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What is the clinical significance of pulmonary hypertension in acute respiratory distress syndrome? A review

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Abstract

Elevated pulmonary arterial pressures appear to be a prominent feature of the acute respiratory distress syndrome (ARDS). Current clinical guidelines for the management of ARDS do not specifically address treatment of pulmonary hypertension or associated right ventricular dysfunction because the clinical significance of this entity remains unclear. Interpretation of elevated pulmonary arterial pressures, pulmonary vascular resistance, and transpulmonary gradient as well as signs of right ventricular dysfunction is confounded by the effects of positive pressure ventilation. There does not appear to be a consistent relationship between the diagnosis of pulmonary hypertension or right ventricular failure and mortality in patients with ARDS, but it is unclear if right ventricular failure contributes to the mortality risk *per se* or if the underlying cause of pulmonary hypertension, including intravascular micro and macro thrombosis, are simply markers for systemic dysregulation of coagulation and fibrinolysis that may lead to multiorgan failure in ARDS. While studies of pulmonary vasodilator therapies have not shown a mortality benefit in ARDS, such trials have targeted improved oxygenation rather than improved pulmonary hemodynamics so that the possible contribution of improved right ventricular function to better outcomes has not been directly tested in large trials. Future studies are needed to determine if treatment of pulmonary hypertension and associated right ventricular dysfunction will affect mortality in patients with ARDS.

Keywords

pulmonary hypertension; acute cor pulmonale; right ventricular failure; acute respiratory distress syndrome; acute lung injury

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Introduction

Pulmonary arterial hypertension was first identified as being a common feature of the acute respiratory distress syndrome (ARDS) by Zapol and Snider in 1977.[1] Elevated mean pulmonary artery pressures and pulmonary vascular resistance were identified based on hemodynamic studies, and both pre and post-mortem studies identified the presence of widespread fibrin thrombosis of small and large pulmonary arteries as well as pulmonary vascular remodelling in patients with ARDS.[2, 3] While subsequent studies have confirmed the prevalence of pulmonary hypertension in ARDS and have investigated downstream effects including the development of acute cor pulmonale, significant debate remains regarding the clinical significance of this entity in ARDS. Multi-organ failure rather than refractory hypoxemia or acute cor pulmonale has been most consistently reported as the leading cause of death in ARDS[4-7], raising the question of whether pulmonary hypertension is simply an epiphenomenon of systemic alterations of coagulation and fibrinolysis that subsequently leads to death.[8] Clinical trials with pulmonary vasodilator therapies have not identified a mortality benefit to date, relegating these therapies for rescue of refractory hypoxemia rather than as part of conventional clinical management for ARDS.[9] Several recent excellent reviews have focused on the pathophysiology of pulmonary hypertension[10] and strategies for right ventricular protection in ARDS.[11] The purpose of this review is to provide a critical assessment of the current literature to date regarding the clinical significance of pulmonary hypertension in ARDS.

Key considerations when evaluating studies on pulmonary hypertension in ARDS

There are some important limitations to be kept in mind when reviewing published literature on pulmonary vascular disease in ARDS. In general, studies in ARDS have been complicated by a lack of a uniform definition for the syndrome since it was first described in 1967,[12] with major changes proposed in 1988, 1994, and 2011 in both severity scoring and case definition.[13-15] Efforts to identify the incidence of pulmonary artery hypertension have been further hampered by different methods used to estimate abnormal pulmonary vascular pressures (computed tomography vs. echocardiography) when compared to the gold standard, direct measurement of intracavitary pressures using pulmonary artery catheters. In addition, different methods and different criteria to define right heart dysfunction (pulmonary arterial catheter pressure measurement vs. transthoracic or trans-esophageal echocardiography) have been proposed and studied. Temporal changes in the standard of care in ARDS with the introduction of lung protective ventilation[16] and conservative fluid management[17] may also have led to changes in the observed prevalence of pulmonary vascular disease, both by changing the disease progression and lowering intravascular pressures.[18] Finally, the vast majority of available studies are both observational and small; statistical analyses in these studies are generally performed at the univariate level precluding adjustment for important confounders in the relationship between pulmonary vascular disease and mortality. All of these issues must be kept in mind when reviewing the literature on pulmonary vascular disease in ARDS.

