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Prevalence of pulmonary hypertension associated with severe acute respiratory distress syndrome: Predictive value of computed tomography

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Abstract *Objective:* To evaluate the prevalence of pulmonary hypertension associated with severe acute respiratory distress syndrome (ARDS) and to asses the value of pulmonary artery trunk diameter (PAT) to predict pulmonary hypertension. *Design:* Prospective study *Setting:* University teaching hospital and ARDS referral center. *Patients:* 103 patients with ARDS, who received both right heart catheterization and chest computed tomography. *Interventions:* None. *Measurements and results:* 95 patients (92.2%) with ARDS had pulmonary artery hypertension, 16 of them (16.8%) mild, 72 (75.8%) moderate, and 7 (7.4%) severe, as assessed by right heart catheterization. Of the patients with moderate and severe pulmonary hypertension, 43 had a pulmonary artery trunk diameter ≥ 29 mm yielding a sensitivity of 0.54 and a specificity of 0.63. Pulmonary artery trunk diameter correlated significantly but weakly with mean pulmonary artery pressure ($r = 0.34$, $p = 0.0004$). The positive predictive value was 0.83, and the negative predictive value was 0.28. The diagnosis of pulmonary hypertension by PAT diameter measurements was incorrect in 43.7% of patients with ARDS. *Conclusions:* Pulmonary artery hypertension has a high prevalence in patients with severe ARDS. Measurement of PAT diameter on admission CT scan is an unreliable tool for identification of ARDS patients with pulmonary hypertension.

Keywords Extracorporeal membrane oxygenation · Pulmonary artery catheter · Right heart failure

Introduction

Pulmonary hypertension (PH) is a feature of various advanced chronic diseases of the pulmonary vasculature, lung parenchyma, or airways. Detecting PH provides important prognostic information [1] and can define the need for inhalational vasodilator therapy [2] or other medications such as bosentan [3] or sildenafil [4]. In patients with primary pulmonary hypertension and chronic heart or pulmonary disease, attempts have been made to estimate pulmonary artery pressure (PAP) by less-invasive techniques such as echocardiography [5, 6], computed tomography (CT) [7], or magnetic resonance imaging [8]. While echocardiography has been shown to be inaccurate

in as much as 50% of patients with advanced lung disease when compared with right heart catheterization [9], a pulmonary artery trunk (PAT) diameter of 29 mm measured on CT scans had an excellent diagnostic yield in detecting PH in patients with advanced lung disease, with a sensitivity of 87% and a specificity of 89% [7].

In patients with acute respiratory distress syndrome (ARDS), PH is a frequent observation [10, 11], although little is known about the prevalence and magnitude of PH in patients with severe ARDS. That PH might be of relevance in patients suffering from ARDS is suggested by Squara et al., who observed that patients dying from ARDS had a significantly higher PAP than survivors and concluded that lowering PAP may by itself be an important therapeutic strategy [11]. Obviously, recognizing increased PAP and its decrease implies correct identification of patients with increased PAP.

Direct measurement of PAP by pulmonary artery catheterization (PAC), the gold standard for measuring pulmonary artery pressure (PAP), has been shown to be safe and not associated with increased morbidity and mortality in severely ill patients with sepsis and ARDS [12]. Nevertheless, alternative and less invasive methods would be welcome in many patients. In this respect, CT scanning is of particular interest, since CT scanning in ARDS patients is often helpful in defining pathology and treatment strategy, and in chronic cardiopulmonary disease can predict PH fairly reliably [7]. However, ARDS is an acute illness and, therefore, the extent of pulmonary artery distension or its adaptation to increased pressure is unknown, as is the transferability of results obtained in chronic illness to severe ill ARDS patients.

Therefore, we performed this study to assess (1) the prevalence of PH in patients with severe ARDS, and (2) if an increased pulmonary artery trunk diameter (≥ 29 mm) measured by CT scan on admission is reliable for predicting PH in patients with ARDS.

Material and methods

One hundred three (103) patients referred with the diagnosis of ARDS and receiving both chest CT and a pulmonary artery catheter (PAC) on admission as a routine work-up were analyzed. All patients had been referred to our unit for advanced ARDS treatment from other hospitals and were mechanically ventilated in the pressure-controlled mode with pure oxygen, with a respiratory rate of 20 breaths per minute, an inspiratory-to-expiratory ratio of unity, a positive end-expiratory pressure (PEEP) of 10 cmH$_2$O or more, and a peak inspiratory pressure to achieve a tidal volume of approximately 6 ml/kg, as recommended elsewhere [13]. ARDS was defined as described elsewhere [14] and by a lung injury score (LIS) greater than 2.5 [15].

