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SPECIAL FEATURE

Right Heart Protective Ventilation Strategies in Acute Respiratory Distress Syndrome

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Mr. Kallet reports no financial relationships relevant to this field of study.

The pulmonary vascular system must conduct the entire cardiac output through the lungs. Unlike other organs, the lungs possess a massive capillary system imbedded into a considerably less dense, air-tissue structure. As such, the pulmonary vasculature functions as a low-resistance, high-capacitance system reflected in the design of the right ventricle (RV): a thin-walled muscular chamber. Relatively small changes in pulmonary arterial pressure (PAP) are associated with large volume changes.

Given these limitations, RV performance is vulnerable to the effects of both pulmonary disease and positive pressure ventilation. A hallmark of acute respiratory distress syndrome (ARDS) is pronounced pulmonary arterial and capillary endothelial injury resulting in arterial and microvascular thrombosis; vascular constriction from the effects of hypoxemia; hypercapnia and acidosis; vascular compression from pulmonary edema; and alveolar hyperinflation caused by mechanical ventilation.[1-4] Over time, these acute changes evolve into a chronic phase characterized by vascular smooth muscle hypertrophy, fibrosis, and capillary obliteration.[5]

Pulmonary arterial hypertension (PAH) is defined as a mean PAP ≥ 25 mmHg when the corresponding pulmonary arterial occlusion pressure (PAOP) is < 15 mmHg.[6] PAH can lead to RV dysfunction and acute cor pulmonale (ACP), characterized by severe RV dilation and paradoxical septal motion during systole, eventually causing left ventricular failure and

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progressive systemic hypotension if not reversed.[7] It should be noted, however, that moderate RV dilation itself is not indicative of dysfunction; when combined with interventricular dyskinesia, it represents RV overload.[8] The incidence of ACP in patients with ARDS is 22-25% and 50% in those with severe ARDS. [8-11] Patent foramen ovale with right-to-left intracardiac shunting occurs in approximately 16-19% of patients with ARDS and may further complicate management of hypoxemia.[8,9]

Prior to the advent of lung protective ventilation (LPV) strategies, there was a strong association between severity of PAH and mortality in ARDS. Mortality rates of 88% were reported in those with pulmonary vascular obstruction on angiography vs 50% in those with elevated pulmonary vascular resistance (PVR) but no vascular obstruction.[12] Patients whose right atrial pressure exceeded PAOP also had a mortality risk that was five-fold greater.[13] A large study of hemodynamic profiles in ARDS found that an elevated right over left ventricular stroke work index ratio was also highly predictive for mortality.[14]

Even in the era of LPV, increased pulmonary vascular resistance remains a common finding in ARDS, although the exact relationship between ACP and mortality in ARDS has become less clear. Some studies have reported a mortality rate of 32% in ARDS, regardless of the presence or absence of ACP.[8] Others argue that ACP does not appear to influence mortality in ARDS when not aggravated by mechanical ventilation strategies (e.g., high positive end-expiratory pressure [PEEP], high plateau pressure [Pplat]).[15] In contrast, Boissier et al found that in moderate-to-severe ARDS managed with LPV, the development of ACP carries a significantly higher hospital mortality (67% vs 49%).[16] Likewise, a post-hoc analysis of the ARDS Network FACTT study found that patients with an elevated transpulmonary gradient (mean PAP-PAOP > 12 mmHg) also had a substantially higher mortality rate (30% vs 19%).[17]

The concepts of LPV and right heart protective ventilation strategies have been considered together. However, the latter approach imposes substantially stricter limitations on ventilator settings that render its application in patients with severe ARDS problematic, particularly in those with chest wall restriction. Carefully gathered observational data have reported that elevated Pplat is associated with both an increased incidence of ACP and mortality in ARDS. In particular, there appears to be an additive effect between elevated Pplat, ACP, and mortality risk. For example, those with a Pplat of 27-35 cm H_2O and ACP had a three-fold higher mortality than those with normal RV function.[15] Therefore, targeting a Pplat for LPV should consider current right heart function. The suggested goal is a Pplat < 26 cm H_2O.[15] Furthermore, a right heart protective approach targets a driving pressure (Pplat-PEEP) < 17 cm H_2O; in light of more recent evidence, some have even argued for a driving pressure target of < 15 cmH_2O.[18,19] As a result, PEEP would be limited to < 12 cm H_2O (at least in the presence of ACP). Proponents of this approach also advocate strongly for routine echocardiographic evaluation of patients early in the course of severe ARDS.