Search Strategy

A thorough literature search was conducted to retrieve all studies relevant to the topic. No restrictions for language or date were applied. We focused on trials performed in human subjects. Peer-reviewed journal articles and published abstracts were identified from various sources from inception through May 24, 2013. We searched MEDLINE (PubMed) using the following terms: ("Hypertension, Pulmonary"[Mesh] OR pulmonary hypertension[tiab] OR pulmonary arterial hypertension[tiab] OR pulmonary artery hypertension[tiab] OR pulmonary hypertensive[tiab] OR pulmonary vascular[tiab] OR vd/vt[tiab] OR dead space[tiab] OR right ventricle[tiab] OR right ventricular[tiab]) AND ("Respiratory Distress Syndrome, Adult"[Mesh] OR "Acute Lung Injury"[Mesh] OR acute respiratory distress syndrome[tiab] or adult respiratory distress syndrome[tiab] or shock lung[tiab] OR acute lung injur*[tiab]) NOT ("Animals"[MeSH] NOT "Humans"[MeSH]). EMBASE was searched using the following terms: 'pulmonary hypertension'/exp OR 'heart right ventricle'/exp AND 'adult respiratory distress syndrome'/de NOT ([animals]/lim NOT [humans]/lim). The reference lists from included articles were hand-searched for additional relevant studies.

Pulmonary vascular pathology in ARDS

Pulmonary vascular obstruction with reduction in the cross sectional area of the pulmonary vasculature has been described in both early and late ARDS. Pre-mortem bedside angiography performed in newly inserted pulmonary artery catheters first identified the presence of pulmonary artery filling defects in patients with ARDS; the presence of these defects was highly correlated with the presence of disseminated intravascular coagulation, high pulmonary vascular resistance, and mortality. [2] Open lung biopsies in patients with ARDS have also demonstrated widespread fibrin thrombosis of both large and small pulmonary arteries.[19] Subsequent postmortem studies evaluating the chronicity of these lesions found that while pulmonary vascular obstruction in those who died less than 10 days after intubation was largely due to thrombosis in combination with hemorrhage and edema, those who died after 10 days of intubation had fibrocellular intimal obliteration of the pulmonary vasculature resulting in many fewer perfused arterioles. Longer term survivors have extensive pulmonary vascular remodelling. [20, 21] In conjunction with these anatomical changes, early studies also support the role of pulmonary vascoconstriction in elevated pulmonary vascular resistance.[22] Pulmonary vasodilator trials demonstrated a fall in pulmonary vascular resistance and pressure in the presence of elevated pulmonary arterial pressures and resistance.[23] Such an observation confirms pathologic vasoconstriction. While clear anatomic lesions and pathologic vasoconstriction have been found to explain the presence of pulmonary arterial hypertension in ARDS, the contribution of these processes to mortality remains unclear.

Prevalence of disease

The current diagnostic criteria for the diagnosis of pulmonary hypertension due to non-cardiac causes requires invasive hemodynamic assessment to document a mean pulmonary artery pressure (mPAP) greater than 25 mm Hg with a pulmonary artery occlusion pressure

(PAOP) less than 15 mm Hg at rest. Additional requirements are an elevated pulmonary vascular resistance (PVR) of greater than 3 Woods units. An elevated transpulmonary gradient (TPG, defined as mPAP minus PAOP greater or equal to 12 mm Hg) is sometimes used when simultaneous measurements of cardiac output and pulmonary blood flows are not available.[24] One important caveat for this definition is that these criteria have been developed for spontaneously breathing subjects at rest and it is unclear how they translate to mechanically ventilated patients in the acute setting who may have a hyperdynamic circulation in response to systemic inflammation or are receiving vasopressors for shock. It is clear that positive pressure ventilation dynamically alters these hemodynamic measures through complex cardiopulmonary interactions and by simply raising intrapleural and thus juxtacardiac pressures. Thus an elevated intracavitary mPAP measured by pulmonary artery catheterization may not be a faithful measure of transmural pressure and pulmonary vascular disease, especially in patients with high airway pressures. Potkin et al [25] first described the effect of positive end expiratory pressure (PEEP) on measured hemodynamic variables; serial up-titration of PEEP from 0 to 20 cm H_20 led to an increase in mPAP from 24 to 31 mm Hg and PVR from 151 to 197 dynes.s.m^2/cm^5. Fougeres et al [26] recently extended this study by acutely up-titrating PEEP then investigating the impact of a passive leg raise to simulate a volume challenge at high PEEP. With high PEEP, mPAP on average increased from 25 to 28 mm Hg, TPG increased from 14.5 to 16.4 mm Hg, and PVR from 310 to 385 dynes.s.m^2/cm^5. A passive leg raise led to a significant decrease in mPAP, TPG, and PVR to 26.9 mmHg, 13.5 mm Hg, and 321 dynes.s.m^2/cm^5 respectively. All these changes were statistically significant, underlying the concomitant contribution of positive pressure ventilation and volume status to the hemodynamic parameters that are used to diagnose pulmonary hypertension. Additional studies also highlight the impact of permissive hypercapnea on these parameters, with one study demonstrating a transient increase in mPAP by 8.8 mmHg with no impact on PVR in the first 36 hours of ventilation. [27]