Measurements

Following patients' arrival by helicopter or ambulance equipped for transport of critically ill patients, PAT diameter was measured by CT scan. All patients were examined using a standardized protocol. CT images were obtained after central venous injection (100 ml) of non-ionic iodinated contrast agent (iobitridol, Guerbet, Sulzbach, Germany) at a flow of 3 ml/s, using an automated injector (Liebel, Flarsheim, Germany). Contrast-enhanced CT scans were acquired 35 s after the start of injection to examine the thorax from the upper-abdomen to the neck. In all patients, scanning was performed using an expiratory breath hold technique with a single breath hold at adjusted PEEP, a voltage of 120 kV, and a current of 50–150 mA. Contiguous reconstructed sections were obtained with 5-mm collimation in the mediastinum and lung kernel and stored on optical disk in a digital picture archiving and communication system (PACS, Centricity, GE Medical, Dornstadt, Germany) for further review.

The pulmonary artery trunk (PAT) diameter was measured independently by two investigators (M.B., H.K.) within 3 cm below the pulmonary artery bifurcation at its widest portion, as described elsewhere [7, 16], and the mean value was used for further analysis.

Following CT scanning, the patients were transported to our ICU, where mean pulmonary artery pressure, referenced to the mid axillary line, was measured at end expiration within 120 min of the CT scan, using a flow-directed catheter (Edwards Lifesciences, Unterschleissheim, Germany). During this period, the patterns of mechanical ventilation, including PEEP, were kept constant. All vascular pressures were recorded at end expiration as displayed on the oscilloscopes of the respirator (Evita 4, Dräger Medical, Lübeck, Germany) and hemodynamic monitor (Siemens 1281, Erlangen, Germany). For cardiac output measurements by thermodilution, 10 ml of cold saline was injected in triplicate, and mean values were used for further calculations such as pulmonary vascular resistance and right ventricular stroke work index. Simplified acute physiologic score [17] and sepsis-related organ failure assessment [18] were calculated from lowest values obtained within the first 24 h after admission.

Definitions

To evaluate the prevalence of PH in patients with ARDS, we defined PH as presence of a mean pulmonary artery pressure of at least 25 mmHg, following the US National Institutes of Health (NIH) and the World Health Organization (WHO) [19]. For further correlations a mean PAP of 30 mmHg (moderate PH) and more was used. Pulmonary artery trunk (PAT) diameter was considered increased with a diameter of ≥ 29 mm, in accordance with others [7, 20].

Right ventricular failure was defined as an enlarged right atrium (> 4 cm) and right ventricle (right ventricular

end-diastolic area greater than left ventricular end-diastolic area) during trans-esophageal echocardiography in the presence of normal left ventricular dimension and contractility and the demand for inotropic support in the presence of pulmonary artery hypertension.

Statistical analysis

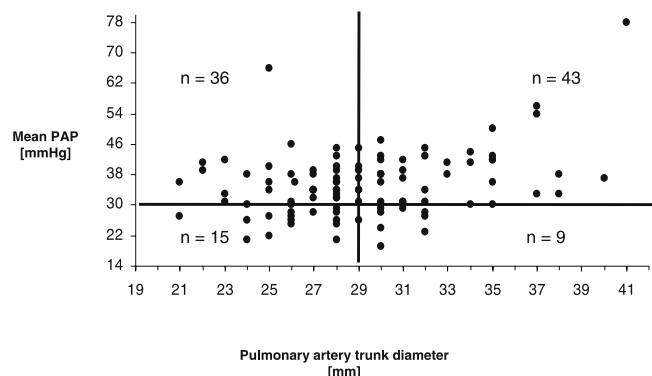All metric data are presented as means ($\pm$ standard deviation, SD). Correlations were performed using the Pearson correlation analysis. A *p* value of less than 5% was considered statistically significant. The software SAS 8.02 (SAS Institute, Cary, NC, USA) was used for statistical analysis. For comparison of groups, the Wilcoxon rank test was used, if variables were continuous. Fisher's exact test was used for dichotomous variables. Otherwise, the chi-square test was used.

