Pulmonary Vascular Dysfunction Is Associated with Poor Outcomes in Patients with Acute Lung Injury

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Rationale: Despite the recognition that acute lung injury (ALI) can elevate pulmonary artery (PA) pressure and right ventricular afterload, the impact of pulmonary vascular dysfunction on outcomes of these patients is not well defined.

Objectives: To investigate the impact of pulmonary vascular dysfunction in patients with acute lung injury.

Methods: Secondary analysis of the Fluid and Catheter Treatment Trial. A total of 501 patients who received a PA catheter were evaluated for associations between increases in transpulmonary gradient (TPG) (PA mean pressure – PA occlusion pressure) or pulmonary vascular resistance index (PVRI) and 60-day mortality, ventilator-, intensive care unit (ICU)-, and cardiovascular-free days (days with mean arterial pressure $\geq$ 60 mm Hg off vasopressor support).

Measurements and Main Results: We were able to measure the TPG in 475 (95%) and the PVRI in 470 (92%) patients. Patients with an elevated baseline TPG had an increased 60-day mortality (30 versus 19%; $P = 0.02$), and lower numbers of median ventilator- [25–75% quartiles] (15 [0–22] versus 19 [7–24]; $P = 0.005$), ICU- (14 [0–21] versus 18 [5–22]; $P = 0.005$), and cardiovascular-free days (23 [12–27] versus 25 [18–27]; $P = 0.03$). The median PVRI (305 [204–431] dyne $s/cm^5/m^2$) was elevated early in the course of ALI. PVRI was statistically higher in patients who died (326 [209–518] versus 299 [199–416]; $P = 0.01$). In individual multivariate models, TPG and PVRI remained independent risk factors for 60-day mortality and decrease in the number of ventilator-, ICU-, and cardiovascular-free days.

Conclusions: Pulmonary vascular dysfunction is common in ALI, and is independently associated with poor outcomes. Future trials targeting pulmonary vascular dysfunction may be indicated.

Keywords: acute lung injury; pulmonary vasculature

Acute lung injury (ALI) is a common and devastating cause of respiratory failure occurring in nearly 200,000 individuals in the United States each year (1). Patients with ALI are defined clinically by the acute onset of severe hypoxemia with associated bilateral infiltrates on chest radiograph, which are unexplained by, *but may coexist with* elevated left atrial pressures. Despite the identification of specific ventilator and fluid strategies for the management of patients with ALI, the mortality remains unacceptably high at 30–50% (2, 3).

The pulmonary vasculature is a high-capacitance, low-resistance system, permitting large increases in blood flow without significant changes in pulmonary artery (PA) pressure (PAP). The right ventricle (RV) provides sustained, low-pressure perfusion to the pulmonary vasculature and, ultimately, the left ventricle, but depends on this low resistance to function properly (4). This

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Acute lung injury (ALI) can adversely impact the pulmonary vascular bed by a variety of mechanisms. Although pulmonary vascular dysfunction in ALI is believed to be detrimental, its relationship to patient outcomes is unknown, especially in the era of lung-protective ventilation.

What This Study Adds to the Field

We demonstrate an association between pulmonary vascular dysfunction and adverse outcomes, including increased mortality in patients with ALI. Pulmonary vascular dysfunction could represent a future therapeutic target for this disease.

delicate balance can be perturbed by a variety of pathologic conditions. ALI is a recognized cause of pulmonary hypertension and RV dysfunction (5–9). The mechanism for this increase in RV afterload is multifactorial, but includes factors such as hypoxic, hypercapnic, and mediator-induced vasoconstriction, vascular compression by edema and fibrosis, vascular wall remodeling, *in situ* thrombosis and thromboembolism, reduced lung volume, and increased alveolar pressure (5, 8, 10, 11). Other factors that adversely influence RV afterload in ALI include increases in pleural pressures and transpulmonary pressures related to decreasing lung compliance and increased intrathoracic pressures associated with mechanical ventilation and positive end-expiratory pressure (PEEP) (12). Although previous studies have suggested that pulmonary vascular dysfunction may adversely impact outcomes in patients with acute respiratory distress syndrome (ARDS)/ALI, this relationship remains poorly defined (13–15). Furthermore, as standard of care now dictates a “lung protective ventilator strategy” with adherence to a plateau pressure of less than 30 cm H₂O, it is unclear whether previous observations regarding pulmonary vascular dysfunction and outcomes are still relevant to current treatment strategies (2).

