Alveolar Dead Space Fraction is Not Associated with Early RV Systolic Dysfunction in Pediatric ARDS

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Abstract

Primary Hypothesis: We hypothesized that higher alveolar dead space fraction (AVDSf) at PARDS onset would be associated with right ventricular (RV) systolic dysfunction within the first 24 hours of PARDS. Study Design and Methods: We performed a retrospective single-center cohort study of PARDS patients with clinically obtained echocardiograms within 24 hours. Primary exposure was AVDSf at PARDS onset. Primary outcome was RV systolic dysfunction as defined by RV global longitudinal strain (GLS) (> - 18%). Secondary outcomes included pulmonary hypertension (PH) and RV systolic dysfunction as defined by other echocardiogram parameters, and measures of oxygenation. Unadjusted and adjusted logistic and linear regression were used to investigate AVDSf associations with outcomes. Results: Seventy-six patients were included: median age 6.2 years, 50% female, and 66% with moderate or severe PARDS. Median AVDSf was 0.2 (IQR 0.1-0.3), 32% had RV dysfunction, and 24% had PH. Unadjusted and adjusted logistic regression showed no association between AVDSf and RV systolic dysfunction or PH by any echocardiographic measure. Unadjusted and adjusted linear regression demonstrated the association of AVDSf with both oxygenation index and PaO $_2$/FiO $_2$. AVDSf did not discriminate RV dysfunction (AUROC for RV GLS was 0.51, 95% CI 0.36-0.66). Conclusion: AVDSf at PARDS onset was not associated with RV systolic dysfunction or PH within 24 hours but was associated with metrics of hypoxemia and may be more reflective of pulmonary causes of ventilation-perfusion mismatch. Future investigations should focus on clarifying the clinical utility of AVDSf in relation to existing metrics throughout the course of PARDS.

INTRODUCTION

Pediatric acute respiratory distress syndrome (PARDS) has a high morbidity and mortality rate. While mortality rates are decreasing over time and vary across regions, overall mortality continues to be between 15-20%[1-3] with multi-organ dysfunction syndrome and refractory shock accounting for up to 60% of mortality[4,5]. Right ventricular (RV) systolic dysfunction and pulmonary hypertension (PH) have been independently associated with worse outcomes in PARDS, presumably by further impairing oxygenation and increasing the risk of multiple organ dysfunction syndrome[6,7]. Early detection and treatment of RV dysfunction and/or PH in PARDS may improve patient outcomes.

The lung physiologic dead space ratio (VD/VT) can be estimated through the Enghoff modification of the Bohr formula[8]. This is also known as the alveolar dead space fraction (AVDSf) and is a measure of ventilation-perfusion mismatch that represents the proportion of inhaled air not participating in gas exchange. It is an easily obtained clinical variable at the bedside, requiring only measurement of end-tidal carbon dioxide ($PetCO_2$) and arterial partial pressure of CO_2 ($PaCO_2$). AVDSf is low in healthy children and increases in

the setting of pulmonary injury and low cardiac output[9]. Higher AVDSf at the onset of PARDS is associated with mortality[10,11]. As it is affected by perfusion abnormalities from intrinsic pulmonary vascular disease, AVDSf may be a marker for risk of developing RV systolic dysfunction or acute cor pulmonale in adults[12]. However, the prognostic utility of AVDSf in PARDS may also be due to lung overdistension, iatrogenic generation of dead space, or reflect the risks associated with unsafe ventilator pressures. Whether AVDSf is primarily a marker of decreased pulmonary blood flow in the setting of RV dysfunction or PH or is primarily a marker of pulmonary overdistension in children with PARDS is unknown.

The primary objective of this study was to determine the association between AVDSf at PARDS onset with evidence of RV systolic dysfunction by 2D speckle tracking echocardiography. Our hypothesis was that higher AVDSf at PARDS onset would be associated with evidence of RV systolic dysfunction as measured by RV global longitudinal strain on clinically obtained echocardiograms within 24 hours of PARDS onset.

