CHEST

# The Right Ventricle in ARDS

*Vasileios Zochios, MD; Ken Parhar, MD; William Tunnicliffe, MBBCh; Andrew Roscoe, MBChB; and Fang Gao, PhD*

ARDS is associated with poor clinical outcomes, with a pooled mortality rate of approximately 40% despite best standards of care. Current therapeutic strategies are based on 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 (RVD), is commonly encountered in moderate to severe ARDS and is reported to be one of the major determinants of mortality. The prevalence rate of echocardiographically evident RVD in ARDS varies across studies, ranging from 22% to 50%. Although there is no definitive causal relationship between RVD and mortality, severe RVD is associated with increased mortality. Factors that can adversely affect RV function include hypoxic pulmonary vasoconstriction, hypercapnia, and invasive ventilation with high driving pressure. It might be expected that early diagnosis of RVD would be of benefit; however, echocardiographic markers (qualitative and quantitative) used to prospectively evaluate the right ventricle in ARDS have not been tested in adequately powered studies. In this review, we examine the prognostic implications and pathophysiology of RVD in ARDS 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.

CHEST 2017; 152(1):181-193

**KEY WORDS:** ARDS; cor pulmonale; critical care echocardiography; right ventricular dysfunction

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

**ABBREVIATIONS:** ACP = acute cor pulmonale; ASE = American Society of Echocardiography; CRRT = continuous renal replacement therapy; CVP = central venous pressure; Ea = arterial elastance; $ECCO_2R$ = extracorporeal $CO_2$ removal; Ees = right ventricular elastance; ET-1 = endothelin 1; FRC = functional residual capacity; iNO = inhaled nitric oxide; LVEDA = left ventricular end-diastolic area; PAC = pulmonary artery catheter; PAOP = pulmonary artery occlusion pressure; PAP = pulmonary artery pressure; PEEP = positive end-expiratory pressure; PPV = pulse pressure variation; PVR = pulmonary vascular resistance; PVRi = pulmonary vascular resistance index; RCT = randomized controlled trial; RV = right ventricular; RVD = right ventricular dysfunction; RVEDA = right ventricular end-diastolic area; RVFAC = right ventricular fractional area change; TAPSE = tricuspid annular plane systolic excursion; TEE = transesophageal echocardiography; TPG = transpulmonary gradient; TTE = transthoracic echocardiography

**AFFILIATIONS:** From the Department of Critical Care Medicine (Drs Zochios and Tunnicliffe), University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Edgbaston; the Institute of Inflammation and Ageing (Prof Gao and Dr Zochios), Centre of Translational Inflammation Research, University of Birmingham, Birmingham; the Department of Cardiothoracic Anesthesia and Critical Care Medicine (Dr Roscoe), Papworth Hospital NHS Foundation Trust, Papworth Everard, Cambridge; the Academic Department of Anesthesia, Critical Care, Pain and Resuscitation (Prof Gao), Heart of England NHS Foundation Trust, Birmingham, England, and The 2nd Affiliated Hospital and Yuying Children's Hospital Wenzhou Medical University, Wenzhou, China; and the Department of Critical Care Medicine (Dr Parhar), the University of Calgary, Calgary, AB, Canada.

**CORRESPONDENCE TO:** Vasileios Zochios, MD, Department of Critical Care Medicine, University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Mindelsohn Way, Edgbaston, Birmingham, B15 2GW, UK; e-mail: vasileioszochios@doctors.org.uk



**DOI:** http://dx.doi.org/10.1016/j.chest.2017.02.019

meta-analysis that included 89 ARDS studies (53 observational, 36 randomized controlled trials [RCTs]), Phua et al[7] found that the overall pooled weighted mortality was 44.3% (95% CI, 41.8-46.9). In a recent RCT comparing conservative (oxygen saturation as measured by pulse oximetry, 88%-92%) vs 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 effects and that hypoxemia may not be the leading cause of mortality in ARDS.[8] Conversely, 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 and pulmonary vasculature, which is often underappreciated in ARDS.[10] As a result, the right ventricle 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 right ventricular dysfunction (RVD) in ARDS and its effect on clinical outcomes, examine the current state of knowledge of the pathophysiology of RVD, identify gaps, and explore the use of novel imaging markers and preventive and therapeutic strategies. Unanswered questions such as the effectiveness of "low-lung-stress" ventilation, timing of prone positioning and whether RVD alone should be an indication for prone positioning, the role of extracorporeal life support, and the natural history of RVD in ARDS survivors is also discussed.

## Definitions

There are various definitions for RVD and RV 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) < 17 mm, pulsed Doppler S wave < 9.5 cm/s, RV fractional area change (RVFAC) < 35%, and RV ejection fraction < 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 right ventricle to provide adequate blood flow through the pulmonary circulation at a normal central venous pressure (CVP).[11] Acute cor pulmonale (ACP) refers to acute dilatation or dysfunction (or both) of the right ventricle in the context of acute lung disease (eg, ARDS) and associated pulmonary vascular dysfunction.[14] ACP is a form of RVD that is due to an acute increase in RV afterload that may lead to RVF and is defined echocardiographically as septal dyskinesia with a ratio of right ventricular end-diastolic area (RVEDA) to left ventricular end-diastolic area (LVEDA) > 0.6 (> 1 for severe dilatation). In the right ventricle focused view, RV diameter > 41 mm at the base and > 35 mm 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 lung disease. Assessment of the right ventricle by echocardiography is discussed further in the section on diagnosis in this review.