To assess independent predictors of death, logistic regression modeling, combined with a backward variable elimination, was employed. The required level of significance for a variable to remain in the model was set to 0.05. Logistic regression was also applied to establish relations between high values of PAP (PAP $\geq$ 25 mmHg) and PAT (and compliance). As a measure of association, we report the area under the receiver-operating-characteristics (ROC) curve. For assessment of interobserver variability in measurements of PAT, we calculated the concordance correlation of Lin [21].

Fig. 1 Plot of mean pulmonary artery pressure (*PAP*) obtained by right heart catheterization and pulmonary artery trunk diameter measured on computed tomography scans of patients with acute respiratory distress syndrome. Threshold for pulmonary artery hypertension with computed tomography (pulmonary artery trunk diameter $\geq$ 29 mm, *vertical bar*), and with right heart catheterization (mean pulmonary artery pressure $\geq$ 30 mmHg, *horizontal bar*)

Results

Ninety-five (95) patients (92.2%) had a pulmonary hypertension associated with ARDS, 16 of them (16.8%) graded mild, 72 (75.8%) graded moderate, and seven (7.4%) graded severe. The etiology for the ARDS was sepsis in 32 (31.1%), trauma in seven (6.7%), aspiration in eight (7.8%), and pneumonia in 56 patients (54.4%), respectively.

Mean pulmonary artery trunk diameter in ARDS patients averaged 29.2 ± 4.1 mm at a mean pulmonary artery pressure (PAP) of 35.4 ± 8.8 mmHg (Table 1). The interobserver concordance in respect to the measurement of the PAT diameter was high, with a concordance correla-

Table 1 Cardiopulmonary variables of patients ($n = 103$) with acute respiratory distress syndrome on admission (means $\pm$ SD)

Variable	–
Pulmonary artery trunk diameter (mm)	29.2 ± 4.1
Mean pulmonary artery pressure (mmHg)	35.4 ± 8.8
Pulmonary vascular resistance index (dyne s cm^{-5} m^{-2})	370 ± 163
Right ventricular stroke work index (gm m^{-2})	11 ± 4.8
PEEP (mbar)	15.8 ± 3.7
PaCO$_2$ (mmHg)	80 ± 34
Compliance (ml mbar^{-1})	29.5 ± 13.9
Minute ventilation (l min^{-1})	9.4 ± 2.3
Venous admixture (Q$_s$/Q$_t$, %)	42 ± 13
Cardiac index (l min^{-1} m^{-2})	4.4 ± 1.5
Central venous pressure (mmHg)	15.3 ± 4.4
Pulmonary capillary wedge pressure (mmHg)	16 ± 5.4
Norepinephrine (μg kg^{-1} min^{-1})	0.5 ± 0.9
Epinephrine (μg kg^{-1} min^{-1})	0.4 ± 1.3
PaO$_2$/FiO$_2$-ratio (mmHg)	94 ± 37
Lung injury score	3.4 ± 0.4
Age (years)	43 ± 15
Simplified acute physiologic score (SAPS II)	45 ± 13
Sepsis-related organ failure assessment (SOFA)	11 ± 4
Continuous renal replacement therapy [n]	61
Inhalational nitric oxide [n]	48
Extracorporeal membrane oxygenation [n]	21

Table 2 Stratified distribution of values of mean pulmonary artery pressures (*PAP*) and pulmonary artery trunk (*PAT*) diameters in patients with acute respiratory distress syndrome

		PAP (mmHg)		Σ
		< 30	≥ 30	
PAT (mm)	< 29	15	36	51
	≥ 29	9	43	52
Σ		–	24	79	103

Table 3 Causes of death in patients with acute respiratory distress syndrome

Causes of death	n (%)
Septic multiple organ failure	19 (51.3%)
Right ventricular failure	11 (29.7%)
Miscellaneous	7 (19%)
Mesenteric infarction	2
Myocardial infarction	1
Brain infarction	1
Pulmonary embolism	1
Pulmonary bleeding	1
Liver failure	1
Total	37/103 (35.9%)

tion coefficient of 0.9. There was a significant correlation between PAT diameter and PAP ($r = 0.34$, $p < 0.001$). $PaCO_2$ correlated with lung injury score (LIS, $r = 0.4$, $p = 0.003$), PaO_2/FiO_2 ($r = -0.41$, $p < 0.001$), compliance (-0.42, $p < 0.001$), but only weakly with PAP ($r = 0.21$, $p = 0.03$) and PAT ($r = 0.24$, $p = 0.16$).