MATERIALS AND METHODS

Study Design and Data Source

This was a retrospective analysis of a single-center prospective cohort study as previously described[13] who were admitted with PARDS between July 1, 2012, and April 30, 2018, requiring conventional invasive mechanical ventilation, and who had a clinically indicated echocardiogram performed within 24 hours of PARDS onset. Other inclusion criteria were availability of paired end tidal $PetCO_2$and $PaCO_2$ measurements as well as echocardiogram images of sufficient quality to perform RV strain analyses. Patients were excluded for PARDS onset outside of the study center PICU, chronic invasive mechanical ventilation, invasive mechanical ventilation >7 days, and for respiratory failure primarily secondary to congestive heart failure, fluid overload, or exacerbation of chronic lung disease. Patients with paired PetCO2 and PaCO2 values that yielded a negative AVDSf were also excluded. The study was approved by the Children's Hospital of Philadelphia's (CHOP) Institutional Review Board with a waiver of the need for informed consent.

Definitions

The first qualifying arterial blood gas for the diagnosis of PARDS was used for the AVDSf calculation and was considered the onset of PARDS for purposes of this study. AVDSf was calculated using the Enghoff modification of the Bohr formula: AVDSf = ($PaCO_2$ - $PetCO_2$) / $PaCO_2$. Echocardiograms were analyzed as previously described (Himebauch 2018). Echocardiographic measures of RV systolic function included: qualitative assessment (normal or mildly, moderately, or severely diminished), fractional area change (FAC), tricuspid annular plan systolic excursion (TAPSE), RV peak systolic global longitudinal strain (RV GLS), and RV peak systolic strain (also known as free wall strain). Abnormal FAC was defined as less than 35%. Abnormal TAPSE was defined as a value less than -2 standard deviations below published pediatric normal values for age[14] and calculated through an online calculator (parameterz.blogspot.com). Abnormal RV GLS and strain were defined as values greater than -18% and greater than -21%, respectively, as less negative values reflect worse function. As pulmonary arterial catheters are rarely used in clinical practice, echocardiographic surrogates of pulmonary hypertension were defined as flattening or bowing of the septal position in systole in the parasternal short-axis view, tricuspid regurgitant velocity > 2.8 m/s^2, or RV systolic pressure estimate greater than $\frac{1}{2}$ systemic systolic pressure at the time of echocardiogram.

Primary Exposure and Outcomes:

The primary exposure was AVDSf at PARDS onset analyzed as a continuous variable. The primary outcome was RV systolic dysfunction as defined by abnormal RV GLS (dichotomous as defined above). Secondary outcomes included echocardiogram evidence of pulmonary hypertension and RV systolic dysfunction as defined by RV strain, TAPSE z-score, FAC, and qualitative assessments as well as measures of oxygenation including oxygenation index (OI = mPaw x FIO_2 x 100 / PaO_2) and PaO_2/FiO_2ratio.

Data Analysis and Power Calculations

Statistical analyses were performed with Stata 16.1 (StataCorp, College Station, TX, USA). Summary data

for continuous variables were reported as median with interquartile ranges (IQR) and for categorical variables as numbers with percentages. Continuous data were compared using the Wilcoxon Rank-Sum test and categorical data were compared by Fisher exact test. The associations between AVDSf at onset and echocardiographic findings within the first 24 hours as well as oxygenation metrics were assessed with univariable and multivariable logistic regression. Given the relatively small number of patients with echocardiographic abnormalities, potential confounders were included into the logistic regression model one variable at a time to not overfit the model. Additional analyses included the use of AVDSf as a binary variable based on various cutoffs and the use of RV dysfunction measures as continuous variables. To test the ability of AVDSf to discriminate patients with RV systolic dysfunction or PH, area under the receiver operating curves (AUROC) were calculated. P-values < 0.05 were considered significant for all analyses.