## Epidemiology and Prognosis

The reported incidence of RVD in ARDS varies across studies (22%-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 course of ARDS and that severe RVD is associated with increased mortality even during lung-protective mechanical ventilation.

In a prospective multicenter study (N = 200), Lhéritier et al[19] showed that patients with ARDS and RVD (assessed by transthoracic echocardiography [TTE] or transesophageal echocardiography [TEE] and defined as ACP), received prone mechanical ventilation and vasoactive therapy more frequently and required a higher dose of inhaled nitric oxide (iNO) as a rescue therapy than did 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] that 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 ($P < .01$). 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 patients with ARDS. Increased baseline TPG was associated with higher 60-day mortality (30% vs 19%; $P < .02$), and PVRi was statistically higher in nonsurvivors (326 [209-518] vs 299 [199-416]; $P = .01$). Of note, the median PVRi was highest (304.6 [204.3-430.9]) early in the course of ARDS (day 0 and day 1).

**TABLE 1** ] Characteristics of Studies Evaluating the Prognostic Value of Right Ventricular Dysfunction Assessed by Echocardiography for Mortality in Patients With ARDS

| Study/Year | Type | ARDS Definition/ Ventilation Strategy | No. | Diagnostic Modality: TTE/TEE/ PAC | Timing of Echocardiography Following Diagnosis of ARDS | Definition of RVD | Prevalence of RVD | Outcome | Nonsurvivors (No.) | Nonsurvivors With RVD (No.) | *P* Value (< .05 Statistically Significant) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Wadia et al[15]/ 2016 | Retrospective | Berlin/LPV | 14 | TTE | Within 2 wk | Not defined (authors examined changes in TAPSE, MPI, FAC before and after ARDS) | 42.9% | 30-d mortality | 8 (57%) | . . . | .002 (for TAPSE) |
| Shah et al[16]/ 2016 | Retrospective | Berlin/LPV | 38 | TTE | Within 2 wk | TAPSE < 17 mm | 55% | 30-d mortality | 18 (47%) | . . . | .004 |
| Mekontso Dessap et al[17]/ 2016 | Prospective observational | Berlin/LPV | 752 | TEE | Within 3 d | Septal dyskinesia with dilated right ventricle (RVEDA/LVEDA > 0.6) | 22% | Hospital mortality | 322 (43%) | 78/164 (48%) (31 of 54 [57%]) in severe RVD) | .17 .03 |
| Lazzeri et al[18]/ 2016 | Prospective observational | Berlin/LPV | 21 | TEE/TTE | Prior to VVECMO implantation | sPAP > 40 mm Hg or dilated right ventricle or septal dyskinesia with dilated right ventricle (RVEDA/LVEDA > 0.6) or TAPSE < 16 mm Hg | 90.5% 9.5% 47.6% | ICU mortality | 12 (57.1%) | . . . | .004 .04 |
| Lhéritier et al[19]/ 2013 | Prospective observational | American and European consensus/ LPV | 201 | TEE/TTE | Within 48 h | Septal dyskinesia with dilated right ventricle (RVEDA/LVEDA > 0.6) | 22.5% | 28-d mortality | 46 (23%) | 11 of 45 (24%) | .79 |
| Boissier et al[20]/ 2013 | Prospective observational | Berlin/LPV | 226 | TEE | Within 3 d | Septal dyskinesia with dilated right ventricle (RVEDA/LVEDA > 0.6) | 22% | 28-d mortality ICU mortality | 114 (50%) | 28 of 49 (57%) 31 of 49 (63%) | < .01 .04 .02 |

*(Continued)*

**TABLE 1** ] *(Continued)*

| Study/Year | Type | ARDS Definition/ Ventilation Strategy | No. | Diagnostic Modality: TTE/TEE/ PAC | Timing of Echocardiography Following Diagnosis of ARDS | Definition of RVD | Prevalence of RVD | Outcome | Nonsurvivors (No.) | Nonsurvivors With RVD (No.) | *P* Value (< .05 Statistically Significant) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Hospital mortality | | 33 of 49 (67%) | |
| Guervilly et al[21]/ 2012 | Prospective randomized | American and European consensus/ CMV vs HFOV | 16 (CMV vs HFOV) | TEE | Within 48 h | RVEDA/LVEDA > 0.6 (RVD) RVEDA/LVEDA > 0.9 (RVF) | 56% (during CMV) 25% (during HFOV) | ICU mortality | 9 (56%) | . . . | < .01 |
| Bull et al[22]/ 2010 | Retrospective observational | American and European consensus/ LPV | 475 | PAC | . . . | TPG > 24 mm Hg (assessed pulmonary vascular dysfunction) | . . . | 60-d mortality | 49% | 41 | .0006 |
| Osman et al[23]/ 2009 | Prospective observational | American and European consensus/ LPV | 145 | PAC | After 24 h | (1) mPAOP > 25 mm Hg and (2) CVP > PAOP and (3) SVI < 30 mL/m$^2$ | 9.6% | 28-d mortality 90-d mortality | 98 (68%) | 9 of 14 (64%) | .75 .56 |
| Vieillard-Baron et al[24]/ 2001 | Prospective | American and European consensus/ LPV | 75 | TEE | After 2 d of respiratory support | RVEDA/LVEDA > 0.6 + septal dyskinesia (ACP) RVEDA/LVEDA > 1 (severe ACP) | 25% | 28-d mortality | 24 (32%) | . . . | < .2 |

ACP = acute cor pulmonale; CMV = conventional mechanical ventilation; CVP = central venous pressure; FAC = fractional area change; HFOV = high-frequency oscillatory ventilation; 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; RVD = right ventricular dysfunction; RVEDA = right ventricular end-diastolic area; RVF = right ventricular failure; sPAP = systolic pulmonary arterial pressure; SVI = stroke volume index; TAPSE = tricuspid annular plane systolic excursion; TEE = transesophageal echocardiography; TPG = transpulmonary gradient; TTE = transthoracic echocardiography; VVECMO = venovenous extracorporeal membrane oxygenation.