Not surprisingly then, elevated mPAP is found in a large proportion of mechanically ventilated patients with ARDS. Zapol et al [1] first reported a 100% prevalence of pulmonary artery hypertension in 30 patients with severe ARDS with P/F ratios of less than 100. Subsequent large multicenter studies have examined the prevalence of pulmonary hypertension in ARDS and report figures ranging from 73%[28] to 92%[29] early in the course of ARDS; variation in prevalence seems to be related to both the severity of ARDS and the ventilation strategy used (see Table 1 for comprehensive list of studies).

Given the difficulty in interpreting elevated mPAP, PVR, and TPG in a mechanically ventilated patient, the presence or absence of right ventricular failure has been proposed as a better clinical parameter. Estimates of acute right ventricular dysfunction in ARDS using pulmonary artery catheters have used the criteria of central venous pressure greater than PAOP (CVP>PAOP), with one large study reporting an incidence of 9.6%.[30] Other studies have used estimates of right ventricular function and ejection fraction based on thermodilution, although the presence of tricuspid regurgitation, which may also be impacted by mechanical ventilation,[31] complicates and perhaps invalidates this measurement approach. The gold standard for the diagnosis of acute right ventricular dysfunction remains trans-esophageal echocardiography (TEE), with the presence of right ventricular dilatation (defined as the right to left end diastolic area ratio greater than 0.6 for

moderate dilatation and 1 as severe dilatation) combined with paradoxical septal motion as the diagnostic criteria for right ventricular failure (or acute *cor pulmonale*, ACP,[32]). Using this definition, the incidence of right ventricular failure has been reported from 22-27% [32, 33] in larger trials, although smaller trials report rates ranging from 7% to 56%, [28, 34-36]. A recent study has identified an association between the use of low tidal volume ventilation and a decreased incidence of acute right ventricular failure.[32]

The diagnosis of right ventricular dysfunction using either pulmonary artery catheterization or trans-esophageal echocardiography is also affected by ventilator settings, with tidal volume, plateau pressures, and PEEP having a direct impact on assessed right ventricular function.[37-39] However, echocardiography can provide a comprehensive evaluation of both systolic and diastolic right ventricular function. High tidal volumes have been demonstrated to increase right ventricular output impedance.[40] In an univariate analysis of 352 ARDS patients who received bedside transesophageal echocadiography, the incidence of acute cor pulmonale as defined by TEE was associated with higher plateau pressures, with the incidence being 20% for plateau pressures 18-26, 39% for plateau pressures 27-35, and 42% for plateau pressures >35 cm H_2O.[41] High PEEP has also been associated with an increase in the right to left ventricular end diastolic ratio[26] as well as right ventricular dilatation[39] even in the presence of stable plateau pressures. The clinical significance of these effects of PEEP are unclear as recent meta-analyses of randomized trials of higher versus lower PEEP strategies suggest a qualitative interaction such that higher PEEP strategies may be beneficial in the more severe subgroup and perhaps harmful in the milder end of the ARDS spectrum.[42, 43]

Association between pulmonary arterial hypertension or right ventricular failure and mortality in ARDS