Initial power analysis using the assumptions of abnormal RV GLS rate of 35% in the population and a difference in AVDSf between groups of 0.15 with a standard deviation of 0.2 resulted in a total population of 65 patients required for the study (80% power, alpha = 0.05).

RESULTS

During the study timeframe, 115 patients had a clinically performed echocardiogram completed within 24 hours of PARDS onset with 76 patients meeting full inclusion criteria (Figure 1). Median age was 6.2 years (IQR 1.9-9.8), 50% were male, and 22 patients (32%) were immunocompromised (Table 1). The most common diagnoses were infectious pneumonia (43%) and sepsis (29%) and the distribution of PARDS severity was: 34% mild, 34% moderate, and 32% severe (Table 1). Median time between $PaCO_2$ and $EtCO_2$values was 15 min and median time from ARDS diagnosis to echocardiogram was 1.2 hours (IQR -4.6 to 4.4). Mortality was 34%.

Median RV GLS value for the cohort was –21.0% (IQR –24.3 to -16.8) with 24 patients (32%) having abnormal RV GLS (> -18%). 17 patients (24%) were found to have PH. The median values (IQRs) for other echocardiographic measures of RV systolic function are displayed in Supplemental Table 1. There were no differences in the distribution of AVDSf between those with and without abnormal RV GLS or those without or without echocardiographic evidence of PH (Figure 2).

Unadjusted logistic regression showed no association of AVDSf at onset with the primary outcome of echocardiographic evidence of RV systolic dysfunction defined as RV GLS > -18% nor with the secondary outcome of echocardiographic evidence of PH within 24 hours of PARDS diagnosis (Table 2). This remained true when adjusting individually for other clinically important covariates including immunocompromised status, PRISM III score, OI, iNO use, and age (Table 2). Similar analyses showed no association of AVDSf at onset with other secondary outcomes of echocardiographic measures of RV systolic function (Supplemental Table 2). Sensitivity analyses were performed including the use of AVDSf as a binary variable based on various cutoffs (0.15, 0.25, and 0.35) and the use of RV dysfunction measures as continuous variables with the regression models showing no association between AVDSf at onset with measures of RV systolic dysfunction or PH (data not shown).

AVDSf at onset did not discriminate RV systolic dysfunction with AUROC 0.51 (95% CI 0.36-0.66) for abnormal RV GLS and AUROC 0.56 (95% CI 0.44-0.73) for PH. Similarly, AVDSf at onset did not discriminate PH or RV systolic dysfunction as measured by other echocardiographic parameters (Supplemental Figure 1).

AVDSf at onset was associated with secondary outcome measures of oxygenation (OI and P/F ratio) in both unadjusted and adjusted linear regression models (Table 3). There was no difference in AVDSf at onset between different ARDS severities (Kruskal-Wallis p=0.3678, Cuzick non-parametric test of trend p=0.214, Supplemental Figure 2).

DISCUSSION

In this retrospective cohort study of PARDS patients with clinically obtained echocardiograms, there was no association between AVDSf at PARDS onset and RV systolic dysfunction or pulmonary hypertension within 24 hours of PARDS diagnosis. AVDSf was, however, associated with measures of oxygenation at

PARDS onset, suggesting that the primary determinant of AVDSf was ventilation-perfusion mismatch from pulmonary overdistension or increased intrapulmonary shunt rather than reduced pulmonary blood flow from increased pulmonary vascular resistance.

In pediatrics, elevated AVDSf, RV systolic dysfunction, and PH have all been independently associated with mortality and worse outcomes in PARDS[6,7,10,11]. As alveolar dead space is increased in low cardiac output states and in intrapulmonary shunt, elevated AVDSf likely reflects a combination of these physiologies. Our primary hypothesis was that higher AVDSf would be associated with echocardiographic evidence of RV systolic dysfunction and PH due to an increase in pulmonary vascular resistance. However, this was not demonstrated in this cohort of patients who had clinical echocardiograms performed a median of 1.2 hours from the qualifying arterial blood gas.