Mekontso Dessap et al[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 mm Hg) were assessed using TEE. Twenty-two percent of the cohort (95% CI, 19%-25%) had RVD (defined as ACP) and 7.2% of patients had severe RV dilatation (RVEDA to LVEDA > 1). Hospital mortality did not differ between patients with and those without RVD but was significantly higher in patients with a severely dilated right ventricle (31 of 54 [57%]) vs 291 of 698 [42%]; $P = .03$), 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 that was unresponsive to therapeutic interventions aimed at decreasing RV afterload and "protecting" the right ventricle.[17] Conversely, patients with a mildly dilated right ventricle 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 and those without RVD as defined by the authors. Patients enrolled had only a single transesophageal echocardiographic study during the first 3 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, or the reversibility of RVD with progression of ARDS (Table 1). Whether patients with ARDS experience 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 right ventricle.

## Pathophysiology

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

### Why Is the Right Ventricle 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 with low mean arterial pressure can occur. This can develop into 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) $Pa_{O_2}$ to $F_{IO_2}$ ratio < 150 mm Hg, (3) $Pa_{CO_2}$ ≥ 48 mm Hg, and (4) driving pressure (plateau pressure – total positive end-expiratory pressure) ≥ 18 cm $H_2O$. These variables had a statistically significant correlation with RVD. Patients with an RVD score ≥ 2 had a higher incidence of RVD (19%, 34%, and 74% for risk scores of 2, 3, and 4, respectively). The authors recommended that echocardiography be routinely performed in all patients with ARDS with a score ≥ 2. There is a lack of data that illustrate a sequential relationship between any of the four parameters listed and the 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 preceding 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 vasodilators, endothelial injury, arteriolar hypoxic pulmonary vasoconstriction, hypercapnia, acidemia, in situ thrombosis, and muscularization of nonmuscular arteries (pulmonary vascular remodeling).[27-29] Raised PVR may lead to acute distention of the thin-walled and "afterload-sensitive" right ventricle, 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 LV diastolic filling and reducing LV 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 $CO_2$

Contributors to acute hypercapnia in ARDS include physiological factors such as increased alveolar dead space causing ventilation-perfusion mismatch and clinical factors such as a low tidal volume/high respiratory rate ventilatory strategy 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 $Ca^{2+}$ influx.[34,35] Pulmonary vasoconstriction induces an increase in arterial elastance (Ea) of the pulmonary vascular system, whereas the RV system is characterized by RV elastance (Ees). The ratio Ees to Ea reflects the mechanoenergetic aspects of right ventricle/pulmonary vascular coupling, which is of paramount importance for cardiovascular performance, as it determines RV systolic pressure and RV stroke volume. When the Ees to Ea ratio is $> 1$, the system is coupled, providing adequate RV performance, stroke work, and right coronary blood flow. A hypercapnia-induced increase in RV afterload results in increased Ea, and RVD may develop due to uncoupling between the RV and pulmonary circulations.[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 to hypercapnia alone.[38] A secondary analysis of the ARDS Network trial data[3] showed that hypercapnic acidemia in patients with ARDS who underwent mechanical ventilation with high tidal volumes (12 mL/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 because of 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 experience RVD.[40] Vieillard-Baron et al[24] found that $Paco_2$ is an independent predictor of RVD in patients with ARDS receiving protective ventilation ($P < .0001$). In another study that included 200 patients with moderate to severe ARDS, $Paco_2 > 60$ mm Hg was strongly associated with RVD (OR, 3.70; 95% CI, 1.32-10.38; $P = .01$].[19]

### Positive-Pressure Ventilation

Patients with ARDS typically have considerably reduced functional residual capacity (FRC) and overall lung compliance and a need for 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 nonphysiological 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 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 relationship 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 RV

outflow impedance in the context of ARDS has been evaluated by pulmonary artery flow velocity using TEE. High PEEP (13 ± 4 cm $H_2O$) was associated with a significant reduction in RV stroke index.[47] High plateau pressure (> 27 cm $H_2O$) 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 a lack of prospective data on whether a "low-pressure" ventilatory approach is "protective of the right ventricle." 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 extrapulmonary), 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 with RV function. A proposed mechanism for RVD in sepsis is increased PVR due to endothelial dysfunction and altered vasoreactivity, despite systemic vasodilatation (SVR).[26,50,51]

## Diagnosis of Acute RVD

### *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 sequelae may be initiated.

Arterial line monitoring can detect the development of pulse pressure variation (PPV) and allows real-time BP 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 in 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 breathing spontaneously and must be receiving an appropriate controlled tidal volume and have 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 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 "nonresponders"). 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]

### *Pulmonary Artery Catheter*

The traditional method of diagnosing RVD was to use a PAC. Given the potential risks of placement and the 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, the usual findings suggestive of RVD include an elevated CVP (> 20mm Hg), a CVP greater than pulmonary artery occlusion pressure, a low cardiac index (< 2 L/min/$m^2$), and mixed venous oxygen saturation < 55%. The PVR is usually elevated in ARDS.[22] In addition, a PAC can be used to estimate the transpulmonary gradient (mean PA pressure – pulmonary artery occlusion pressure), which is also a marker of pulmonary vascular dysfunction that better estimates the resistance of the pulmonary vasculature in ARDS in which 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 physiological interventions are made. However, the use of a PAC in ARDS should probably be reserved for those patients with echocardiographic evidence of severe RVD

who are at risk of RVF or patients with established RVF to guide inodilator therapy or pulmonary vasodilator therapy, or both, 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.