Thirty-seven (37) patients (35.9%) died, 29.7% of them due to right heart failure (Table 3). Patients who died had a significantly lower compliance (24.6 ± 12.1 ml mbar^{-1} vs. 30.6 ± 12.1 ml mbar^{-1}, $p = 0.033$), were older (51 ± 13 years vs. 37 ± 13 years, $p < 0.0001$), and were on mechanical ventilation for a longer time prior to admission to our ICU (9 ± 9 days vs. 5 ± 6 days, $p = 0.013$). Truncus diameter was not different between survivors and non-survivors (28.9 ± 4.3 mm vs. 30.6 ± 4.3 mm). A logistic regression analysis revealed older age (odds ratio (OR): 1.083, 95% confidence interval (CI): 1.03–1.13; $p = 0.0001$), $PaCO_2$ (OR: 1.02, CI: 1.01–1.04; $p = 0.007$), and sequential organ failure assessment score on admission (SOFA, OR: 1.2, CI: 1.03–1.4; $p = 0.017$) as independent predictors of death.

Seventy-nine (79) patients with PH (83.2%) had moderate or severe pulmonary hypertension associated with ARDS. Of these, 43 had a PAT diameter of 29 mm or greater, yielding a sensitivity of 0.54. Specificity averaged 0.63. The positive predictive value was 0.83 (43/52), whereas the negative predictive value was 0.28 (15/51). The optimal discrimination point was determined from ROC analysis as PAT = 29 mm.

In patients with moderate or severe pulmonary hypertension, correlations were found between $PaCO_2$ and LIS ($r = 0.36$, $p = 0.006$), PaO_2/FiO_2 ($r = -0.37$, $p < 0.001$), compliance ($r = -0.4$, $p < 0.001$), and PAT diameter ($r = 0.33$, $p = 0.003$), but not with PAP ($r = 0.18$, $p = 0.11$). Furthermore, PaO_2/FiO_2 was correlated with compliance ($r = 0.38$, $p < 0.001$).

Logistic regression of PAP ≥ 25 mmHg vs. PAP < 25 mmHg on PAT did not reveal a significant predictive value for PAT (OR = 1.07, CI: 0.86–1.33, $p = 0.53$). Accordingly, the area under the ROC curve was at 0.55, only marginally above the value 0.5 of the straight line. Adding compliance to the logistic model did not advance the predictive power.

Discussion

Our data show that pulmonary hypertension has a high prevalence in patients with severe ARDS. Of patients referred to our ARDS center, 92.2% met the definition for PH. Even when using the threshold for moderate PH (≥ 30 mmHg), 79 patients (76.7%) still presented with PH. Most important, PAT diameter on the CT scan performed immediately after admission was unreliable in predicting PH in patients with severe ARDS, with a negative predictive value of only 0.28. Furthermore, the prediction was incorrect in as much as 44% of patients. Even a threshold of PAT diameter greater than 29 mm resulted in an incorrect assumption of PH in 17.3% of patients, whereas 70.6% of patients with a PAT diameter of less than 29 mm did have PH.

With reported specificities and sensitivities of 89% and 87%, respectively, a PAT diameter of 29 mm predicts PH fairly well in patients with chronic pulmonary disease [7]. In patients with severe ARDS and hence rapid onset pulmonary arterial hypertension, we showed that, while a PAT diameter of 29 mm is the optimum cutoff point for PH detection, it has much less specificity and sensitivity than in chronic conditions.

Possibly, pulmonary vascular changes in chronic pulmonary arterial hypertension lead to remodeling of the pulmonary artery, resulting in increased diameter. Nevertheless, due to its incorrect prediction in almost half of the patients, PAT diameter measurements are inappropriate for clinical decision-making in ARDS.

PH in ARDS has received revived attention, as permissive hypercarbia can cause acute cor pulmonale [22], and even short-lasting elevations of PAP can lead to impairment of right ventricular function [23]. The interpretation of these results remains speculative, as the outcome of patients with ARDS and PH has not yet been determined. An

indication of the relevance of PH arises from the observation that patients who died from ARDS had a significantly higher PAP over a period of 3 weeks than patients who survived [11]. The importance of looking at PAP is underlined by right heart failure being the second most common cause of death in our patients. Whether therapeutic strategies in lowering PAP [2–4] are of value in patients with ARDS is unclear. In any case, before treatment, a reliable but less invasive measurement of PAP than right heart catheterization would be welcome.