In 2006, the ARDS Network published the results of the Fluid and Catheter Treatment Trial (FACTT) (clinical trial registered with www.clinicaltrials.gov [NCT00281268]) (3, 16). This trial was a prospective, randomized, multicenter controlled study designed, in part, to investigate whether hemodynamic data obtained from a PA catheter (PAC), as compared with a central venous catheter, influenced outcomes in patients with ALI. Although the use of a PAC did not improve outcome of these patients in this study, the results provide a unique opportunity to examine the association between pulmonary vascular dysfunction and outcome in patients with ALI. We hypothesized that pulmonary vascular dysfunction, defined as an increase in transpulmonary gradient (TPG) and increased pulmonary vascular resistance, will be associated with worsening outcomes in patients with ALI.

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METHODS

We examined data on the 501 patients who were randomized and received a PAC as part of the National, Heart, Lung, and Blood Institute-sponsored multicenter FACTT, performed by the ARDS Network. Patients were enrolled within the first 48 hours after meeting the American European Consensus Conference diagnostic criteria for ALI. All enrolled patients were receiving positive pressure ventilation by endotracheal tube. Additional inclusion and exclusion criteria and details of this study are described elsewhere (3). Screening for eligible patients was conducted at 20 North American centers between June 8, 2000 and October 3, 2005. The trial was halted on July 25, 2002, for a review by the Office of Human Research Protection, and resumed unchanged except for the introduction of a modified consent form on July 23, 2003.

Independent Variables

We were unable to accurately stratify patients according to the more commonly used criteria for PA hypertension (mean PAP > 25 mm Hg and a PA occlusion pressure [PAOP] < 15 mm Hg), because 59% of the 501 patients with PACs in place had a PAOP of 15 mm Hg or greater before receipt of the first protocol-mandated instruction on fluid management. Therefore, we used two validated measures of pulmonary vascular dysfunction: the TPG and the pulmonary vascular resistance index (PVRi) (17–19). TPG is defined as the mean PAP minus the PAOP (20–24). A value of 12 mm Hg or greater has been defined as an elevated TPG (20). The PVRi is a measure of resistance across the pulmonary vascular bed, incorporating measurement of both pressure and flow, and is defined as: $(\text{mean PAP} - \text{PAOP})/\text{cardiac index}$. The normal range for PVRi is 255–285 dyne s/cm (5, 25, 26). The mean PAP was calculated as: $(2 \times [\text{PA diastolic pressure}] + \text{PA systolic pressure})/3$ for both formulas.

On Day 0, a TPG could only be obtained for 416 patients (83%), and a Day-0 PVRi was available on only 385 patients (77%) of patients with a PAC. On Day 1, a TPG could only be obtained for 449 patients (89%), and a Day-0 PVRi was available on only 443 patients (88%) of patients with a PAC. By combining the available data from Days 0 and 1, we were able to determine a TPG for 475 (93%) and a PVRi for 470 (92%) patients. We were able to measure a Day-5 TPG on 171 (49%) of the 349 patients who had an elevated TPG on Days 0 or 1, and a Day-7 TPG for 106 (30%). The significant attrition was predominately due to PAC removal and patient demise. To assess the varying effects of TPG on outcome, we analyzed TPG as a continuous and a dichotomous variable. When more than one value of TPG was available from Days 0, 1, 5, or 7, we used the highest recorded TPG level. The cutoff value for TPG, when categorized as a dichotomous variable, was predefined as part of our analysis plan and based on the standard definition of TPG elevation (>12 mm Hg). We analyzed PVRi as a continuous variable in all of our analyses, and again used the highest recorded PVRi level when more than one level was measured for Days 0, 1, 5, or 7.