### *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. Lhéitier et al[19] 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%). The main limitation of the TEE approach is that serial repeated studies are more labor intensive and are potentially risky.[19,58,59] RVD determined by echocardiography is commonly defined as the presence of features of pressure or volume overload (or both) of the right ventricle.[14] RV volume overload is defined as dilatation of the right ventricle. 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 right ventricle using echocardiography. Two-dimensional echocardiography provides a visual image of the right ventricle. 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 right ventricle is considered dilated when the RVEDA to LVEDA ratio is $> 0.6$.[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 TAPSE has two potential pitfalls, however; it assumes the single segment represents the function of the entire right ventricle, and its measurement is angle dependent.[63]

The role of echocardiographic markers of global RV systolic function (such as RV index of myocardial performance, Doppler tissue imaging-derived S' wave velocity, RV strain, and RV strain rate or three-dimensional echocardiographic RV ejection fraction[12]) as early predictors of RVD in ARDS have 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[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.

### *Advanced Cardiac Imaging and Biomarkers*

Currently there is a limited role for advanced cardiac imaging such as cardiac CT or MRI. The latter 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 exist on the role of B-type natriuretic peptide in the prognostication of patients with ARDS with RVD. In contrast, a recent study looking at patients with moderate to severe ARDS demonstrated that an elevated troponin level, in conjunction with echocardiographic findings of RVD, identified a high-risk subgroup with elevated mortality.[18]

## Treatment

The treatment of RVD can be divided into several physiological targets, including optimizing RV preload, increasing RV contractility, and reducing RV afterload. Extracorporeal life support (venovenous or venoarterial extracorporeal membrane oxygenation [ECMO], extracorporeal $CO_2$ removal [$ECCO_2R$]) may be considered as rescue therapy in refractory cases of ARDS and RVF.

### *Optimization of RV Preload*

Meticulous management of volume status is crucial for a failing right ventricle, as both low and high filling pressures may result in reduced cardiac output. In patients in whom hypovolemia is suspected, volume loading may increase cardiac output.[66] This must be

done cautiously, as elevated pulmonary pressures (mean pulmonary artery pressure [PAP] > 30 mm Hg), as seen in ARDS, may prevent a resultant increase in RV contractility and cardiac output.[30] Excessive volume loading inhibits stroke volume by altering the geometry of the right ventricle, 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 min) 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 and reduce RV dilatation and ventricular interdependence. The use of diuretic agents is the simplest approach, but hemofiltration and continuous renal replacement therapy (CRRT) may be required if renal function is inadequate. However, there is no empirical evidence to support the routine use of diuretic agents or CRRT in patients with ARDS with RVF, and this recommendation is based on clinical experience only. In addition, overdiuresis or excessive fluid removal on CRRT may rapidly lead to "underfilling" of the right ventricle (which is preload dependent) and a decrease in stroke volume.

### *Increasing RV Contractility*

Ensuring that the right ventricle has an appropriate heart rate and rhythm can be among the simplest methods of improving RV contractility. Right atrial contraction contributes up to 40% of RV filling and is of more importance when RV compliance is poor.[70,71] Maintaining sinus rhythm avoids atrioventricular dyssynchrony and ensures the contribution of atrial kick to RV filling. Patients with atrial fibrillation should be considered for restoration of sinus rhythm by pharmacologic 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 pulmonary pressure.

Maintenance of an appropriate systemic pressure while not excessively increasing or even decreasing PAP are the traits of an ideal vasopressor. Norepinephrine has been shown in both animal models and humans to increase SVR while reducing PAP.[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 be not 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 units/min), vasopressin causes pulmonary vasodilation, 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] Because of the profound systemic vasodilating capabilities of these agents, systemic hypotension can result, and thus they often need to be paired with a vasoconstrictor. Vasopressin, in contrast to norepinephrine, has been shown to be more beneficial at reducing PAP.[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 pulmonary capillary wedge pressure when using milrinone.[78] Levosimendan, a calcium sensitizing agent with inotropic and vasodilatory properties, has been shown to improve RV performance in patients with ARDS and septic shock.[79] As an inodilator, it could potentially improve right ventricle/pulmonary vascular coupling, but it does not have a proven mortality benefit in the treatment of patients with ARDS and RVF.[79] Levosimendan is approved for use in Europe but does not have US Food and Drug Administration approval. The aforementioned inotropic agents should be used with caution, as they can cause tachyarrhythmias and hypotension.

