect of ventilatory strategy on PVR.

There is a lack of data demonstrating the links between the rate of change in PVR and its implications for the management and prognosis of patients with ARDS. A potentially novel approach for these patients would be the use of pulmonary vasodilators early in the course of ARDS and testing of the hypothesis that this strategy might improve clinical outcomes.

3. Echocardiography

The availability of and experience with critical care echocardiography has increased exponentially over the past decade. Now echocardiography is generally readily available and accessible in the ICU. Lhe´ritier et al showed that TEE is superior to TTE for diagnosing RVD in mechanically ventilated patients with moderate to severe ARDS. The authors found that using TEE as a reference the sensitivity of TTE for diagnosing RVD in ARDS was only 60% (95% CI 41-77%).[19] Main limitation of the TEE approach is that serial repeat studies are more labor intensive and potentially of risk. [19, 58, 59] RVD by echocardiography is commonly defined as the presence of features of pressure and/or volume overload of the right ventricle. [14] RV volume overload is defined as dilation of the RV. RV pressure overload is defined as dyskinetic movement of the septum during end-systole. RV volume overload can lead to pressure overload and vice versa. [60]

There are several qualitative and quantitative methods of interrogating the RV using echocardiography.

2D echocardiography provides a visual appearance of the RV. Based on this, RV global systolic function can be estimated. Measurement of the RV end-diastolic dimensions and volumes can be made, and comparison with the left ventricle can be performed. The RV is considered dilated when the RVEDA:LVEDA ratio is greater than 0.6.[61, 62] In addition, evidence of systolic and diastolic septal dyskinesia (suggestive of RV pressure overload) can be determined on parasternal short axis and apical four chamber views.

Quantitative assessment of RV function can be performed by several methods. TAPSE can be obtained routinely and correlates well with RV function [12, 15, 16, 58] Interpretation of the TAPSE has two potential pitfalls however, it assumes the single segment represents the function of the entire RV, and its measurement is angle dependent.[63]

The role of echocardiographic markers of global RV systolic function (such as right ventricular index of myocardial performance (RIMP), Doppler tissue imaging (DTI) - derived S'wave velocity, RV strain and RV strain rate or three-dimensional (3D)

echocardiographic RV ejection fraction (EF) [12]) as early predictors of RVD in ARDS has not been studied to date. The prognostic implications of measures of diastolic RVD in ARDS (such as the ratio of early tricuspid inflow to annular diastolic velocity (E/E')[63]) have not been investigated either. It is possible that a predictive model based on echocardiographic and clinical (Berlin ARDS criteria and Mekontso Desapp clinical risk score) data could be developed to facilitate clinical decision making in patients with ARDS.

4. Advanced Cardiac Imaging and Biomarkers

Currently there is limited role for advanced cardiac imaging such as cardiac computed tomography (CT) or magnetic resonance imaging (MRI). MRI is hindered by its availability and also the need for low heart rates to enable appropriate gating and study acquisition (this is often technically difficult with critically ill patients). Attempts to demonstrate cardiac CT's ability to predict RV failure have been largely unsuccessful to date.[64, 65]

Limited data exists on the role of BNP in the prognostication of ARDS patients with RVD. In contrast, a recent study looking at patients with moderate to severe ARDS demonstrated that an elevated troponin, in conjunction with echo findings of RVD, identified a high-risk subgroup with elevated mortality. [18]

TREATMENT

The treatment of RV dysfunction can be divided into several physiological targets including optimization of RV preload, increasing RV contractility, and reducing RV afterload. Extracorporeal life support (veno-venous or veno-arterial extracorporeal membrane oxygenation (ECMO), extracorporeal CO_2 removal ($ECCO_2R$)) may be considered as rescue therapy in refractory cases of ARDS and RVF.

1. Optimization of RV preload

Meticulous management of volume status is crucial for the failing RV, as both low and high filling pressures may result in reduced CO. In patients where hypovolemia is suspected volume loading may increase CO.[66] This must be done cautiously as elevated pulmonary pressures (mean PAP greater than 30 mmHg), as seen in ARDS, may prevent a resultant increase in RV contractility and CO.[30] Excessive volume loading inhibits stroke volume by altering the geometry of the RV resulting in RV dilatation, ventricular interdependence, and impaired LV diastolic compliance. [67] RV dilatation may also cause increased tricuspid regurgitation and right sided venous congestion. A 'mini-fluid challenge' (100 ml of colloid or crystalloid fluid over 1 minute) has been shown to predict fluid responsiveness in patients with circulatory failure receiving low tidal volume ventilation and may be a safer, yet rational approach in patients with suspected RVD as a small rise in cardiac filling pressures may lead to a greater increase in stroke volume during administration of a 'mini-fluid bolus' (steep portion of the Frank-Starling curve). [68, 69]

When found, the treatment of elevated filling pressures could be instituted in an attempt to restore RV geometry, reduce RV dilation and ventricular interdependence. The use of diuretics is the simplest approach but hemofiltration and renal replacement therapy (CRRT) may be required if renal function is inadequate. However, there is no empirical evidence to support routine use of diuretics or CRRT in ARDS patients with RVF and this recommendation is based on clinical experience only. In addition, over-diuresis or excessive fluid removal on CRRT may rapidly lead to 'under-filling' of the RV (which is pre-load dependent) and decrease in stroke volume.