Is pulmonary hypertension in ARDS important in determining the clinical course of a patient with ARDS? Several studies using either pulmonary artery catheters or echocardiography to evaluate the presence or absence of pulmonary hypertension and right ventricular failure have yielded conflicting results (see Table 1). Two studies performed in subjects who did not receive lung protective ventilation have supported an association. In a multivariate analysis based on a multicenter European observational study of ARDS, both the right ventricular to left ventricular stroke work ratio (RVSW/LVSW) and the systolic pulmonary arterial pressure were independent predictors of mortality.[44] A multivariate analysis based on a single center study of 259 patients with ARDS found that CVP>PAOP as a metric to diagnose right ventricular failure was associated with increased hospital mortality.[45] A single center study performed in subjects receiving lung protective ventilation found that in a multivariate analysis, right ventricular failure as assessed by trans-esophageal echocardiography was associated with an increased risk of 28-day mortality; in this patient population, however, ICU mortality was higher than 28-day mortality suggesting that the subjects had a prolonged ICU course.[46] Perhaps the most convincing evidence comes from an ancillary study based on the ARDS Network's Fluid and Catheter Treatment Trial (FACTT), where both the trans-pulmonary gradient and median highest pulmonary vascular

resistance index was associated with mortality, although any recorded value of PAP or CVP>PAOP was not.

Conversely, a number of studies do not support the association between pulmonary vascular dysfunction or acute *cor pulmonale* and mortality in patients with ARDS. While an early study by a Jardin and colleagues found an association between RV dysfunction based on trans-esophageal echocardiography and death in ARDS,[47] subsequent studies from this group found no association between either systolic pulmonary artery pressures or acute *cor pulmonale* and mortality.[32, 48] Three additional large studies also dispute an association between pulmonary vascular disease or right ventricular failure and mortality in ARDS,[30, 34, 49] with two performed in the era of lung protective ventilation.

Further conflicting evidence regarding the association comes from mortality studies in ARDS. While most deaths in patients with ARDS are due to multi-organ dysfunction or sepsis,[4-7] one study with 103 participants did report that 29.7% of deaths in their cohort was due to right ventricular failure, with 51.3% due to sepsis related multi-organ failure.[29] More recently, Thille and coworkers reported that for patients with severe ARDS as defined by the new Berlin definition, the syndrome of refractory hypoxemia was observed in the 6 hours prior to death in 27% and both refractory hypoxemia and shock in an additional 21%. [50] It is unclear if pulmonary vascular disease and/or right heart failure contributed to these outcomes.

Finally, another metric proposed to assess pulmonary vascular disease in ARDS is the proportion of dead space ventilation (V_D/V_T). Increased V_D/V_T is thought to correlate with the degree of pulmonary vascular injury, and has been postulated to be a surrogate indicator for pulmonary hypertension though airway pressures may also modulate this measure. Increased V_D/V_T has been consistently associated with mortality in patients with ARDS. One study estimated an increased odds of death by 45% for every 0.05 increase in V_D/V_T; [51] this finding has been corroborated in an independent cohort.[52] However, V_D/V_T does not seem to correlate well with either pulmonary artery pressure [34] or right ventricular ejection fraction [53] using invasive hemodynamic measures. This does not preclude an association between pulmonary vascular dysfunction and mortality in ARDS. Rather, elevated pulmonary arterial pressures from pulmonary vascular dysfunction may be a surrogate marker for a systemic process that leads to pulmonary and systemic vascular dysfunction, perhaps from dysregulated coagulation, fibrinolysis, and microvascular thrombosis; such a hypothesis would suggest that treatment of PAH with vasodilator therapy would not necessarily improve mortality in ARDS.

Pulmonary vasodilator therapies in ARDS

A number of trials have been performed to evaluate the impact of both intravenous and inhaled pulmonary vasodilators on mortality outcomes in ARDS (see Table 2 for all identified randomized controlled trials evaluating therapies targeting pulmonary vascular dysfunction or acute cor pulmonale in ARDS). To date, none of these therapies have shown an impact in mortality although a number of caveats should be noted. First, all of these randomized controlled trials evaluated either fixed doses or titrated doses based on

improvements in oxygenation. No studies titrated vasodilators to changes in pulmonary arterial pressures or right ventricular function. From trials of different ventilator strategies in ARDS, we know that acute improvements in oxygenation are not necessarily associated with better clinical outcomes,[16, 54] and it may well be the case that pulmonary vasodilator therapy titrated to oxygenation is focused on an endpoint that is not associated with survival. Only a few of these studies specifically assessed the impact of these vasodilators at the studied doses on pulmonary hemodynamics or right ventricular function. From these small studies it remains unclear if improved right ventricular function with pulmonary vasodilation improves outcomes.