Also in contrast to traditional LPV approaches, even moderate hypercapnia should be avoided as both respiratory and metabolic acidosis increase pulmonary vascular resistance, and hypercapnia itself can exacerbate hypoxic pulmonary vasoconstriction.[20-22] The recommended target is a $PaCO_2$ < 60 mmHg, as values greater than this are associated with a nearly four-fold increased risk for ACP.[10,18] Strategies to avoid hypercapnia can include upward titration of respiratory rate and removal of additional apparatus dead space (e.g., heat-moisture exchangers). These strategies, however, can in turn become problematic, as high respiratory rates during LPV are associated with intrinsic PEEP that can impair RV function and CO_2 excretion when inspiratory time is not shortened.[23] In turn, if inspiratory time is abbreviated too much in an effort to reduce dynamic gas trapping (e.g., to pediatric levels of < 0.7 seconds), this can also exacerbate hypercapnia by magnifying airway dead space.

What arterial pH should be targeted to protect RV function in severe ARDS is unclear. In an animal model of acute lung injury, severe respiratory acidosis (pH = 7.13) increased mean PAP and PVR by 65% and 80%, respectively. [26] These values returned towards normal when extracorporeal CO_2 removal returned pH to 7.36. In a lactic acidosis model, mean PAP rises significantly at pH < 7.20 and approaches 50 mmHg at a pH of 7.[10,20] Thus, in severe ARDS, adjusting supportive therapy to achieve an initial pH target > 7.20 (and ideally > 7.30) appears to be reasonable.

Despite LPV, even a moderate PEEP level (13 cm H_2O) impairs RV function.[27] Acute respiratory acidosis exacerbates this, where deterioration in RV function occurs at even lower levels of PEEP (11 cm H_2O).[22] However, the impact of PEEP on RV function may depend more on whether its application results in lung recruitment vs overdistension. Both atelectasis and alveolar overdistension are significant causes of RV afterload. A recent study suggests that when PEEP primarily causes alveolar recruitment, the negative impact on RV function is minimized.[22] Other investigators have reported that moderate PEEP levels (14 cm H_2O) with LPV and recruitment maneuvers did not negatively impact RV function in postoperative cardiac surgery patients whose chest compliance was similar to ARDS (35-40 mL/cm H_2O).[28] Recruitment maneuvers reduce atelectasis so that increases in functional (aerated) lung tissue may help reduce alveolar overdistension. Nonetheless, cardiac surgery patients typically do not exhibit pronounced pulmonary arterial and microvascular obstruction characteristic of ARDS. Generalizing these findings to ARDS requires caution.

Eighty percent of hypoxic pulmonary vasoconstriction occurs when local alveolar PO_2 falls below 50-70 mmHg (the remaining 20% is attributable to abnormally low mixed venous PO_2).[29,30] Its impact on RV function would be proportional to the extent of parenchymal damage. This invites speculation that early, parsimonious use of recruitment maneuvers in severe ARDS, when the lung is more amenable to recruitment and before RV function is irreversibly impaired, paradoxically might reduce RV strain and lessen the likelihood of ACP developing later in the course of ARDS. An alternative or complementary approach is prone positioning, which physicians advocate to enhance the stabilizing effects of PEEP and facilitate lung recruitment.[18] Patients with ARDS and ACP placed prone for 18 hours had a significant decrease in Pplat and $PaCO_2$ corresponding with an even more impressive improvement in RV function.[11] As local alveolar PO_2 primarily determines the magnitude of pulmonary hypoxic vasoconstriction, establishing a PaO_2 target for right heart protective ventilation

Table 1: Elements of a Right Heart, Lung-Protective Ventilation Strategy

Variable / Therapy	Goal/Impact
Pplat	≤ 26 cm H_2O
Driving pressure (Pplat-PEEP)	≤ 15 cm H_2O
PEEP	≤ 10 cm H_2O*
pH	At least > 7.20; goal of > 7.30
$PaCO_2$	< 60 mmHg
PaO_2	≥ 60 mmHg
Prone positiong	Initiate early (< 72 hours) in severe ARDS with sessions lasting > 16 hours day
Acidosis management: THAM	Attenuates PAH indirectly by buffering hydrogen ion and binding CO_2 **Bolus Dosage:** THAM (0.3 mol/L) = 0.3 x body weight (kg) x base deficit (mEq/L) Do not exceed 2 mmol/kg /30 min or 5 mmol/kg/h **Continuous Infusion Dosage:** 0.3-0.6 mmol/kg/hr (not to exceed 15 mmol/kg/day or 3.5 L of 0.3m/L solution See reference 20 for adjustments during renal insufficiency
Inhaled selective pulmonary vasodilator	Inhaled nitric oxide or aerosolized prostaglandins directly reduce pulmonary vascular resistance through smooth muscle relaxation or indirectly through reduction of hypoxic pulmonary vasoconstriction Inhaled NO: 2-20 ppm Inhaled prostacyclin: 10-50 ng/kg/min