A priori, we determined the covariates that would be used in multivariate regressions based on known associations with either the presence of pulmonary vascular dysfunction or outcome in patients with ALI. The variables that were selected because of their known association with outcome were sex, race, age, APACHE (Acute Physiology and Chronic Health Evaluation) III score, the presence of shock, and fluid treatment strategy (liberal versus conservative). The variables that were included in our analyses because of their known effects on pulmonary vascular dysfunction were the level of PEEP and the $\text{PaO}_2/\text{FiO}_2$ ratio. The presence of shock was defined as either a mean arterial blood pressure less than 60 mm Hg or the requirement of vasopressor agents to maintain a mean arterial blood pressure of 60 mm Hg or greater. Information for all of these variables was collected at the time of enrollment into the study.

Ventilator, Weaning, and Fluid Protocols

Ventilation, according to the ARDS Network protocol of lower tidal volumes, was begun within 1 hour after randomization, and continued until Day 28 or until the patient was breathing without assistance. Investigators performed a daily weaning screen on every patient in an attempt to standardize the process of liberation from mechanical

ventilation. In the FACTT study, all patients received hemodynamic management, as dictated by the protocol, within 2 hours of enrollment, which was continued for 7 days or until 12 hours after the patient could breathe without assistance.

Outcome Variables

The primary outcome variables assessed in this study were: (1) death at 60 days; (2) ventilator-free days from Day 1 to Day 28; (3) intensive care unit (ICU)-free days from Day 1 to Day 28; and (4) cardiovascular-free days from Day 1 to Day 28. A cardiovascular-free day was defined as a day that the patient was not hypotensive (mean arterial blood pressure of <60 mm Hg, or required vasopressor agents to maintain a mean arterial blood pressure of >60 mm Hg). Consistent with the FACTT, we assumed that patients who went home alive and without the use of a ventilator before Day 60 were alive at 60 days.

Statistical Analysis

Data that were normally distributed are reported as means ($\pm$ SD). Data that were not normally distributed are reported as medians and 25–75% quartiles. Chi-square test of independence was used to examine categorical variables at baseline, *t* tests were used to compare continuous characteristics of two groups that were normally distributed, and nonparametric analyses were used to analyze variables that were not normally distributed. Several multiple regression models were performed. Logistic regression models were used to determine the effect of TPG, after adjusting for covariates, on death. Analysis of covariance (ANCOVA) was used to examine the effect of TPG, after adjusting for covariates on ventilator-, ICU-, and cardiovascular-free days. Similar logistic regression models and ANCOVA were performed with PVRi as the primary independent variable of interest.

Covariates included in all of the analyses were sex, race (White versus non-White), age (≥ 65 yr versus <65 yr), APACHE III score (defined as continuous variable), the presence of shock (yes or no), level of PEEP (≥ 10 cm H_2O versus <10 cm H_2O), the $\text{PaO}_2/\text{FiO}_2$ ratio (≤ 200 versus >200), and fluid treatment strategy (liberal versus conservative). SAS 9.1 (SAS Institute, Cary, NC) was used for all analyses, and *P* less than 0.05 was considered statistically significant.

Protection of Human Subjects

The institutional review boards of each participating medical center or hospital approved the original FACTT study. Patients or their surrogates provided informed consent before enrollment. The study was conducted in accordance with the established ethical standards of the medical centers and with the principles of the Declaration of Helsinki (27). The ARDS Network deidentified the clinical information before allowing our analysis. The data and safety monitoring board conducted interim analyses after the enrollment of 82 patients and after the enrollment of approximately every 200 patients. Sequential stopping rules for safety and efficacy used the methods of O'Brien and Fleming (28). Additional institutional review board approval for deidentified data analysis was obtained from the University of Colorado Denver Health Sciences Center (COMIRB 08-0827).

