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High values of the pulmonary artery wedge pressure in patients with acute lung injury and acute respiratory distress syndrome

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Abstract *Objective:* To determine the incidence and severity of pulmonary artery wedge pressure (PAWP) elevation in patients with ALI/ARDS. In addition, to examine the effects of clinical variables on the presence of a high PAWP (>18 mmHg) and the effect of an elevated PAWP on mortality. *Design and patients:* Post hoc analysis of 120 patients with or at high risk of ARDS, enrolled in a randomized controlled trial of pressure- and volume-limited ventilation. Patients with or at high risk of congestive heart failure were excluded from the original study. *Setting:* Eight tertiary intensive care units. *Measurements and results:* Pulmonary artery catheters were inserted at the discretion of the attending physician, and PAWP was collected every 8 h when present. Of 120 subjects 71 (59%) had a pulmonary artery catheter (44 at randomization, 27 later). The mean maximum PAWP reading among patients was 22.5 mmHg (95% CI 21.2–23.8) and mean median was 16.6 mmHg (95% CI 15.6–17.5). Patients who met standard criteria for ARDS were more likely to develop a high PAWP. In a multivariate stepwise logistic regression model a persistently elevated PAWP (median >18 mmHg) was a strong predictor of mortality after correction for baseline differences (OR estimate 6.82; 95% CI 1.66–37.81). *Conclusions:* We conclude that in this group of patients a PAWP higher than 18 mmHg is common. Mandating a PAWP of 18 mmHg or less may negatively impact clinical trials in which ARDS is an inclusion/exclusion criteria or an endpoint.

Keywords Acute lung injury · Acute respiratory distress syndrome · Congestive heart failure · Pulmonary artery catheters · Pulmonary artery wedge pressure

Introduction

The current American-European Consensus Conference (AECC) definitions of acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) both include the acute onset of hypoxemia, bilateral infiltrates on chest radiography, and no clinical evidence of left atrial hypertension [1]. If a pulmonary artery wedge pressure (PAWP) measurement is available, left atrial hypertension is defined as a value greater than 18 mmHg. PAWP may vary considerably with the degree of fluid resuscitation, the effect of positive end-expiratory pressure (PEEP), mean airway pressure, and the accuracy of its reading, and hence high values may not necessarily reflect left ventricular dysfunction [2, 3]. Some patients may therefore be deemed not to have ARDS/ALI simply because of an elevated PAWP that is not related to left ventricular dysfunction. This is concerning to clinicians because treatments aimed at congestive heart failure may vary significantly from those targeted at ARDS/ALI. Additionally, this may have a significant impact on the enrollment into and interpretation of clinical trials, complicating comparisons between studies. Given our concerns, we set out to examine the incidence and severity of a

high PAWP (>18 mmHg) in a cohort of patients with or at high risk for ALI/ARDS in the context of a multicenter, randomized, controlled trial (RCT) evaluating pressure and tidal volume limited mechanical ventilation [4].

Patients and methods

We studied patients who had been enrolled in a previous RCT comparing two different ventilatory strategies in patients with, or at high risk of ARDS [4]. Inclusion criteria for this RCT included: (a) endotracheal intubation less than 24 h duration, (b) the presence of one or more risk factor for ARDS, and (c) PaO_2/FIO_2 ratio less than 250. Exclusion criteria for the original study included: (a) cardiogenic pulmonary edema, (b) a PAWP higher than 18 mmHg at randomization, (c) previous heart failure or cor pulmonale, (d) a high risk of cardiac arrhythmias or myocardial ischemia (indicated by the occurrence of ventricular fibrillation, ventricular tachycardia, unstable angina, or myocardial infarction within the preceding month), (e) anticipated duration of mechanical ventilation less than 48 h, (f) very unlikely survival, and (g) exposure to peak inspiratory pressures greater than 30 cmH_2O for longer than 2 h.