*Although low to moderate PEEP levels are advised, it should be assessed based on whether its application results in more lung recruitment (increased oxygenation and compliance and decreased dead space fraction) or more lung overdistension (decreased compliance and increased dead space fraction) *regardless* of the impact on oxygenation.

is purely a matter of conjecture. Because the functional residual capacity is essentially the alveolar volume and one of the primary determinants of PaO_2 (as well as PVR), measures of pulmonary oxygenation efficiency such as PaO_2/FiO_2 may be used as a marker for lung recruitment. Therefore, targeting therapies to treat both hypoxemia (PaO_2 < 60 mmHg) while increasing PaO_2/FiO_2 to some arbitrary thresholds (e.g., > 100 or 200 mmHg), may be a reasonable starting point to guide clinical practice until further evidence is forthcoming.

In terms of medications, THAM (trometamol; tris-hydroxymethyl aminomethane), a non-CO_2 generating buffer, has been used to reduce PVR and manage acidosis during LPV in ARDS.[24] It allows for both correction of acidosis and reduction in $PaCO_2$ without modifying LPV.[25] Inhaled vasodilators such as nitric oxide (NO) also cause impressive reductions in PVR during LPV in severe ARDS. In patients with a mean $PaCO_2$ of 65 mmHg, even small doses of inhaled NO (2 ppm) reduced PVR and decreased mean PAP toward levels measured during normocapnia.[21] Interestingly, the positive effect of inhaled NO was not related to its impact on gas exchange, as these patients had a PaO_2 of approximately 190 mmHg at baseline and $PaCO_2$ was unaffected by NO. Treating acidosis in ARDS with boluses of sodium bicarbonate should be avoided, particularly when dead-space is elevated, as it commonly results in an acute worsening of respiratory acidosis.[25]

In summary, PAH and ACP are common features of ARDS and require careful reconsideration of LPV and other supportive therapies, such as buffering acidosis, inhaled vasodilators, prone positioning, and perhaps venovenous extracorporeal CO_2 removal. In addition, routine echocardiographic evaluation of the effects of these therapies on RV function in patients with severe ARDS appears worthy of serious consideration. In the past 15 years, we have seen tremendous strides in both elucidating the pathophysiology and improving the management of ARDS, resulting in marked reductions in morbidity and mortality. Expanding our focus to consider the role of right heart function to help refine our approach may represent the next step forward. ■

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increase in pulmonary vascular resistance induced by permissive hypercapnia in patients with acute respiratory distress syndrome. *Anesthesiol* 1994;80:1254-1267.
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ABSTRACT & COMMENTARY

Daily Chlorhexidine Bathing Had No Effect on the Incidence of Healthcare-Associated Infections

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Dr. Hoffman reports no financial relationships relevant to this field of study.

SYNOPSIS: In a randomized, crossover study of 9340 patients, daily chlorhexidine bathing did not reduce ventilator-associated pneumonia, central line-associated bloodstream infections, *Clostridium difficile*, or catheter-associated urinary tract infections.

SOURCE: Noto MJ, et al. Chlorhexidine bathing and health care-associated infections: A randomized clinical trial. *JAMA* 2015;313:369-378.