Role of the Funding Source

The National Heart, Lung, and Blood Institute oversaw the study, including data and safety monitoring. The ARDS Network reviewed and approved the manuscript prior to its publication.

RESULTS

A total of 513 patients were randomized to receive a PAC as part of the original study, and 501 patients eventually received a PAC. Complete demographic information and baseline hemodynamic characteristics of the 501 patients who survived compared with those who died are included in Table 1. A mean PAP was obtained in 483 patients. An additional eight patients did not have a simultaneous PAOP recorded during the first 2 days after enrollment. Therefore, a TPG could be determined in 475 (93%) patients. A total of five more patients did not have a cardiac index determined simultaneously, and a PVRi could be determined in only 470 (92%) patients.

TABLE 1. CHARACTERISTICS OF PATIENTS WITH ACUTE LUNG INJURY WHO SURVIVED VERSUS THOSE WHO DIED

Characteristics	No. of Patients	Survived	Died	P Value
Participants, <i>n</i> (%)	475	348 (73)	127 (27)	—
Age, yr	475	48 ± 15	54 ± 17	0.0005
Sex, % male	475	56	53	0.52
Ethnicity, % White	475	68	54	0.004
APACHE III score	465	88 ± 29	110 ± 30	<0.0001
Arterial pH	462	7.37 ± 0.09	7.35 ± 0.11	0.09
P:F ratio	462	162 ± 74	155 ± 74	0.31
PEEP, cm H ₂ O	475	9.2 ± 3.9	9.4 ± 4.1	0.59
Pplat, cm H ₂ O	332	26.1 ± 6.4	26.6 ± 7.5	0.49
Shock at Baseline	475	33%	46%	0.009
Central venous pressure	473	14.1 ± 4.6	13.2 ± 4.5	0.08
PA systolic pressure	475	45.4 ± 13.1	47.2 ± 12.1	0.18
PA diastolic pressure	475	24.5 ± 7.0	25.4 ± 7.4	0.25
PA mean pressure	475	31.3 ± 8.3	32.4 ± 8.3	0.18
PAOP	475	17.3 ± 5.1	16.7 ± 5.0	0.27
PA saturation	331	70.2 ± 10.4	68.6 ± 13.1	0.28
Cardiac index	472	4.5 ± 1.4	4.4 ± 1.6	0.43
TPG	475	14.3 (11.3–18.3)	15.7 (12.3–22.3)	0.009
PVRI	470	299.9 (199.4–416.1)	326.4 (206.4–518.7)	0.03

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; P:F = PaO₂:FiO₂; PA = pulmonary artery; PAOP = pulmonary artery occlusion pressure; PEEP = positive end-expiratory pressure; Pplat = plateau pressure; PVRI = pulmonary vascular resistance index; TPG = transpulmonary gradient.

Values are mean ± SD or % (except TPG and PVRI, which are expressed as median [25–75% quartiles]). Hemodynamic values represent the highest value recorded on day 0 or day 1.

Of the 475 patients for whom a TPG could be determined, 127 of the 475 died (27%; 95% confidence interval [CI], 23–31%). The median number (95% CI) of ventilator-, ICU-, and cardiovascular-free days for the entire cohort of patients was 17 days (0–23 d), 15 d (0–21 d), and 24 d (14–27 d), respectively. Several of the baseline variables, including age, ethnicity, APACHE III score, and the presence of shock, were associated with an increased risk of death (Table 1). Importantly, none of the isolated baseline measures of cardiopulmonary function, including central venous pressure (CVP), PA systolic or diastolic pressures, PAOP, or cardiac index, were significantly different between survivors and nonsurvivors (Table 1).