### *Reducing RV Afterload*

Reducing RV afterload in patients with ARDS with RVD can be achieved through the use of pulmonary

vasodilators, reversal and control of precipitating factors (hypoxemia, hypercapnia, acidemia, hypothermia) and right ventricle-protective mechanical ventilation strategies.[28]

**Pulmonary vasodilators:** It is strongly recommended that inhaled rather than systemic pulmonary vasodilators be used when systemic hypotension is anticipated.[28] iNO increases intracellular cyclic guanosine monophosphate and has been shown to transiently improve the $Pa_{O_2}$ to $F_{IO_2}$ ratio and cardiac output in patients with ARDS and RVD.[80,81] It is recommended that iNO be 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) and its analogues such as iloprost reduce PVR and improve RV performance. Use of nebulized iloprost in patients with ARDS and pulmonary hypertension has been associated with an improvement in gas exchange without causing hemodynamic instability.[28,84] Oral sildenafil, a phosphodiesterase-5 inhibitor, has been shown to decrease RV systolic overload and enhance RV performance in patients with ARDS and RVD.[85]

The use of pulmonary vasodilators should be individualized, as they can worsen oxygenation and shunt fraction.[86] Pulmonary vasodilation 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.

**Right ventricle-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 a right ventricle-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 positioning to unload the right venricle.[44,87]

It has been shown that "low-stress" ventilation with plateau pressure $< 26$ to 28 cm $H_2O$ is associated with a lower incidence of RVD.[48] Driving pressure (plateau pressure – total PEEP) has also been associated with mortality and the development of RVD in ARDS.[20,49,87] It is recommended that plateau pressure be kept at $< 27$ cm $H_2O$ and driving pressure at $< 18$ cm $H_2O$.[44] High PEEP recruits collapsed alveoli but can cause overdistention of functional lung areas. Both atelectasis and overdistention result in increased PVR and high RV afterload. The optimal right ventricle-protective PEEP levels (balance between alveolar recruitment and overdistention) and titration of PEEP remain controversial and the effect of a "low lung stress" ventilation approach on the right ventricle needs to be validated in large RCTs.

Prone ventilation in ARDS can facilitate reduction in RV afterload by recruiting collapsed alveoli without causing overdistention[88] and reducing airway pressure, $Pa_{CO_2}$, RV enlargement, and septal dyskinesia.[89] A multicenter RCT (Proning Severe ARDS Patients [PROSEVA]) showed a mortality benefit in patients with severe ARDS who underwent ventilation in the prone position.[4] In addition, the prone group had a lower incidence of cardiac arrest (6.8% vs 13.5%; $P < .05$) and shock (14.8% vs 21%), which may suggest a positive impact of prone positioning on hemodynamics.[44] A $Pa_{O_2}$ to $F_{IO_2}$ ratio $< 150$ mm Hg is an accepted indication for prone positioning,[4] but timing and optimal duration of prone ventilation in patients with ARDS and RVD have not been established. Whether prone positioning at the onset of mechanical ventilation in severe "Berlin" ARDS prevents RVD remains unknown. A strategy whereby patients with ARDS undergo ventilation in the prone position based on their hemodynamic status (presence of RVD) and not the $Pa_{O_2}$ to $F_{IO_2}$ ratio has not been investigated either.

### *Extracorporeal Life Support*

Venovenous ECMO may be used in cases of severe hypoxemia ($Pa_{O_2}$ to $F_{IO_2}$ ratio $< 150$ mm Hg, on $F_{IO_2} \geq 0.6$ and PEEP $\geq 5$ cm $H_2O$) despite optimization of mechanical ventilation settings (higher PEEP and mean airway pressure, lung recruitment maneuvers), neuromuscular blockade, and inhaled pulmonary vasodilators.[4,90] Venovenous ECMO in ARDS has been shown to effectively unload the right ventricle by correcting hypoxemia or hypercapnia, or both, and facilitating a least-damaging (low-pressure) ventilatory approach.[90]

Venoarterial ECMO is an option for mechanical circulatory support in patients with ARDS and RVF and cardiogenic shock that is refractory to vasoactive drugs. Venoarterial ECMO (percutaneous or intrathoracic) provides respiratory and cardiovascular support as deoxygenated blood bypasses both the failing right ventricle and the lungs, enhancing unloading of the right ventricle.[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] $ECCO_2R$ devices can be used as adjuncts to invasive mechanical ventilation and could potentially help preserve or restore optimal right ventricle-arterial coupling and prevent RVF in patients with ARDS.[92] Experimental evidence suggests that $ECCO_2R$ facilitates protective ventilation, reduces minute ventilation by 50%, and improves RV function.[93]

Although extracorporeal life support can theoretically reverse physiological causes of RVD (hypoxemia/hypercapnia) and facilitate right ventricle-protective ventilation, its effect on RVD and ARDS mortality has yet to be proved in rigorous controlled trials.

## Conclusions

RVD and RVF are associated with adverse outcomes in patients with ARDS. Understanding the pathophysiology of RVD and the 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 vasodilation and prone positioning, that may improve prognosis in ARDS. Echocardiographic markers such as TAPSE and RV tissue doppler imaging 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 right ventricle-protective ventilatory strategy combined with extracorporeal support may be key in the management of patients with established RVD and form part of ARDS management guidelines if validated in prospective pragmatic trials.