The goal of this study was to determine if daily bathing with chlorhexidine decreased the incidence of healthcare-associated infections. Subjects were 9340 patients enrolled between July 2012 and July 2013 who were admitted to one of five ICUs (cardiovascular, neurological, surgical, trauma, medical) in a single academic teaching institution. The units performed once-daily bathing of all patients with cloths impregnated with 2% chlorhexidine or disposable non-antimicrobial cloths as a control. Physicians performed each treatment for a 10-week period followed by a 2-week washout period during which patients bathed with non-antimicrobial cloths before crossing over to the alternate bathing treatment for 10 weeks. Each unit crossed over between bathing assignments three times during the study. The primary study outcome was a composite of ventilator-associated pneumonia (VAP), central line-associated bloodstream infections (CLABSI), *C. difficile*, or catheter-associated urinary tract infections (CAUTI). Trained infection control personnel blinded to group assignment determined the infections. During chlorhexidine bathing, 55 infections occurred (4 CLABSI, 21 CAUTI, 17 VAP, and 13 *C. difficile*) vs 60 infections during the control bathing period (4 CLABSI, 21 CAUTI, 8 VAP, 16 *C. difficile*), a rate of 2.86 per 1000 patient days with chlorhexidine vs 2.90 per 1000 patients during the control period, a non-significant difference ($P = 0.95$). There were also no significant between-group differences after adjusting for baseline values or difference in outcomes in any of the five ICUs.

■ COMMENTARY

The emergence of multidrug resistant organisms and adverse effects of hospital-acquired infections on patient outcomes, including increased length of stay, morbidity, and costs, has prompted an extensive search for better ways to prevent such events. One proposed approach has focused on decolonization as a means to decrease exposure in high-risk patients, such as those admitted to an ICU. Findings of the present study, designed to test benefits of daily chlorhexidine bathing, did not support a benefit of this strategy. This outcome contrasts with findings of two prior studies, one of which used a similar crossover design.[1,2]

There are several differences between these prior studies and the present study, which may explain the discrepant findings. Similar to the present study, Climo et al used a multicenter, non-blinded, cluster, randomized design and enrolled a large patient sample (n = 7727).[1] However, they included both ICUs and units that admitted bone marrow transplant patients and employed chlorhexidine bathing for 24 weeks compared to 10 weeks in this study. Moreover, the reduction in bloodstream infections primarily appeared to result from a decrease in positive blood culture results caused by skin contamination bacteria. In addition, infection rates were lower initially in this study, whereas Climo et al reported a high prevalence of multi-drug resistant organisms in the control period.[1] The second study by Huang et al tested a multi-component, decolonization intervention (of which chlorhexidine bathing was one component) and therefore is not directly comparable.[2]

Taken together, findings from this and prior studies suggest that chlorhexidine bathing can be successful, but success may vary depending on the characteristics of the patient population and infection rates in the targeted units. This study came about as a quality improvement project to determine if findings of prior studies could be replicated in the data collection institution. Findings indicated no benefit, suggesting that this approach (situation specific testing) might be the best option before universal adoption. There are also concerns about costs and emergence of resistant organisms, which were not explored but should be considered when decontamination is implemented on a long-term basis. ■

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ABSTRACT & COMMENTARY

Is Catheter-Directed Thrombolysis "Perfect" for the Treatment of PE?

By Samuel Nadler, MD, PhD

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Dr. Nadler reports no relationships relevant to this field of study.

SYNOPSIS: Catheter-directed thrombolysis safely reduced mean pulmonary artery pressures and right ventricular strain in massive and submassive PE.

SOURCE: Kuo WT, et al. Pulmonary embolism response to fragmentation, embolectomy, and catheter thrombolysis (PERFECT): Initial results from a prospective multicenter registry. *Chest* 2015 April 9 [Epub ahead of print].

Pulmonary embolism (PE) that is associated with hemodynamic instability and right heart strain carries significant mortality, and in severe cases, can be treated with thrombolysis. However, systemic thrombolysis is associated with major bleeding complications and hemorrhagic stroke, which mitigates its overall benefit. Catheter-directed thrombolysis (CDT) allows thrombolytics to be delivered directly into the thrombus, thereby lowering the required dose and potentially reducing these associated complications, which can result in improved overall outcomes.

The PERFECT study is a prospective registry of 101 patients receiving CDT in six centers in the United States and one in Europe. Patients included in this study had massive (28/101)

or submassive (73/101) PEs within the main or lobar pulmonary artery leading to right ventricular strain or hemodynamic instability, were ≥ 18 years of age, had no contraindication to therapeutic anticoagulation, and did not have tumor thrombus. Massive PE was defined as sustained hypotension or the requirement of inotropic support. Submassive PE was defined by RV strain assessed by echocardiography or CT scanning. Tissue plasminogen activator (tPA), or urokinase, was infused into the clot using standard infusion catheters or ultrasound-assisted infusion catheters (USAT). Massive PEs were pre-treated with mechanical thrombolysis or thrombectomy prior to infusion. Clinical success was defined as stabilization of hemodynamic parameters, improvement of pulmonary artery pressure, and survival to hospital discharge. This was accomplished in 85.7% (24/28) and 97.3% (71/73) of patients with massive and submassive PE, respectively. There were six deaths reported, but no major procedure-related complications, major hemorrhages, or hemorrhagic strokes. Minor bleeding occurred in 12.9% (13/101), all of which were self-limiting and did not require blood transfusions. These episodes were due to hematoma formation at the access site (6/13) as well as two episodes of hemoptysis and hematuria, and one episode each of epistaxis, vaginal bleeding, and IV site bleeding.