2. Increasing RV contractility

Ensuring the RV has an appropriate heart rate and rhythm can be amongst the simplest methods of improving RV contractility. Right atrial contraction contributes up to 40% of RV filling and is of more importance when the RV compliance is poor.[70, 71] Maintaining sinus rhythm avoids atrio-ventricular dyssynchrony and ensures the contribution of atrial

kick to RV filling. Patients with atrial fibrillation should be considered for restoration of sinus rhythm by pharmacological means or cardioversion. Likewise if heart block is present, placement of a temporary atrial pacemaker could be considered. Tachyarrythmias can also lead to a reduction in filling time and thus heart rate should be optimized to diastolic filling.

Initiation of vasoactive support can be important not only in improving RV contractility but also in preventing hemodynamic instability. Hypotension can lead to RV ischemia and subsequent further impairment of RV function that can quickly spiral into a vicious cycle. Targeted systemic pressure should be higher than the pulmonary pressure.

Maintenance of an appropriate systemic pressure while not excessively increasing or even decreasing the pulmonary artery pressures (PAPs) are the traits of an ideal vasopressor. Norepinephrine has been shown in both animal models and in man to increase SVR while reducing PAPs.[71, 72] Norepinephrine at high doses was shown to increase PVR over SVR preferentially and thus at high doses should be used cautiously. Phenylephrine has been shown to not be as effective as norepinephrine, and in certain situations to actually worsen RV function[29]. Vasopressin is also another vasopressor that preferentially increases SVR over PVR and thus can be useful to maintain systemic pressure without worsening RV afterload. At low doses (<0.03 U/min), Vasopressin causes pulmonary vasodilatation, but at higher doses it increases PVR and causes coronary vasoconstriction and should therefore be used with caution.[73, 74]

Dobutamine and milrinone are inodilators that provide inotropism and vasodilation of the systemic and pulmonary vasculature.[75, 76] Due to the profound systemic vasodilating capabilities of these agents, systemic hypotension can result and thus they are often need to be paired with a vasoconstrictor. Vasopressin, in contrast to norepinephrine, has been shown to be more beneficial at reducing PAPs.[77] When comparing dobutamine and milrinone, although there are equivalent reductions in PVR and improvements in cardiac output between the agents, there appears to be a greater reduction in SVR and PCWP when using milrinone. [78] Levosimendan, a calcium sensitizing agent with inotropic and

vasodilatory properties has been shown to improve RV performance in ARDS patients with septic shock.[79] As an inodilator, it could potentially improve RV-pulmonary vascular coupling but it does not have a proven mortality benefit in the treatment of ARDS patients with RVF.[79] Levosimendan is approved for use in Europe but does not have Food and Drug Administration approval in the United States. The aforementioned inotropic agents should be used with caution as they can cause tachyarrhythmias and hypotension.

3. Reducing RV Afterload

Reducing RV afterload in ARDS patients with RVD can be achieved through the use of pulmonary vasodilators, reversal and control of precipitating factors (hypoxemia, hypercapnia, acidemia, hypothermia) and 'RV-protective' mechanical ventilation strategies. [28]

Pulmonary Vasodilators

It is strongly recommended that inhaled rather than systemic pulmonary vasodilators are used when systemic hypotension is anticipated.[28] Inhaled NO (iNO) increases intra-cellular cyclic guanosine monophosphate and has been shown to transiently improve P_aO_2/F_iO_2 ratio and CO in ARDS patients with RVD.[80, 81] It is recommended that iNO is used as a short term therapy to improve oxygenation indices in ARDS as it does not improve mortality regardless of ARDS severity and has also been associated with acute kidney injury.[28, 82, 83] Inhaled prostanoids such as prostaglandin-I_2 (prostacyclin, PGI_2) and its analogues such as iloprost, reduce PVR and improve RV performance . Use of nebulized iloprost in ARDS patients with pulmonary hypertension has been associated with an improvement in gas exchange without causing hemodynamic instability.[28, 84] Oral sildenafil, a PDE-5 inhibitor has been shown to decrease RV systolic overload and enhances RV performance in ARDS patients with RVD. [85]

The use of pulmonary vasodilators should be individualized as they can worsen oxygenation and shunt fraction. [86] Pulmonary vasodilatation early in the course of ARDS, in patients at risk of RVD (eg RVD risk score >2), and its impact on clinical outcomes has not been studied.