## Acknowledgments

**Financial/Nonfinancial disclosures:** None declared.

## References

1. Ashbaugh D, Bigelow B, Petty T, Levine B. Acute respiratory distress in adults. *Lancet*. 1967;290(7511):319-323.
2. Amato M, Barbas C, Medeiros D, Magaldi R, Schettino G. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med*. 1998;338(6):347-354.
3. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342(18):1301-1308.
4. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159-2168.
5. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-2575.
6. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363(12):1107-1116.
7. Phua J, Badia JR, Adhikari NKJ, et al. Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. *Am J Respir Crit Care Med*. 2009;179(3):220-227.
8. Panwar R, Hardie M, Bellomo R, et al. Conservative versus liberal oxygenation targets for mechanically ventilated patients. A pilot multicenter randomized controlled trial. *Am J Respir Crit Care Med*. 2016;193(1):43-51.
9. Repessé X, Charron C, Vieillard-Baron A. Acute respiratory distress syndrome: the heart side of the moon. *Curr Opin Crit Care*. 2016;22(1):38-44.
10. Biswas A. Right heart failure in acute respiratory distress syndrome: an unappreciated albeit a potential target for intervention in the management of the disease. *Indian J Crit Care Med*. 2015;19(10):606-609.
11. Greyson CR. Pathophysiology of right ventricular failure. *Crit Care Med*. 2008;36(1 suppl):S57-S65.
12. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1-39.
13. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18(12):1440-1463.
14. Jardin F, Dubourg O, Bourdarias JP. Echocardiographic pattern of acute cor pulmonale. *Chest*. 1997;111(1):209-217.
15. Wadia SK, Shah TG, Hedstrom G, Kovach JA, Tandon R. Early detection of right ventricular dysfunction using transthoracic echocardiography in ARDS: a more objective approach. *Echocardiography*. 2016;33(12):1874-1879.
16. Shah TG, Wadia SK, Kovach J, Fogg L, Tandon R. Echocardiographic parameters of right ventricular function predict mortality in acute respiratory distress syndrome: a pilot study. *Pulm Circ*. 2016;6(2):155-160.
17. Mekontso Dessap A, Boissier F, Charron C, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. *Intensive Care Med*. 2016;42(5):862-870.
18. Lazzeri C, Cianchi G, Bonizzoli M, et al. Pulmonary vascular dysfunction in refractory acute respiratory distress syndrome before veno-venous extracorporeal membrane oxygenation. *Acta Anaesthesiol Scand*. 2016;60(4):485-491.
19. Lhéritier G, Legras A, Caille A, et al. Prevalence and prognostic value of acute cor pulmonale and patent foramen ovale in ventilated patients with early acute respiratory distress syndrome: a multicenter study. *Intensive Care Med*. 2013;39(10):1734-1742.
20. Boissier F, Katsahian S, Razazi K, et al. Prevalence and prognosis of cor pulmonale during protective ventilation for acute respiratory distress syndrome. *Intensive Care Med*. 2013;39(10):1725-1733.
21. Guervilly C, Forel J-M, Hraiech S, et al. Right ventricular function during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. *Crit Care Med*. 2012;40(5):1539-1545.
22. Bull TM, Clark B, McFann K, Moss M. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. *Am J Respir Crit Care Med*. 2010;182(9):1123-1128.
23. Osman D, Monnet X, Castelain V, et al. Incidence and prognostic value of right ventricular failure in acute respiratory distress syndrome. *Intensive Care Med*. 2009;35(1):69-76.
24. Vieillard-Baron A, Schmitt JM, Augarde R, et al. Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. *Crit Care Med*. 2001;29(8):1551-1555.

25. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-2533.
26. Zochios V, Jones N. Acute right heart syndrome in the critically ill patient. *Heart Lung Vessel*. 2014;6(3):157-170.
27. Snow RL, Davies P, Pontoppidan H, Zapol WM, Reid L. Pulmonary vascular remodeling in adult respiratory distress syndrome. *Am Rev Respir Dis*. 1982;126(5):887-892.
28. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. *Crit Care*. 2010;14(5):R169.
29. Zapol WM, Kobayashi K, Snider MT, Greene R, Laver MB. Vascular obstruction causes pulmonary hypertension in severe acute respiratory failure. *Chest*. 1977;71(2 suppl):306-307.
30. Sibbald WJ, Driedger AA. Right ventricular function in acute disease states: pathophysiologic considerations. *Crit Care Med*. 1983;11(5):339-345.
31. Gan CT, Holverda S, Marcus JT, et al. Right ventricular diastolic dysfunction and the acute effects of sildenafil in pulmonary hypertension patients. *Chest*. 2007;132(1):11-17.
32. Carvalho CRR, Barbas CSV, Medeiros DM, et al. Temporal hemodynamic effects of permissive hypercapnia associated with ideal peep in ARDS. *Am J Respir Crit Care Med*. 1997;156(5):1458-1466.
33. Takeshita K, Suzuki Y, Nishio K, et al. Hypercapnic acidosis attenuates endotoxin-induced nuclear factor-[kappa] B activation. *Am J Respir Cell Mol Biol*. 2003;29(1):124-132.
34. Stengl M, Ledvinova L, Chvojka J, et al. Effects of clinically relevant acute hypercapnic and metabolic acidosis on the cardiovascular system: an experimental porcine study. *Crit Care*. 2013;17(6):R303.
35. O'Croinin D, Ni Chonghaile M, Higgins B, Laffey JG. Bench-to-bedside review: permissive hypercapnia. *Crit Care*. 2005;9:51-59.
36. Morimont P, Lambermont B, Ghuysen A, et al. Effective arterial elastance as an index of pulmonary vascular load. *Am J Physiol Circ Physiol*. 2008;294(6):2736-2742.
37. Morimont P, Lambermont B, Desaive T, Blaffart F, Dauby P, Defraigne J-O. Right ventriculoarterial coupling in acute respiratory distress syndrome (ARDS) and expected benefits of CO2 removal therapy [abstract]. *J Crit Care*. 2013;28(6):e30.
38. Nichol AD, O'Cronin DF, Howell K, et al. Infection-induced lung injury is worsened after renal buffering of hypercapnic acidosis. *Crit Care Med*. 2009;37(11):2953-2961.
39. Salmon AA, Hotchkiss JR. Hypercapnic acidosis in ARDS: a tolerated side effect or an important therapeutic modality? *Crit Care*. 2007;11(1):304.
40. Dessap AM, Charron C, Devaquet J, et al. Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. *Intensive Care Med*. 2009;35(11):1850-1858.
41. Jardin F, Genevray B, Brun-Ney D, Bourdarias JP. Influence of lung and chest wall compliances on transmission of airway pressure to the pleural space in critically ill patients. *Chest*. 1985;88(5):653-658.
42. Chiumello D, Chidini G, Calderini E, Colombo A, Crimella F, Brioni M. Respiratory mechanics and lung stress/strain in children with acute respiratory distress syndrome. *Ann Intensive Care*. 2016;6(1):11.
43. Vieillard-Baron A, Loubieres Y, Schmitt JM, Page B, Dubourg O, Jardin F. Cyclic changes in right ventricular output impedance during mechanical ventilation. *J Appl Physiol*. 1999;87(5):1644-1650.
44. Paternot A, Repesse X, Vieillard-Baron A. Rationale and description of right ventricle-protective ventilation in ARDS. *Respir Care*. 2016;61(10):1391-1396.
45. Shekerdemian L, Bohn D. Cardiovascular effects of mechanical ventilation. *Arch Dis Child*. 1999;80(5):475-480.
46. Puybasset L, Cluzel P, Gusman P, Grenier P, Preteux F, Rouby JJ. Regional distribution of gas and tissue in acute respiratory distress syndrome. I. Consequences for lung morphology: CT Scan ARDS Group. *Intensive Care Med*. 2000;26(7):857-869.
47. Schmitt JM, Vieillard-Baron A, Augarde R, Prin S, Page B, Jardin F. Positive end-expiratory pressure titration in acute respiratory distress syndrome patients: impact on right ventricular outflow impedance evaluated by pulmonary artery Doppler flow velocity measurements. *Crit Care Med*. 2001;29(6):1154-1158.
48. Jardin F, Vieillard-Baron A. Is there a safe plateau pressure in ARDS? The right heart only knows. *Intensive Care Med*. 2007;33(3):444-447.
49. Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015;372:747-755.
50. Furian T, Aguiar C, Prado K, et al. Ventricular dysfunction and dilation in severe sepsis and septic shock: relation to endothelial function and mortality. *J Crit Care*. 2012;27(3):319.e9-319.e15.
51. Chan CM, Klinger JR. The right ventricle in sepsis. *Clin Chest Med*. 2008;29(4):661-676.
52. Michard F, Boussat S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med*. 2000;162(1):134-138.
53. Michard F, Chemla D, Richard C, et al. Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. *Am J Respir Crit Care Med*. 1999;159(3):935-939.
54. Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. *Crit Care*. 2014;18(6):650.
55. Michard F, Richards G, Biais M, Lopes M, Auler JO. Using pulse pressure variation or stroke volume variation to diagnose right ventricular failure? *Crit Care*. 2010;14(6):451; author reply 451.
56. Jardin F, Gueret P, Dubourg O, et al. Right ventricular volumes by thermodilution in the adult respiratory distress syndrome. *Chest*. 1985;88:34-39.
57. Rajaram SS, Desai NK, Kalra A, et al. Pulmonary artery catheters for adult patients in intensive care. *Cochrane Database Syst Rev*. 2013;2(2):CD003408.
58. Fichet J, Moreau L, Genée O, et al. Feasibility of right ventricular longitudinal systolic function evaluation with transthoracic echocardiographic indices derived from tricuspid annular motion: a preliminary study in acute respiratory distress syndrome. *Echocardiography*. 2012;29(5):513-521.
59. Stanko LK, Jacobsohn E, Tam JW, De Wet CJ, Avidan M. Transthoracic echocardiography: impact on diagnosis and management in tertiary care intensive care units. *Anaesth Intensive Care*. 2005;33(4):492-496.
60. Ryan T, Petrovic O, Dillon JC, Feigenbaum H, Conley MJ, Armstrong WF. An echocardiographic index for separation of right ventricular volume and pressure overload. *J Am Coll Cardiol*. 1985;5(4):918-927.
61. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F. Echo-Doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit. *Am J Respir Crit Care Med*. 2002;166(10):1310-1319.
62. Frémont B, Pacouret G, Jacobi D, Puglisi R, Charbonnier B, de Labriolle A. Prognostic value of echocardiographic right/left ventricular end-diastolic diameter ratio in patients with acute pulmonary embolism: results from a monocenter registry of 1,416 patients. *Chest*. 2008;133(2):358-362.
63. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23(7):685-713.
64. Beiderlinden M, Kuehl H, Boes T, Peters J. Prevalence of pulmonary hypertension associated with severe acute respiratory distress syndrome: predictive value of computed tomography. *Intensive Care Med*. 2006;32(6):852-857.
65. Chung JH, Kradin RL, Greene RE, Shepard JAO, Digumarthy SR. CT predictors of mortality in pathology confirmed ARDS. *Eur Radiol*. 2011;21(4):730-737.