Physiologic Measurements

In linear regression, the Day-0 TPG was well correlated with mean PAP ($r^2 = 0.61$; $P < 0.0001$), systolic PAP ($r^2 = 0.58$; $P < 0.0001$), diastolic PAP ($r^2 = 0.48$; $P < 0.0001$), and PVRI ($r^2 = 0.61$; $P < 0.0001$). It was poorly correlated with the PAOP ($r^2 = 0.02$; $P < 0.01$), and not correlated with the CVP ($P = 0.2$) or the cardiac index ($P = 0.9$). Similar correlations were obtained between the TPG and the same hemodynamic measures with values from Day 1 (data not shown). Of interest, CVP and PAOP from Day 0 were also well correlated ($r^2 = 0.43$; $P < 0.0001$; $\text{PAOP} = 6.5 + 0.74 \times \text{CVP}$).

Analysis of TPG

The median highest TPG (and 95% CI) on Days 0 or 1 for all patients was 14.7 (11.7–18.7). TPG was statistically higher in those patients who died compared with those who survived (15.7 mm Hg [12.3–22.3 mm Hg] versus 14.3 mm Hg [11.3–18.3 mm Hg]; $P = 0.009$) (Table 1). Spearman correlations demonstrated that TPG had a small, but significant negative correlation with number of ventilator-free days ($R = -0.16$; $P = 0.0007$), ICU-free days ($R = -0.18$; $P < 0.0001$), and cardiovascular-free days ($R = -0.18$; $P < 0.0001$).

A total of 73% of the patients ($n = 349$) had an elevated TPG (categorized as ≥ 12 mm Hg) on Days 0 or 1. The characteristics of these two groups (TPG ≥ 12 mm Hg and TPG < 12 mm Hg) are displayed in Table 2. Patients with a TPG of 12 or greater had a significantly increased 60-day

mortality (30 versus 19%; $P = 0.02$), fewer ventilator- (15 d [0–22 d] versus 19 d [7–24 d]; $P = 0.005$), ICU- (14 d [0–21 d] versus 18 d [5–22 d]; $P = 0.005$), and cardiovascular-free days (23 d [12–27 d] versus 25 d [18–27 d] $P = 0.03$) when compared with patients with a TPG of less than 12 mm Hg.

When patients were further stratified into three groups based on their highest TPG (< 12 mm Hg, ≥ 12 mm Hg and < 24 mm Hg, and ≥ 24 mm Hg), higher TPG was associated with greater 60-day mortality (19 versus 27 versus 49%; $P = 0.0006$ for trend) (Figure 1).

To examine the impact on survival of a persistently elevated TPG, we evaluated the outcomes of patients with an elevated TPG at Days 0 or 1 and an elevated TPG at Days 5 and 7 versus those with an elevated TPG at Days 0 or 1 and a normal TPG at Days 5 and 7. Patients with a persistently elevated TPG at Day 5 had a significantly increased 60-day mortality compared with those who normalized their TPG at Day 5 (36 versus 19%; $P = 0.01$). Similarly, patients with a persistently elevated TPG at Day 7 had a significant increase in 60-day mortality (39 versus 22%; $P = 0.02$).

Because values were missing for at least one variable, 23 of the patients (5% of patients with a calculable PVRI or TPG, respectively) were excluded from these regression models. To investigate the role of potential confounding variables and effect modification, a multivariate analysis was fit for 60-day mortality. No interaction terms were found to be significant in this model, and there was no collinearity between any of the independent variables. The effect of the TPG on 60-day mortality remained in a multivariate analysis ($P = 0.038$; odds ratio [OR], 1.03; 95% CI, 1.02–1.05 for each unit of TPG elevation). The area under the curve, represented by the C statistic (= 0.75) indicating the model, explained more variability than chance. The Hosmer and Lemeshow goodness-of-fit test was not rejected ($P = 0.4$), indicating adequate model fit. To ensure conformity to a normal distribution for TPG, we also examined the effects of a logarithmic transformation of TPG. In a multivariate logistic model, the effect of log TPG on 60-day mortality remained significant ($P = 0.016$; OR, 4.474; 95% CI, 1.32–15.12). The C statistic (= 0.75) indicating the model explained more variability than chance. The Hosmer and