When evaluating the impact of vasodilator therapy, several observations can be made. First, systemic vasodilators do not improve and may worsen arterial oxygenation,[55] although in at least one study they appear to reduce pulmonary vascular resistance.[23, 56] Second, inhaled nitric oxide, the best studied pulmonary vasodilator, does not have a sustained impact on arterial oxygenation as the initial beneficial effect is transient and disappears within 48 hours after initiation of therapy.[57-62] Third, doses of vasodilators that improve oxygenation appear to differ from doses that improve pulmonary hemodynamics or right ventricular function.[63, 64] Therefore these negative trials of pulmonary vasodilators have not systematically evaluated the potential beneficial effects of lowering pulmonary artery pressures and improving right ventricular function directly. Interestingly, one study using a porcine model of septic shock found that nitric oxide synthase inhibition led to increased pulmonary pressures and subsequent death from right ventricular failure with no impact on left ventricular function. This suggests additional potential benefits of using nitric oxide over other pulmonary vasodilators in septic shock and potentially in ARDS as well.[65]

Several non-vasodilator therapies have targeted right ventricle function directly. Levosimendan is both a pulmonary vasodilator and a cardiac inotrope, and in a small pilot study of 35 patients with ARDS and septic shock, a 24 hour infusion led to decreased mPAP, TPG, and a higher right ventricular ejection fraction although no mortality data was reported.[66] In an observational trial of 42 subjects with severe ARDS with P/F ratio <100, the prone position led to a significant reduction in right ventricular enlargement and septal dyskinesia seen in acute cor pulmonale.[35] Therapies targeting dysregulated coagulation have also been studied. Drotrecogin alpfa (activated), a recombinant activated protein C that has since been withdrawn from the market, was studied in a randomized controlled trial of patients with ARDS but without septic shock.[67] Oxygenation indices were not improved but there was a significant reduction in dead space fraction. Mortality, however, was not different between treatment and control groups although overall mortality was low at 13.5% compared to 26-35% reported in other randomized controlled trials in ARDS.[68] It is unclear, therefore, whether this trial was null due to the low overall mortality in the cohort or whether attempts to modulate the dysregulation of coagulation observed in patients with ARDs is ineffective. Several other small observational studies have looked at other attempts to modulate dysregulated coagulation; one uncontrolled study of 5 patients with ARDS who received streptokinase found an improvement in mPAP, PVR, and P/F ratio with angiography demonstrating recanalization of thrombosed pulmonary arteries.[69] A phase I study of nebulized heparin was able to demonstrate safety but no improvement in oxygenation, lung compliance, or dead space fraction.[70] Additional studies targeting either

right ventricular function or dysregulated coagulation are needed. Until such trials are done, no definitive conclusion regarding the utility of these therapies can be drawn from the available evidence.

Finally, a recent follow-up study from a randomized controlled trial for fixed-dose inhaled nitric oxide[61] evaluated pulmonary function tests 6 months after hospital discharge in survivors of ARDS. The treatment group had a significantly higher TLC (5.54±1.42 vs 4.81±1 liters) as well as percent predicted FEV_1, FVC, and FEV_1/FVC. While this study was hampered by issues including a significant loss to follow-up (only 92 out of 302 survivors participated), it generates interesting hypotheses about alternative endpoints to therapies for pulmonary hypertension in ARDS for future study. The puzzling finding of increased renal toxicity with inhaled nitric oxide in a recent meta-analysis[71] will need to be better understood before undertaking large randomized trials designed to improve pulmonary function.

Conclusion

A high prevalence of pulmonary arterial hypertension and right ventricular failure has been reported in ARDS yet the contribution, if any, of acute *cor pulmonale* to mortality or other adverse outcomes is unclear. Traditional diagnostic criteria for pulmonary arterial hypertension in this patient population may be unreliable, in part due to the effects of positive pressure ventilation and a circulation not at rest during the stress of acute illness and its treatment. It is unclear if pulmonary arterial hypertension is an epiphenomen of the widespread dysregulation in coagulation and fibrinolysis that also leads to systemic vascular dysfunction, multi-organ dysfunction, and death,. Randomized controlled trials of pulmonary vasodilator therapy to date do not suggest a mortality benefit but have not targeted changes in pulmonary arterial pressures or right ventricular function directly; it remains unclear if improvement in these variables improves outcomes. Future intervention studies evaluating therapies targeting improvement in pulmonary arterial pressures or right ventricular function may help determine if normalization of pulmonary hemodynamics or strategies to protect right ventricular function improves survival. Studies targeting dysregulated coagulation, endothelial function, and fibrinolysis are needed to see if prevention of pulmonary or systemic arterial thrombi alters outcomes. Finally, a consensus on diagnostic criteria for pulmonary arterial hypertension in mechanically ventilated patients is needed.