AVDSf at onset also did not discriminate echocardiographic measures of RV dysfunction and PH. We did find associations between AVDSf and secondary outcomes of measures of oxygenation (OI, P/F ratio) at PARDS onset. It may be that very early during PARDS higher AVDSf could be more reflective of intrapulmonary shunt as positive pressure is being initiated and titrated to maximize lung recruitment. In one study of sheep models of early ARDS, increases in estimated AVDSf by PET scans were attributable primarily to redistribution of perfusion likely related to mechanisms including hypoxic pulmonary vasoconstriction and gravitational effects with redistribution of perfusion away from non-dependent lung regions with no change in mean pulmonary artery pressures[15]. Further, compared to other PARDS cohorts, our study cohort had a relatively high AVDSf at onset (median 0.2, IQR 0.1-0.3) and had a higher severity of illness. This may have created selection bias in our sample that could have biased toward the null hypothesis.

One recent adult study demonstrated that increases in AVDSf were associated with relative increases in echocardiographic surrogates for pulmonary vascular resistance over the course of ARDS[12], suggesting that a changing and increasing AVDSf over time may be an indicator of those who may be at risk for RV systolic dysfunction. As new or persistent RV systolic dysfunction during the first 8 days of PARDS is associated with worse outcomes[7], future studies in pediatric patients should investigate the longitudinal association of changing AVDSf as a marker or potential predictor of PARDS-related pulmonary hypertension or subsequent RV dysfunction. Similar to studies showing that oxygenation metrics and pulmonary mechanics early in PARDS are not associated with pulmonary injury and outcomes[4,13,16], it is possible that using AVDSf at later time points or the trajectory of AVDSf will have more value, particularly as PARDS pathophysiology evolves into worsening hypoxemia and/or multiple organ dysfunction syndrome. As pulmonary arterial catheters are rarely used in modern PARDS management, prospective and protocolized echocardiograms may also allow for other non-invasive surrogates of elevated pulmonary vascular resistance or RV-pulmonary arterial coupling to be more fully investigated. Alternatively, it is possible that pulmonary, rather than vascular, physiology ultimately determines AVDSf. In either case, the clinical utility of AVDSf should be clarified in future studies.

Our study has limitations including its retrospective design and single-center cohort. We selected PARDS patients who had a clinically obtained echocardiogram and available $PetCO_2$ data, which restricted our cohort to approximately 22% of the total patients from the PARDS database during the study timeframe. As discussed above, this resulted in a cohort with a higher severity of illness with bias toward patients more likely to have hemodynamic instability or specific diagnoses, such as sepsis. Therefore, generalizability to all PARDS patients may be limited. Another limitation from our retrospective design was the quality of $ETCO_2$ data available for review. $ETCO_2$ values were directly recorded from the electronic medical record using the closest value within an hour of the first qualifying blood gas at PARDS onset and had a median time from blood gas of 15 min. However, it is possible that the $ETCO_2$ value may have changed at the time of the blood gas. Approximately one-third of the patients with echocardiograms did not have EtCO2 data available or had an EtCO2 recorded that yielded a negative AVDSf when calculated. Finally, ideally alveolar dead space as measured by volumetric capnography would also be included as the correlation of alveolar dead space estimated with that method compared to AVDSf is reduced in patients with hypoxemia[8,9].

In this retrospective cohort study, alveolar dead space fraction at PARDS onset was not associated with RV systolic dysfunction or pulmonary hypertension identified by echocardiography within 24 hours of PARDS

onset and may be more closely associated with ventilation-perfusion mismatch from pulmonary overdistension or increased intrapulmonary shunt. Future investigations should focus on clarifying the clinical utility of AVDSf in relation to existing metrics throughout the course of PARDS.