All patients in the original study who had a pulmonary artery (PA) catheter placed during their stay in the intensive care unit (ICU) were included in this analysis. PA catheters were inserted at the discretion of the attending physicians and were present either at the time of randomization or were inserted later. PA catheters were inserted in 71 of 120 patients (59%); 44 were present at the time of randomization, and 27 were inserted later. All 44 patients who had a PA catheter at enrollment had a PAWP of 18 mmHg or lower at that time since a high PAWP was an exclusion criteria. The 71 patients with PA catheters included in this analysis did not differ significantly from those without PA catheters according to baseline age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II, number of ARDS risk factors, or PaO_2/FIO_2 ratio.

The PAWP was collected every 8 h when a PA catheter was present, as was cardiac index as measured by the thermodilution technique. The PAWP was measured at end-expiration after a stable wedge tracing had been achieved. No corrections were made for the level of positive end-expiratory pressure. Other hemodynamic and ventilatory variables, including PEEP, FIO_2, PaO_2, and mean arterial pressure were also collected every 8 h. Standard indicators of disease severity including the APACHE II and the Multiple Organ Dysfunction Score (MODS) [5] were collected at study entry. Throughout the original study the type and amount of intravenous fluid that was administered was determined by the attending physician; no specific fluid administration protocols were used.

The a priori hypotheses of this study were that high PAWP (>18 mmHg) would be common in patients with ALI/ARDS, and, based on a previous study [6], that a high PAWP would be an independent predictor of mortality.

We calculated the incidence of a high PAWP by determining the percentage of patients with a PA catheter who had at least one PAWP measured higher than 18 mmHg. Severity of elevation was demonstrated by calculating the mean maximum (overall mean of individual patient maximum values), and the mean median values of PAWP. In addition, we expressed the number of high readings (PAWP >18 mmHg) over the total number of PAWP readings per patient and report the percentage of patients with more than 30% of PAWP measurements higher than 18 mmHg.

To determine whether changes in PAWP were due to the development of congestive heart failure we divided the subjects into three groups: those with a persistently elevated PAWP (median >18 mmHg), those with transient PAWP elevation (median ≤18 mmHg but at least on high PAWP reading), and those with no PAWP elevation. We then calculated the overall median of the individual patient medians for cardiac index in each of the three groups.

We calculated the effect of the presence of a number of demographic and physiological variables on the incidence of PAWP elevation (at least one reading >18 mmHg) using χ^2 testing. In addition, to explore the effect of PEEP on PAWP we divided the PAWP readings into less than or equal to 18 vs. greater than 18 mmHg and compared mean PEEP levels between these groups. Finally, to explore findings reported by previous investigators [6], we constructed a multivariate stepwise logistic regression model examining the effect of a persistently high PAWP (median PAWP >18) on mortality. All statistical analyses were carried out using standard software (SAS; SAS Institute, Cary, N.C., USA).

Results

A total of 842 PAWP readings were taken in the 71 patients (mean 12 per patient). In 58 patients (82%) there was at least one measurement of PAWP that was high (>18 mmHg). The mean maximum PAWP reading among patients was 22.5 mmHg (95% CI 21.2–23.8). The mean median was 16.6 mmHg (95% CI 15.6–17.5); the frequency of the median readings for the patients are shown in Fig. 1. When we expressed the number of PAWP readings above 18 mmHg as a percentage of the total number PAWP measurements, 52% of patients had more than 30% of their PAWP readings classified as high.

Treatment group (high stretch vs. low stretch), timing of PA catheter insertion (initial vs. later), cause of lung injury (direct vs. indirect), mean PEEP level, mean PEEP level on days one through three, and the develop-