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Key Points

- The presence of elevated pulmonary arterial pressures and right ventricular dysfunction is directly and dynamically affected by positive pressure ventilation; traditional diagnostic criteria for pulmonary hypertension may not apply to mechanically ventilated patients
- While widespread thrombosis of both small and large pulmonary arteries and pulmonary vascular remodeling associated with elevated pulmonary arterial pressures has been identified in patients with ARDS, it remains unclear whether the associated pulmonary hypertension in this setting directly contributes to mortality
- Randomized trials of vasodilator therapies in ARDS have targeted improvements in oxygenation rather than improved pulmonary hemodynamics and have not shown a mortality benefit; it is not clear whether such therapies targeted at lowering pulmonary arterial pressures or optimizing right ventricular function would improve outcomes

Table 1

Observational studies of pulmonary artery hypertension or right ventricular failure in ARDS[†]

Author	Study period	N	P/F ratio	Tidal Volume	PEEP (cm H_2O)	Diagnostics	Definition of PAH	Definition of RV failure	Prevalence of PAH	Prevalence of RV failure	Outcome Association	Study Mortality
Zapol et al 1977 [1]	1977	30	-	-	Strategy: 10	PA catheter	mPAP≥25 mm Hg	-	100%	-	Not explicitly tested	80% [a]
Greene et al 1981 [2]	1977-1979	40	-	-	-	PA catheter and bedside pulmonary angiography	-	-	48% (with pulmonary arterial filling defects)	-	Pulmonary arterial filling defects associated with mortality (79% vs 39%, p<0.05) in univariate analysis	63% [a]
Jardin et al 1985 [47]	1985	23	-	11.1±3.8 ml/kg	Strategy: 5 to 15	PA catheter and TTE	-	RV EDA/LV EDA ≥1 with septal dyskinesis	-	21.7%	Not explicitly tested though all with RV failure died	47.8% [a]
Squara et al 1998 [44]	1985-1987	586	132±67	Strategy: 10 ml/kg	8.4±4	PA catheter	-		-	-	RVSW/LVSW (OR 10-35 and systolic PAP (OR 10.4-10.08) associated with death	39% [a]
Monchi et al 1998 [45]	1992-1995	259	101 [75-138]	8.6 [IQR 7.1-9.5] ml/kg reported	-	PA catheter[c]	-	CVP>PAOP	-	-	CVP>PAOP associated with death (OR 1.5-17.1)	35% hospital mortality
Vieillard-Baron et al 2001[b] [32]	1996-2001	75	-	Strategy: 6 to 9 ml/kg, plateau < 30 cm H_2O	7±3	TEE	-	RV EDA/LV EDA>0.6 with septal dyskinesis	-	25.3%	No association between sPAP or ACP and death on univariate testing	32% [a]
Page et al 2003[b] [48]	1993-2001	150	134±56 in survivors, 131±86 in nonsurvivors	Strategy: 6-9 ml/kg, plateau <30 cm H_2O	7±2	TEE	-	RV EDA/LV EDA>0.6 with septal dyskinesis	-	24.7%	No association between ACP and death in multivariate analysis	38% hospital mortality
Beiderlinden et al 2006 [29]	-	103	94±37	Strategy: 6ml/kg	Strategy: ≥10	PA catheter, TEE, and contrast enhanced CT	mPAP≥25 mm Hg	RA>4cm and RV EDA > LV EDA with mPAP≥25 mm Hg	92.2%	-	Backward selection model did not include measures of PA pressure as predictor although it does not appear that PAH or RV failure explicitly tested	35.9% [a]
Jardin et al 2007[b] [41]	1980-2006	352	-	Not recorded, but divided into 3 groups (mean plateau 18-26, 27-35, and over 35 cm H_2O)	-	TTE and TEE	-	RV EDA/LV EDA>0.6 with septal dyskinesis	-	28.9% [d]	Not explicitly tested although mortality also associated with plateau	Range from 46-60% depending on plateau pressures[a] 46% in plateau 18-26 cm H_2O 52% in plateau 27-35 cm H_2O 60% in plateau >35 cm H_2O
Cepkova et al 2007 [34]	2004-2006	42	177 ±80	7±3 ml/kg	9.7±3.6	TTE	PA systolic pressure by tricuspid regurgitant jet.	RV size and function by qualitative assessment	-	-	Univariate analysis with hospital mortality. No difference in mean sPAP in those who died vs survived nor those <7 days ventilator free days out of 28. 11(26%) had	36% hospital mortality