66. Mercat A, Diehl JL, Meyer G, Teboul JL, Sors H. Hemodynamic effects of fluid loading in acute massive pulmonary embolism. *Crit Care Med*. 1999;27(3):540-544.

67. Goldstein JA, Harada A, Yagi Y, Barzilai B, Cox JL. Hemodynamic importance of systolic ventricular interaction, augmented right atrial contractility and atrioventricular synchorny in acute right ventricular dysfunction. *J Am Coll Cardiol*. 1990;16(1):181-189.

68. Mallat J, Meddour M, Durville E, et al. Decrease in pulse pressure and stroke volume variations after mini-fluid challenge accurately predicts fluid responsiveness. *Br J Anaesth*. 2015;115(3):449-456.

69. Ansari BM, Zochios V, Falter F, Klein AA. Physiological controversies and methods used to determine fluid responsiveness: a qualitative systematic review. *Anaesthesia*. 2016;71(1):94-105.

70. Goldstein JA, Barzilai B, Rosamond TL, Eisenberg PR, Jaffe AS. Determinants of hemodynamic compromise with severe right ventricular infarction. *Circulation*. 1990;82:359-368.

71. Kwak YL, Lee CS, Park YH, Hong YW. The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension. *Anaesthesia*. 2002;57(1):9-14.

72. Hirsch LJ, Rooney MW, Wat SS, Kleinmann B, Mathru M. Norepinephrine and phenylephrine effects on right ventricular function in experimental canine pulmonary embolism. *Chest*. 1991;100(3):796-801.

73. Price LC, McAuley DF, Marino PS, Finney SJ, Griffiths MJ, Wort SJ. Pathophysiology of pulmonary hypertension in acute lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2012;302(9):803-815.

74. Tayama E, Ueda T, Shojima T, et al. Arginine vasopressin is an ideal drug after cardiac surgery for the management of low systemic vascular resistant hypotension concomitant with pulmonary hypertension. *Interact Cardiovasc Thorac Surg*. 2007;6(6):715-719.

75. Vizza CD, Rocca GD, Roma AD, et al. Acute hemodynamic effects of inhaled nitric oxide, dobutamine and a combination of the two in patients with mild to moderate secondary pulmonary hypertension. *Crit Care*. 2001;5(6):355-361.

76. Chen EP, Bittner HB, Davis RD, Van Trigt P. Hemodynamic and inotropic effects of nitric oxide in pulmonary hypertension. *J Surg Res*. 1997;69(2):288-294.

77. Jeon Y, Ryu JH, Lim YJ, et al. Comparative hemodynamic effects of vasopressin and norepinephrine after milrinone-induced hypotension in off-pump coronary artery bypass surgical patients. *Eur J Cardiothorac Surg*. 2006;29(6):952-956.

78. Feneck RO, Sherry KM, Withington PS, Oduro-Dominah A. European Milrinone Multicenter Trial Group. Comparison of the hemodynamic effects of milrinone with dobutamine in patients after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2001;15(3):306-315.

79. Morelli A, Teboul JL, Maggiore SM, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. *Crit Care Med*. 2006;34:2287-2293.

80. Fierobe L, Brunet F, Dhainaut JF, et al. Effect of inhaled nitric oxide on right ventricular function in adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1995;151(5):1414-1419.

81. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med*. 1993;328(6):399-405.

82. Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev*. 2016;(6):CD002787.

83. Adhikari NK, Dellinger RP, Lundin S, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. *Crit Care Med*. 2014;42(2):404-412.

84. Sawheny E, Ellis AL, Kinasewitz GT. Iloprost improves gas exchange in patients with pulmonary hypertension and ARDS. *Chest*. 2013;144(1):55-62.

85. Cornet AD, Hofstra JJ, Swart EL, Girbes ARJ, Juffermans NP. Sildenafil attenuates pulmonary arterial pressure but does not improve oxygenation during ARDS. *Intensive Care Med*. 2010;36(5):758-764.

86. Blanch L, Albaiceta GM. Sildenafil for pulmonary hypertension in ARDS: a new pleasant effect? *Intensive Care Med*. 2010;36(5):729-731.

87. Schuchat A. Driving pressure and respiratory mechanics in ARDS. *N Engl J Med*. 2015;372(8):775-776.

88. Galiatsou E, Kostanti E, Svarna E, et al. Prone position augments recruitment and prevents alveolar overinflation in acute lung injury. *Am J Respir Crit Care Med*. 2006;174(2):187-197.

89. Vieillard-Baron A, Charron C, Caille V, Belliard G, Page B, Jardin F. Prone positioning unloads the right ventricle in severe ARDS. *Chest*. 2007;132(5):1440-1446.

90. Reis Miranda D, van Thiel R, Brodie D, Bakker J. Right ventricular unloading after initiation of venovenous extracorporeal membrane oxygenation. *Am J Respir Crit Care Med*. 2015;191(3):346-348.

91. Pellegrino V, Hockings LE, Davies A. Veno-arterial extracorporeal membrane oxygenation for adult cardiovascular failure. *Curr Opin Crit Care*. 2014;20:484-492.

92. Batchinsky AI, Jordan BS, Regn D, et al. Respiratory dialysis: reduction in dependence on mechanical ventilation by venovenous extracorporeal CO2 removal. *Crit Care Med*. 2011;39:1382-1387.

93. Morimont P, Guiot J, Desaive T, et al. Veno-venous extracorporeal CO2 removal improves pulmonary hemodynamics in a porcine ARDS model. *Acta Anaesthesiol Scand*. 2015;59:448-456.