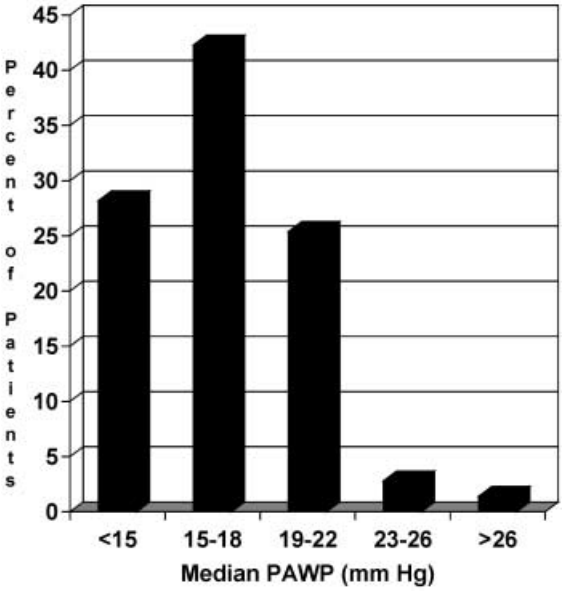

Fig. 1 Frequency of observed patient median PAWP measurements

Table 1 Univariate and multivariate analysis of risk of death

	Odds ratio estimate	95% confidence interval	*p*
Univariate			
Male sex	2.00	0.72–5.67	0.18
Direct lung injury	1.81	0.70–4.85	0.22
Limited ventilation group	1.16	0.45–2.99	0.76
Median PAWP >18 mmHg	6.33	1.72–30.70	0.007
Age (1-year increments)	0.99	0.96–1.02	0.63
MOD score (1-point increments)	1.00	1.00–1.00	0.61
APACHE II (1-point increments)	1.07	1.01–1.15	0.02
Mean PEEP days 1–3 (1-cmH_2O increments)	1.27	1.07–1.54	0.005
Multivariate			
Median PAWP >18 mmHg	6.82	1.66– 37.81	0.007
Mean PEEP days 1–3 (1-cmH_2O increments)	1.27	1.07–1.55	0.007

ment of ARDS by the Murray Lung Injury Score (>2.5) [7] did not significantly affect the incidence of a high PAWP (at least one reading >18 mmHg). The incidence was higher in patients who developed ARDS by AECC criteria [1] than in those who did not (92% vs. 67%, p=0.005 by χ^2 test). The mean level of PEEP used when an elevated PAWP was present was not significantly different than that when PAWP was not elevated (9.8 vs. 9.5 cmH_2O). The overall median of the individual median cardiac index for each group was 5.3 l min^{-1} m^{-2} (range 2.4–12.8) in patients with persistently elevated PAWP (median PAWP >18; n=20), 4.4 l min^{-1} m^{-2} (range 2.1–7.9) in those with transient PAWP elevation (median ≤18 mmHg but at least one high PAWP reading; n=37), and 3.7 l min^{-1} m^{-2} (range 2.6–5.3) in patients with no PAWP elevation (n=13). These differences were not statistically significant.

The multivariate stepwise logistic regression model considered the effect of the following seven variables (one per ten patients) on mortality: gender, risk factor for ARDS (direct vs. indirect), treatment group (high stretch vs. low stretch), PAWP group (median >18 vs. ≤18 mmHg), age, MODS, APACHE II score, and mean PEEP over days 1–3. These variables were selected a priori based on clinical suspicion of relevance. The main causes of mortality in the three groups were MODS, sepsis, withdrawal of care, and respiratory failure. They were not different between the PAWP groups. The results of the univariate analysis are shown in Table 1. In addition, as shown in Table 1 the multivariate analysis revealed a significantly higher risk of death with a high median PAWP (OR=6.8, p=0.007) after correction for other baseline differences. The overall mortality rate among the 71 patients with PA catheters included in this study was 58%. This was significantly higher than the 33% mortality rate observed in the 49 patients who were not included in this study because PA catheters were not employed in their care (p=0.006 by χ^2 test).

Discussion

The distinction between congestive heart failure and ARDS/ALI in hypoxemic, critically ill patients with bilateral infiltrates on chest radiography remains a challenge. The PA catheter and PAWP have long been used to try and clarify this situation. The origins of 18 cmH_2O as a cutoff point between these entities appear to stem from data examining radiographic appearance and hemodynamics in the setting of acute myocardial infarction [8]. While most patients with significant cardiogenic pulmonary edema have a PAWP higher than 18 cmH_2O, our data suggest that the corollary of this statement does not hold true for noncardiogenic pulmonary edema. The precise cause of the elevated PAWP is not always clear, but the high cardiac outputs observed and the fact that patients at high risk for congestive heart failure were excluded, point away from the development of congestive heart failure as the cause. Possible explanations include the effects of positive pressure ventilation, aggressive fluid resuscitation, and increased pleural pressures [2].