Author	Study period	N	P/F ratio	Tidal Volume	PEEP (cm H_2O)	Diagnostics	Definition of PAH	Definition of RV failure	Prevalence of PAH	Prevalence of RV failure	Outcome Association	Study Mortality
											RV dilation, 3(7%) with RV dilation and systolic dysfunction. No association with RV dilation, 3(7%) with RV dilation and systolic dysfunction. No association wi RV dilation, 3(7%) with RV dilation and systolic dysfunction. No association wi RV dilation, 3(7%) with RV dilation and systolic dysfunction. No association wi RV dilation, 3(7%) with RV dilation and systolic dysfunction. No asso	
Osman et al 2009 [30]	1999-2001	145	115±26 in RVF, 98±35 otherwise	8.8±1.9 ml/kg	7±4 cm	PA catheter	-	mPAP>25mmHg, CVP>PAOP, SV index<30 mL m2	-	9.6%	multivariate analysis, RVF not associated with mortality but mPAP and CVP>PAOP was independently associated with mortality	54.4% 28-day mortality 68% 90-day mortality
Dessap et al 2010 [33] [e]	2004-2009	203	114±45 in those without PFO with shunt, 122±58 in those with	6.5±1.0 ml/kg in those without PFO, 6.7±1.2 ml/kg in those with PFO	10±3 cm in those with PFO, 11±4 in those without	TEE	-	RV EDA/LV EDA>0.6 with septal dyskinesis	-	21.7%	-	49.2% ICU mortality 52.7% hospital mortality 37.9% 28-day mortality
Bull et al 2010 [28]	2000-2005	501	162±74 in survivors, 155±74 in non-survivors	Strategy: 6ml/kg	9.2±3.9 in survivors, 9.1±4.1 in non-survivors	PA catheter	TPG≥12 mm Hg	CVP>PAOP	73%	12.0%	In multivariate analysis for 60 day mortality, TPG (OR 1.03 [1.02-1.05]) and PVRi(1.07[1.01-1.13]) associated with mortality but not PAOP≥CVP or any measure of PAP	27% 60-day mortality
Legras et al 2011 [36]	2011	84	-	-	-	TTE and TEE	-	-	-	14.9%	-	-
Boissier et al 2013 [46] [e]	2004-2009	226	120±51 in those without RVF, 111±52 in those with RVF	6.6±1.0 in those without RVF, 6.2±1.2 in those with RVF	9±4 in those without RVF, 8±3 in those with RVF	TEE	-	RV EDA/LV EDA>0.6 with septal dyskinesis	-	21.7%	In multivariate analysis for 28 day mortality, RVF was associated with 28 day mortality (OR 2.18 [1.02-4.67])	50.4% ICU mortality 52.7% hospital mortality 40.3% 28-day mortality

[†] values reported are mean±standard deviation or median [interquartile range]

[a] Mortality measure (ICU vs hospital vs. 28 day vs. 60 day) not defined in study

[b] These 3 studies are from same research group and contain overlapping sets of subjects

[c] PA catheter placed in 200 (77%) subjects

[d] in overall cohort although incidence increased with higher plateau pressures

[e] These 2 studies are from same research group and contain overlapping sets of subjects

Abbreviations: CVP Central venous pressure; ICU intensive care unit; mPAP mean pulmonary artery pressure; PA Pulmonary artery; PAH Pulmonary arterial hypertension; PAOP Pulmonary artery occlusion pressure; PFO Patent foramen ovale; PVRi Pulmonary vascular resistance index (in Woods units); RA Right Atrium; RVF Right ventricular failure; RV EDA/LV EDA Right ventricular end diastolic area to left ventricular end diastolic area ratio; TEE Trans esophageal echocardiography; TPG Trans-pulmonary gradient; TTE Transthoracic echocardiography