TABLE 2. CHARACTERISTICS OF THE SAMPLE

Characteristics	Patients with TPG < 12	Patients with TPG ≥ 12	P Value
Participants, n (%)	126 (27%)	349 (73%)	
Age, yr	46 ± 15	51 ± 16	0.01
Male sex, n (%)	61 (48)	193 (55)	0.18
White ethnicity, n (%)	87 (69)	218 (63)	0.19
Fluid strategy (liberal), n (%)	66 (52)	171 (49)	0.52
APACHE III score	93 ± 33	94 ± 30	0.75
Arterial pH	7.35 ± 0.11	7.37 ± 0.11	0.18
P:F ratio	171 ± 79	156 ± 72	0.05
Pplat	25 ± 6	26 ± 6	0.07
PEEP < 10, n (%)	61 (48)	172 (50)	0.82
Shock at baseline (yes), n (%)	55 (44)	120 (34)	0.07
Death before Day 60, n (%)	24 (19)	103 (30)	0.02
Vent free days	16 ± 10	13 ± 10	0.003
ICU-free days	14 ± 9	12 ± 10	0.006
CV-free days	21 ± 9	19 ± 10	0.02

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CV = cardiovascular; ICU = intensive care unit; PEEP = positive end-expiratory pressure; Pplat = static plateau pressure; P:F = $\text{PaO}_2/\text{FiO}_2$; TPG = transpulmonary gradient.

Data presented are from those patients with adequate data to calculate a TPG at Days 0 or 1. Data presented are means ± SD, unless otherwise noted (total $n = 475$). A CV-free day was defined as a day that the patient was not hypotensive (mean arterial blood pressure of < 60 mm Hg, or required vasopressor agents to maintain a mean arterial blood pressure of > 60 mm Hg).

Lemeshow goodness-of-fit test was not rejected ($P = 0.08$), indicating adequate fit. In individual multivariate models, the highest TPG was significantly associated with a decreased number of ventilator- ($P = 0.0018$), ICU- ($P = 0.0002$), and cardiovascular-free days ($P < 0.0001$).

Analysis of PVRi

The median highest PVRi (and 95% CI) on Days 0 or 1 for all patients was 304.6 (204.3–430.9). PVRi was also statistically higher in those patients who died compared with those who survived (326.4 [206.4–518.7] versus 299.6 [199.4–416.1]; $P = 0.03$) (Table 1). PVRi had a small but statistically significant negative correlation with the number of ventilator- ($R = -0.15$; $P = 0.001$), ICU- ($R = -0.16$; $P = 0.0005$), and cardiovascular-free days ($R = -0.18$; $P = 0.0001$). In individual multivariate logistic and regression models, the effects of the highest PVRi also remained statistically significant on mortality (OR, 1.07; 95% CI, 1.01–1.13 for each 50 unit [$\text{dyne s cm}^{-5}/\text{m}^2$] increase in PVRi; $P = 0.02$), ventilator- ($P = 0.02$), ICU- ($P = 0.007$), and cardiovascular-free days ($P = 0.001$). The C statistic for the logistic model ($= 0.75$) and the Hosmer and Lemeshow goodness-of-fit test was not rejected ($P = 0.24$), indicating adequate fit.

Other Evidence of RV Dysfunction

Elevation of CVP over PAOP, has previously been described as a marker of RV failure and adverse outcomes in ARDS (15). We therefore examined whether this occurrence was related to outcomes in our patient population. On Days 0 or 1, only 44 patients (12%) met this definition of RV failure (CVP > PAOP). There was no difference in 60-day mortality between these patients and those with a CVP less than or equal to PAOP (25 versus 21%; $P = 0.7$).

DISCUSSION

ALI is a major cause of death and disability in ICUs throughout the world. Although studies defining appropriate ventilator

Figure 1. Stratification of 60-day mortality in patients with acute lung injury by increasing transpulmonary gradient (TPG). Elevation of the TPG was associated with higher mortality (19 versus 27 versus 49%; $P = 0.0006$ for the trend).

management have improved patient outcomes, the mortality associated with ALI remains unacceptably high (1, 29).