Other investigators have previously shown an association between death and a persistently high PAWP in patients meeting chest radiographic and hypoxemia criteria for ARDS [6]. Our analysis seems to support this finding. Our patient population likely differed slightly from those studied by Neff and colleagues [6], as our patients were enrolled in a RCT, and also none of our patients had PAWP elevation at enrollment. Nonetheless, even after correction for baseline differences the development of a median PAWP higher than 18 remained a strong risk factor for mortality. We suspect that this is a marker of disease severity, as patients who are more severely ill may need more fluid resuscitation and higher levels of PEEP or mean airway pressure. It is possible to hypothesize, however, that either the management strategy that resulted in the high wedge pressures (such as high levels of PEEP or aggressive volume resuscitation) or the subsequent treatment strategy of the high PAWP (such as

with diuresis or inotropes) may have contributed to the increased mortality. The available data do not allow firm conclusions to be drawn about these hypotheses. Prospective experimental data are probably needed to address these issues definitively. All patients included in the mortality regression analysis had a PA catheter inserted at the discretion of the attending physician. The hypothesis that adverse effects and increased mortality are directly related to the PA catheter, as suggested by Connors et al. [9] is therefore not addressed by our findings.

A limitation of our study is that the PAWP was not measured in a standardized fashion. PAWP data were collected every 8 h when a PA catheter was present. These data were abstracted from the nursing flow sheets where they had been measured and recorded by the nurse, respiratory therapist, or physician, according to usual clinical practice. These personnel did not receive any special training about measuring and recording the PAWP at the time of the study. Additionally we do not have any data about the reliability of any individual PAWP measurement. We would point out, however, that this limitation in fact adds to the generalizability of our results. The process of usual care that occurred in this study is likely to be similar to situations in other ICUs where daily patent care and screening for clinical trials are being carried out. Thus although one may question the accuracy of our readings, it is probable that they are no more or less accurate than measurements that are taken in a wide variety of intensive care units on a daily basis.

The exclusion of patients with PAWP higher than 18 probably increases the AECC definition's specificity, but it appears to do so at the cost of a significant reduction in sensitivity. Although all of our patients had either a low PAWP or a low clinical suspicion of left atrial hypertension, and thus were included in the original RCT, it is probable that a number of similar patients were excluded from this and other studies simply because of an elevated PAWP. Our data suggest that at least a proportion of these patients do not in fact have congestive heart failure as the primary cause of their respiratory failure. At the very least, volume overload and ARDS/ALI appear to coexist in a significant number of patients. This has important implications when ARDS is used either as an inclusion criterion or an endpoint in clinical trials, both in terms of conducting the studies and in the application of their results. It is conceivable that this finding also influences usual patient care in the ICU. A recent consensus conference on PA catheter use states that the PA catheter may "alter treatment and correct misdiagnosis in patients with respiratory failure" [10]. Our results suggest that at the very least the cutoff point for a high PAWP should be reevaluated and potentially increased from its current level of 18 mmHg. As new and potentially costly therapies (such as monoclonal antibodies to cytokines) become available, physicians may find themselves restricted by their own clinical judgement, or by hospital or government agencies, to using these agents only in patients who meet standard ARDS/ALI definitions. At the current time all patients who otherwise fit the AECC ARDS definition but who have a high PAWP would then be excluded from receiving these potentially life-saving therapies.

In the current AECC definition the use of the PAWP is not mandatory [1]. Because of this fact, and the demonstrated association with mortality, ARDS outcomes across centers may be influenced by the use of PA catheters. In centers with a low threshold for measuring PAWP a larger number patients with worse prognoses may be excluded from ARDS studies, whereas centers with a high threshold for PA catheter use may employ clinical suspicion only, and include those same patients. This effect may complicate the already difficult task of comparing results across studies.

We conclude that an elevated (>18 mmHg) PAWP is a common finding in patients with ALI/ARDS who have no risk factors for congestive heart failure. This finding does not seem to be the result of development of de novo congestive heart failure, as indicated by the relatively high cardiac indices that were demonstrated. A high PAWP may be an indicator of poor prognosis in this group of patients. These findings pose problems for both researchers and clinicians alike. We recommend reevaluating the PAWP criterion in future definitions of ALI/ARDS.

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