Table 2

Randomized controlled trials of pharmacologic therapies in ARDS

Author Publication Year	Therapy	N	P/F ratio	Tidal volume	PEEP (cm H_2O)	Oxygenation impact	PAH impact	RV impact	Mortality
Bone et al 1989 [23]	PGE1 30 ng/kg/min for 7 days	100	125.8±35 in PGE1 142±49.4 Placebo	-	9.5(4.8) in PGE1 9.9 (5.1) in control	-	PVR decreased on day 5 and 6, not 7 and 8	-	30 day -control: 48% -treatment: 60%
Troncy et al 1997 [62]	NO 0 .5-40 ppm titrated daily	30	119.4±13.6 in NO 152.1±18.5 in control	-	-	P/F increased on day 1 only	-	-	30 day -control: 53.3% -treatment: 60%
Michael et al 1998 [58]	NO 5-20 ppm for at least 72 hours	40	59±3 in NO 62±4 in control	7.7±1 ml/kg in NO 7.4±1 ml/kg in control	15±1 in NO 16±1 in control	P/F improved at 12 but not 24 and 72 hours	-	-	Not reported [c] -control: 60% -treatment: 73.3%
Abraham et al 1999 [56]	PGE1 0.15-3.6 mcg/kg/hr q6hrs for 7 days	348	146.2±60.7 in PGE1 141.3±66 in control	-	-	Shorter time to achieve P/F >300	-	-	28 day -control:29% -treatment: 32%
Lundin et al 1999 [59]	NO 1-40 ppm for up to 30 days	180	102.8±32.3 NO 100.5±33.0 placebo	-	8.4±2.5 in NO 8.9±2.7 in control	Decreased incidence of severe respiratory failure[a]	-	-	30 day -control: 40.2% -treatment: 44.1% 90 day -control: 43.7% -treatment: 51.6%
Gerlach et al 2003 [60]	NO 10 ppm for 96 hrs	40	113±28 in NO 104±26 in control	635.5 [340-785] ml in NO 651.5 [365-760] ml in control	-	Decreased FiO_2 for <24 hours	-	-	Not reported [c] -control: 80% -treatment: 85%
Taylor et al 2004 [61]	NO 5 ppm up to 28 days	385	133±42 in NO 138±43 in control	10±2.6 ml/kg in NO 10±2.6 in control	10±3 in NO 10±2 in control	Increase PaO_2 for <48 hours	-	-	28 day -control: 20% -treatment: 23%
Morelli et al 2006 [66]	levosimendan 0.2 mcg/kg/min for 24 hours	35	168±19 in Levosimendan 181±20 in control	Strategy: 6-8 ml/kg	-	No change in PaO_2	Decrease in mPAP and TPG in treatment group	Improved RVEF in treatment group	-

Author Publication Year	Therapy	N	P/F ratio	Tidal volume	PEEP (cm H_2O)	Oxygenation impact	PAH impact	RV impact	Mortality
Liu et al 2008 [67]	APC 24 mcg/kg/h for 96hr	75	158±67 in APC 174±63 in control	6.7±1.4 in APC 6.9±1.5 in control	9.4±4.6 in APC 8.5±3.2 in control[b]	No change in PaO_2	Significant reduction in dead space fraction	-	60 day - control: 13.5% - treatment: 13.5%

[†] values reported are mean±standard deviation or median [interquartile range]

[a] severe respiratory failure defined as FiO_2>.9 with PaO2<8 kPa in 3 arterial blood gases 4 hours apart)

[b] Note dead space higher in APC (.62±.12) than placebo (0.55±.12), p=.03

[c] Mortality measure (ICU vs hospital vs. 28 day vs. 60 day) not defined in study

Abbreviations: APC Activated protein C; mPAP Mean pulmonary artery pressure; NO Nitric oxide; PAH Pulmonary artery hypertension; PEEP Positive end-expiratory pressure; PGE1 Prostaglandin E1; PVR Pulmonary vascular resistance; RV Right ventricle; RVEF Right ventricular ejection fraction; TPG Trans-pulmonary gradient