In patients with chronic cardiopulmonary disease, measurements of pulmonary artery diameter have been reported to detect PH [7, 20, 24]. However, serial measurements by CT scan have never been used to monitor either treatment or the course of illness. In contrast, echocardiography has been appraised as an excellent tool for this purpose due to its minimal invasiveness [25]. In a large prospective study on patients evaluated for lung or heart/lung transplantation, however, echocardiography was recently shown to have limited value in diagnosing PH when compared with right heart catheterization. Comparable with our study, PH prediction was incorrect in over 50% of patients [9]. By the same token, an incorrect prediction of PH by echocardiography was found in pregnant women when compared with right heart catheterization [26]. Therefore, a prediction of pulmonary artery pressure by radiological techniques is of questionable value when the pulmonary artery pressure has been estimated by echocardiography [8, 20]. Furthermore, it remains to be shown whether these results are transferable to critically ill, mechanically ventilated patients.

It has been shown that right heart catheterization in patients with acute respiratory distress syndrome changed the therapy in most cases [27], although the benefit of these changes has not been demonstrated. According to our results, PAC is the only reliable tool to identify ARDS patients with PH, and the only method to monitor PAP-lowering therapies.

Our study has limitations. First, all previous radiologic studies on PAT diameter were performed in patients breathing spontaneously at atmospheric pressure. This is an important objection, as mechanical ventilation by increasing alveolar pressure and lung volume may alter intra-mediastinal pressure, decrease transmural pulmonary artery pressure, and hence end-expiratory PAT diameter. However, since variation of positive end-expiratory pressure among patients was small and, due to the low lung compliance in ARDS, increased alveolar pressure is transmitted to only a small extent to the mediastinum, it is very unlikely that mechanical ventilation resulted in much bias. In fact, any bias decreasing PAT diameter would underestimate the presence of PH, i.e., prediction would be even worse. Second, because all patients were referred from other hospitals in severe distress by helicopter or ambulance, they received the CT scanning even before entering the ICU, where a pulmonary artery catheter was subsequently placed. Therefore, we cannot rule out that values of PAP during CT scan may have been somewhat different than after ICU admission. However, any error is likely to be random and of small magnitude, as PAP in patients with ARDS is known to change little over much longer time periods [11].

We report a high incidence of PH in severe ARDS. Furthermore, the magnitude of PH is higher than documented in large randomized trials [13] and observational studies [11], and right ventricular failure as cause of death has not been emphasized. Our patients are different from those included in studies and can be regarded as treatment failures by their referring hospitals referred as emergency admissions to our institution. This raises the question of whether investigations in ARDS patients in general correctly reflect pulmonary hemodynamics in severe ARDS. Our data confirm observations of Hemmila et al. [28], who found PH of similar magnitude in patients with severe ARDS referred to extracorporeal lung support. Interestingly, they recorded PH in the presence of normocarbia, suggesting that structural pulmonary changes rather than hypercarbia are largely responsible for PH in severe ARDS [28]. This assumption is also supported by the weak correlation between $PaCO_2$ and PAP in our patients and no influence of $PaCO_2$ in patients with moderate and severe PH. Therefore, it remains speculative to which extent an increased $PaCO_2$ influences the PAP in patients with already-increased pulmonary vascular resistance due to ARDS or other parenchymal changes. PAP has been reported to be significantly higher in patients dying from ARDS than in surviving patients [11], but, in this latter series, PH was still approximately 7 torr lower than in our patients. Accordingly, the high incidence of right heart failure in our patients with severe ARDS is the consequence of PH. $PaCO_2$, next to older age and SOFA, was an independent predictor of death.

In summary, 92% of patients with severe ARDS admitted to an ARDS treatment center suffer from PH. However, prediction of pulmonary arterial hypertension by PAT diameter measurements is of limited value, as the prediction is incorrect in almost half of the patients. Its sensitivity of 0.54 and specificity of 0.63 make CT scanning an unreliable clinical tool in predicting PH in ARDS patients.

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