'RV-protective' ventilation strategies

Understanding lung-heart clinical crosstalk in ARDS is likely to be of paramount importance, as RVD does occur in patients subjected to lung protective ventilation. The main proposed components of RV-protective ventilation strategy include: 1) minimizing lung stress by limiting plateau and driving pressures; 2) prevention or reversal of pulmonary vasoconstriction by improving oxygenation and strict CO_2 control; and 3) prone position to unload the RV.[44, 87]

It has been shown that 'low-stress' ventilation with plateau pressure less than 26-28 cmH_2O is associated with lower incidence of RVD. [48] Driving pressure (plateau pressure-total PEEP) has also been associated with mortality and development of RVD in ARDS.[20, 49, 87] It is recommended that plateau pressure is kept < 27cmH_2O and driving pressure < 18 cmH_2O. [44] High PEEP recruits collapsed alveoli but can cause overdistension of functional lung areas. Both atelectasis and overdistension result in increased PVR and high RV afterload. The optimal 'RV-protective' PEEP levels (balance between alveolar recruitment and overdistension) and titration of PEEP remain controversial and the effect of 'low-lung stress' ventilation approach on the RV needs to be validated in large RCTs.

Prone ventilation in ARDS can facilitate reduction in RV afterload by recruiting collapsed alveoli without causing overdistension [88] and reducing airway pressure, P_aCO_2, RV enlargement and septal dyskinesia.[89] A multi-center RCT (PROSEVA) showed a mortality benefit in patients with severe ARDS who were ventilated in the prone position.[4] In addition, the prone group had a lower incidence of cardiac arrest (6.8 vs 13.5%, $p<0.05$) and shock (14.8 vs 21%) that may suggest a positive impact of proning

on hemodynamics.[44] P_aO_2:F_iO_2 < 150mmHg is an accepted indication for proning [4] but timing and optimal duration of prone ventilation in patients with ARDS and RVD has not been established. Whether prone position at the onset of mechanical ventilation in severe 'Berlin' ARDS prevents RVD remains unknown. A strategy whereby ARDS patients are ventilated in prone position based on their hemodynamic status (presence of RVD) and not P_aO_2:F_iO_2 ratio has not been investigated either.

4. Extracorporeal Life Support (ECLS)

Veno-venous ECMO (VVECMO) may be used in cases of severe hypoxemia (P_aO_2:F_iO_2 < 150mmHg, on F_iO_2 ≥0.6 and PEEP ≥5 cmH_2O) despite optimization of mechanical ventilation settings (higher PEEP and mean airway pressure, lung recruitment maneuvers), neuromuscular blockade and inhaled pulmonary vasodilators. [4, 90] VVECMO in ARDS has been shown to effectively unload the RV by correcting hypoxemia and/or hypercapnia and facilitating a least damaging ('low-pressure') ventilatory approach.[90]

Veno-arterial ECMO (VAECMO) is an option for mechanical circulatory support in ARDS patients with RVF and cardiogenic shock refractory to vasoactive drugs. VAECMO (percutaneous or intrathoracic) provides respiratory and cardiovascular support as deoxygenated blood bypasses both the failing RV and the lungs enhancing unloading of the RV.[91]

Normocapnia in ARDS can be challenging to achieve with conventional mechanical ventilation. An increase in mechanically triggered mandatory breaths can cause increased auto-PEEP, worsening hypercapnia and RVD.[44] Extracorporeal CO_2 removal ($ECCO_2R$) devices can be used as adjuncts to invasive mechanical ventilation and could potentially help preserve or restore optimal RV-arterial coupling and prevent RV failure in ARDS patients.[92] Experimental evidence suggests that $ECCO_2R$ facilitates protective ventilation, reduces minute ventilation by 50% and improves RV function.[93]

Although ECLS can theoretically reverse physiological causes of RVD (hypoxemia/hypercapnia) and facilitate 'RV-protective' ventilation its effect on RVD and ARDS mortality has yet to be proven in rigorous controlled trials.

CONCLUSIONS

Right ventricular dysfunction and failure is associated with adverse outcomes in patients with ARDS. Understanding of RVD pathophysiology and altered cardiopulmonary interactions in ARDS is crucial for the bedside management of these patients. Future research should focus on validation of clinical risk scoring systems to select patients at risk of RVD, immediate assessment by echocardiography and early implementation of therapeutic measures such as early pulmonary vasodilatation and prone positioning that may improve prognosis in ARDS. Echocardiographic markers such as TAPSE and RV TDI S' velocity could serve as predictors of early RVD and guide therapeutic interventions based on temporal changes in RV function which is another high-yield area of future study. Finally, the 'RV-protective' ventilatory strategy combined with extracorporeal support may be key in management of patients with established RVD and form part of ARDS management guidelines if validated in prospective pragmatic trials.