We now demonstrate that pulmonary vascular dysfunction, defined as an elevation of TPG or PVRi, is both common and independently predictive of adverse outcomes in patients with ALI even when plateau pressures are limited in a lung-protective ventilator strategy. Although the absolute differences for both TPG and PVRi are relatively small between survivors and nonsurvivors, even small impairments to RV function can significantly impact patient outcomes (30–32). Importantly, patients with the greatest elevation of TPG or PVRi in this study were the most adversely impacted, implying a dose effect for pulmonary vascular dysfunction. Furthermore, patients with persistence of pulmonary vascular dysfunction through Days 5 and 7 had significantly worse survival compared with those patients who normalized their TPG. It is also notable that isolated measurements of cardiopulmonary function, such as PAP, cardiac index, or PAOP, were not significantly associated with increased morbidity or mortality. Rather, only measurements assessing the pressure gradient or resistance across the pulmonary vascular bed (TPG or PVRi) were significantly associated with clinically important outcomes, including mortality. The TPG and the PVRi were selected as surrogate indicators of pulmonary vascular dysfunction in our analysis for a variety of reasons. First, a majority of patients (59%) in the FACTT had an elevated PAOP (>15 mm Hg) at the time of enrollment. These patients would have been excluded from analysis if we had used the more traditional definition of pulmonary arterial hypertension (mean pulmonary artery pressure > 25 mm Hg and PAOP < 15 mm Hg). When the pulmonary vascular bed is functioning properly, there should be little difference (<12 mm Hg) between the mean PAP and the PAOP. Measurement of TPG and PVRi elevation identifies patients with pulmonary hypertension “out of proportion” to left heart dysfunction or volume overload. It is interesting that TPG elevation was more closely associated with adverse outcomes in our study as compared with PVRi. The response of the pulmonary vascular bed to flow is an important consideration in vascular function, and, thus, PVRi was also included in our analysis. Elevation of TPG and PVRi are associated with poor prognosis in other clinical scenarios (19, 20, 33–35).

There are limitations to this work. This is a secondary analysis of an existing data set that was not initially designed to assess the impact of pulmonary vascular disease. Thus, one notable limitation is the observational nature of our findings, and our inability to draw conclusions regarding cause and effect.

It is possible that TPG and PVRi elevation are simply markers of severity of illness, thus identifying patients with worse overall outcomes. It is also possible that there were other important unmeasured covariates. However, there were not significant differences between groups in important markers of disease severity, such as APACHE III scores, and the effects of pulmonary vascular dysfunction on outcome remained significant in multivariate analysis. Another limitation of this study is that data regarding the presence of pulmonary hypertension before patient enrollment was not available, thus we cannot definitively state that ALI was the sole cause of the elevated TPG and PVRi. However, as the prevalence of pulmonary hypertension in the general population is low, we believe that it is reasonable to conclude that the high percentage of patients with elevation of the TPG and PVRi was related to their diagnosis of ALI (36, 37).

Impact of the pulmonary vascular bed in ALI has been suspected for some time, and likely involves a variety of mechanisms (5). The hemodynamic data available from the FACTT demonstrate this association in the largest and best-characterized cohort published to date. Furthermore, these measurements were made in the modern era of lung-protective ventilator strategies. One must now question whether targeting this pathologic aspect of ALI could result in improved outcomes. Recent advances in therapeutic options for patients with pulmonary hypertension make this an attractive group to study (38). Previous trials examining the benefit of pulmonary vasodilators, such as inhaled nitric oxide in patients with ARDS/ALI, have not improved patient outcomes (39–41). However, these studies did not stratify patients based on pulmonary vascular dysfunction. Smaller studies examining subsets of patients with RV dysfunction and pulmonary hypertension have demonstrated improvements in physiologic endpoints (42–44). We hypothesize a targeted approach, examining novel therapies aimed specifically at patients with ALI with evidence of pulmonary vascular dysfunction could indeed result in improved outcomes. This hypothesis will require further investigation.

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