■COMMENTARY

The main purposes of this study were to add to the understanding of the safety and feasibility of CDT and build upon the previously reported ULTIMA and SEATTLE II studies.[1,2] This was not a randomized controlled trial of CDT vs systemic thrombolysis. Although this study involved a "real-world population" as the authors note, it was conducted in select centers that already had expertise in this treatment, and therefore, the generalizability of this study is unclear. With that caveat, this study demonstrated efficacy of CDT for reducing mean pulmonary artery pressures and markers of right ventricular strain, similar to previous studies. As there currently seems to be equipoise between systemic thrombolysis and CDT for submassive PE, a well-designed, randomized controlled study should be undertaken to address which treatment modality is best suited for this condition.

This registry sheds light on two other aspects of the management of massive and submassive PE. First, 64.4% (65/101) of patients received inferior venal cava (IVC) filters. It is not clear if these were removable filters and what the indication was for placement. Presumably, there was concern for additional clot burden in the legs. During the infusion of thrombolytics, which averaged greater than 20 hours, no systemic anticoagulation was administered, and this might predispose to extension of lower extremity deep venous thrombosis necessitating IVC filter placement. Second, there seemed to be no benefit to USAT catheters compared with standard infusion catheters. The two systems demonstrated similar reductions in pulmonary artery pressures (-13.76 vs -14.02 mm Hg), average infusion times (23.19 vs 20.76 hours), and average tPA doses (30.27 vs 25.63 mg).

In considering whether CDT is most appropriate for the treatment of submassive PE, some insights can be gained by comparing this registry with the recently published PEITHO trial, a randomized controlled trial of systemic thrombolysis plus heparin vs heparin alone for submassive PE.3 In PEITHO, the 30-day mortality was 2.4% (12/506) vs 3.2% (16/499) in the systemic thrombolytic and heparin-only arms, respectively. In PERFECT, the in-hospital mortality for submassive PE was 2.7% (2/73). Conversely, PEITHO reported major bleeding in 11.5% and 2.4% of patients receiving thrombolytics and heparin vs heparin alone, compared with no reported major bleeding in the much smaller PERFECT study. Thus, this study suggests that CDT is equally effective at treating submassive PE compared with systemic thrombolysis and may lead to fewer complications. However, a randomized controlled trial directly comparing these treatments is needed. ■

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CME QUESTIONS

1. Which of the following is false regarding right heart function ARDS?

a. Function improves when PaCO2 < 60 mmHg.

b. Function improves when plateau pressure (Pplat) is < 27 cm H_2O.

c. Moderate right ventricular dilation by itself is not indicative of dysfunction.

d. Hypoxic pulmonary vasoconstriction occurs more frequently when PaO_2 < 70 mmHg.

e. The incidence of acutecor pulmonale in ARDS isapproximately 25%.

2. The PERFECT study of catheter-directed thrombolysis (CDT) for pulmonary embolism demonstrated:

a. Mortality benefit of CDT vs placebo.

b. Increased risk of stroke associated with CDT compared with placebo.

c. Superiority of ultrasound assisted infusion catheters vs standard infusion catheters.

d. Similar rates of hemorrhagic stroke with CDT vs systemic thrombolysis.

e. None of the above

3. Daily bathing with chlorhexidine resulted in:

a. a significant decrease in VAP in the medical ICU.

b. a significant decrease in CLABSI in the surgical ICU.

c. no change in VAPs or CLABSIs, but a decrease in C. difficile infections.

d. a rate of 3.90 infections per 1000 patient days during bathing with non-microbial cloths.

e. no difference in infection rates when compared with bathing with non-microbialcloths.

CME OBJECTIVES

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[IN FUTURE ISSUES]

See No Lights, Hear No Alarms: How to Sleep in the ICU Environment