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Study reference	Year	Type	ARDS definition/ Ventilation strategy	N	Diagnostic modality: TTE/TEE/PAC	Timing of echocardiography following diagnosis of ARDS	Definition of RVD	Prevalence of RVD	Outcome	Non-survivors (n)	Non-survivors with RVD (n)	*P (<0.05 statistically significant)*	
Wadia et al[15]	2016	Retrospective	Berlin/LPV	14	TTE	Within 2 weeks	Not defined (authors examined changes in TAPSE, MPI, FAC pre- and post- ARDS)	42.9%	30-day mortality	8 (57%)	-	0.002(for TAPSE)	
Shah et al[16]	2016	Retrospective	Berlin/LPV	38	TTE	Within 2 weeks	TAPSE <17mm	55%	30-day mortality	18 (47%)	-	0.004	
Dessap et al[17]	2015	Prospective observational	Berlin/LPV	752	TEE	Within 3 days	Septal dyskinesia with dilated RV (RVEDA/LVEDA >0.6)	22%	Hospital mortality	322 (43%)	78/164 (48%) [31/54 (57%)] in severe RVD]	0.17 0.03	
Lazzeri et al[18]	2015	Prospective observational	Berlin/ LPV	21	TEE/TTE	Prior to VVECMO implantation	sPAP >40 mmHg or dilated RV or Septal dyskinesia with dilated RV (RVEDA/LVEDA >0.6) or TAPSE<16mmHg	90.5% 9.5% 47.6%	ICU mortality	12 (57.1%)	-	0.004 0.04	
Lhe´ritier et al[19]	2013	Prospective observational	American & European consensus/LPV	201	TEE/TTE	Within 48 hours	Septal dyskinesia with dilated RV (RVEDA/LVEDA >0.6)	22.5%	28-day mortality	46 (23%)	11/45(24%)	0.79	
Boissier et al[20]	2012	Prospective observational	Berlin/LPV	226	TEE	Within 3 days	Septal dyskinesia with dilated RV (RVEDA/LVEDA >0.6)	22%	28-day mortality ICU mortality	114 (50%)	28/49 (57%) 31/49 (63%)	<0.01 0.04	

									Hospital mortality		33/49 (67%)	0.02
Guervilly et al[21]	2012	Prospective randomized	American & European consensus/ CMV vs HFOV	16 (CMV vs HFOV)	TEE	Within 48 hours	RVEDA/LVEDA >0.6 (RV Dysfunction) RVEDA/LVEDA >0.9 (RV Failure)	56% (during CMV) 25% (during HFOV)	ICU mortality	9 (56%)	-	<0.01
Bull et al[22]	2010	Retrospective observational	American & European consensus/LPV	475	PAC		TPG > 24 mm Hg (assessed pulmonary vascular dysfunction)	-	60-day mortality	49%	41	0.0006
Osman et al[23]	2009	Prospective observational	American & European consensus/LPV	145	PAC	After 24 hours	(1) mPAOP>25mmHg and (2) CVP>PAOP and (3) SVI<30ml m^{-2}	9.6%	28-day mortality 90-day mortality	98 (68%)	9/14 (64%)	0.75 0.56
Vieillard-Baron et al[24]	2001	Prospective	American & European consensus/LPV	75	TEE	After 2 days of respiratory support	RVEDA/LVEDA >0.6 + Septal dyskinesia (ACP) RVEDA/LVEDA >1 (Severe ACP)	25%	28-day mortality	24 (32%)	-	<0.2

Table 1. Characteristics of studies evaluating the prognostic value of right ventricular dysfunction assessed by echocardiography for mortality in patients with acute respiratory distress syndrome**.**

ACP = acute cor pulmonale; ARDS = acute respiratory distress syndrome; CMV = conventional mechanical ventilation; CVP = central venous pressure; FAC = fractional area change; HFOV = high frequency oscillatory ventilation; ICU = intensive care unit; LVEDA = left ventricular end-diastolic area; LPV = lung protective ventilation; mPAOP = mean pulmonary artery occlusion

pressure; MPI = myocardial performance index; PAC = pulmonary artery catheter; PAOP = pulmonary artery occlusion pressure; RV = right ventricle; RVD = right ventricular dysfunction; RVEDA = right ventricular end-diastolic area; SVI = stroke volume index; TAPSE = tricuspid annular plane systolic excursion; TEE = transesophageal echocardiography; TPG = transpulmonary gradient; TTE = transthoracic echocardiography; VVECMO = veno-venous extracorporeal membrane oxygenation