REFERENCES

1. Wong JJ, Jit M, Sultana R, Mok YH, Yeo JG, Koh JWJC, Loh TF, Lee JH. Mortality in pediatric acute respiratory distress syndrome: a systematic review and meta-Analysis. J Intensive Care Med 2019; 34(7):563-571.
2. Schouten LRA, Veltkamp F, Bos AP, van Woensel JBM, Neto AS, Schultz MJ, Wösten-van Asperen RM. Incidence and mortality of acute respiratory distress syndrome in children: a systematic review and meta-Analysis. Crit Care Med 2016; 44(4):819-829.
3. Orloff KE, Turner DA, Rehder KJ: The current state of pediatric acute respiratory distress syndrome. Pediatr Allergy Immunol Pulmonol 2019; 32(2):35-44.
4. Khemani RG, Smith L, Lopez-Fernandez YM, Kwok J, Morzov R, Klein MJ, Yehya N, Willson D, Kneyber MCJ, Lillie J, et al.; Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) Investigators; Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. Lancet Respir Med 2019; 7(2):115-128.
5. Dowell JC, Parvathaneni K, Thomas N, Khemani RG, Yehya N. Epidemiology and cause of death in pediatric acute respiratory distress syndrome. Crit Care Med 2018;46(11):1811-1819.
6. Himebauch AS, Yehya N, Wang T, Conlon T, Kilbaugh TJ, McGowan FX, Mercer-Rosa L. Early right ventricular systolic dysfunction and pulmonary hypertension are associated with worse outcomes in pediatric acute respiratory distress syndrome. Crit Care Med 2018; 46:e1055-e1062.
7. Himebauch AS, Yehya N, Wang Y, McGowan FX, Mercer-Rosa L. New or persistent right ventricular systolic dysfunction is associated with worse outcomes in Pediatric Acute Respiratory Distress Syndrome. Ped Crit Care Med 2020; 21:e121-e128.
8. Bourgoin P, Baudin F, Brossier D, Emeriaud G, Wysocki M, Jouvet P. Assessment of Bohr and Enghoff dead space equations in mechanically ventilated children. Respir Care 2017;62(4):468-474.
9. Bhalla AK, Rubin S, Newth CJL Ross P, Morzov R, Soto-Campos G, Khemani R. Monitoring dead space in mechanically ventilated children: volumetric capnography versus time-based capnography. Resp Care 2015; 60:1548-1555
10. Bhalla AK, Belani S, Leung D, Newth CJL, Khemani RG. Higher dead space is associated with increased mortality in critically ill children. *Crit Care Med* 2015; 43(11): 2439-45.
11. Yehya N, Bhalla AK, Thomas NJ, Khemani RG. Alveolar dead space fraction discriminates mortality in pediatric acute respiratory distress syndrome. *Ped Crit Care Med* 2016; 17(2):101-109.
12. Papolos AI, Schiller NB, Belzer A, Zhuo H, Gotts JE, Bibby D, Calfee CS, Matthay MA. Pulmonary dead space monitoring: identifying subjects with ARDS at risk of developing right ventricular dysfunction. Resp Care 2019; 64(9):1101-1108.
13. Yehya N, Servaes S, Thomas NJ. Characterizing degree of lung injury in pediatric acute respiratory distress syndrome. *Crit Care Med*2015; 43:937-946.
14. Koestenberger M, Ravekes W, Everett AD, Stueger HP, Heinzl B, Gammillscheg A, Cvirn G, Boysen A, Fandl A, Nagel B. Right ventricular function in infants, children, and adolescents: reference values of tricuspid annular plane systolic excursion (TAPSE) in 640 healthy patients and calculation of z score values. J Am Soc Echocardiogr 2009;22:715-719.
15. Beda A, Winkler T, Wellman TJ, De Prost N, Tucci M, Vidal Melo MF: Physiological mechanism and spatial distribution of increased alveolar dead-space in early ARDS: an experimental study. Acta Anaesthesiol. Scand 2021;65:100-108.
16. Yehya N, Thomas NJ. Disassociating lung mechanics and oxygenation in pediatric acute respiratory distress syndrome. Crit Care Med 2017;45(7):1232-1239.

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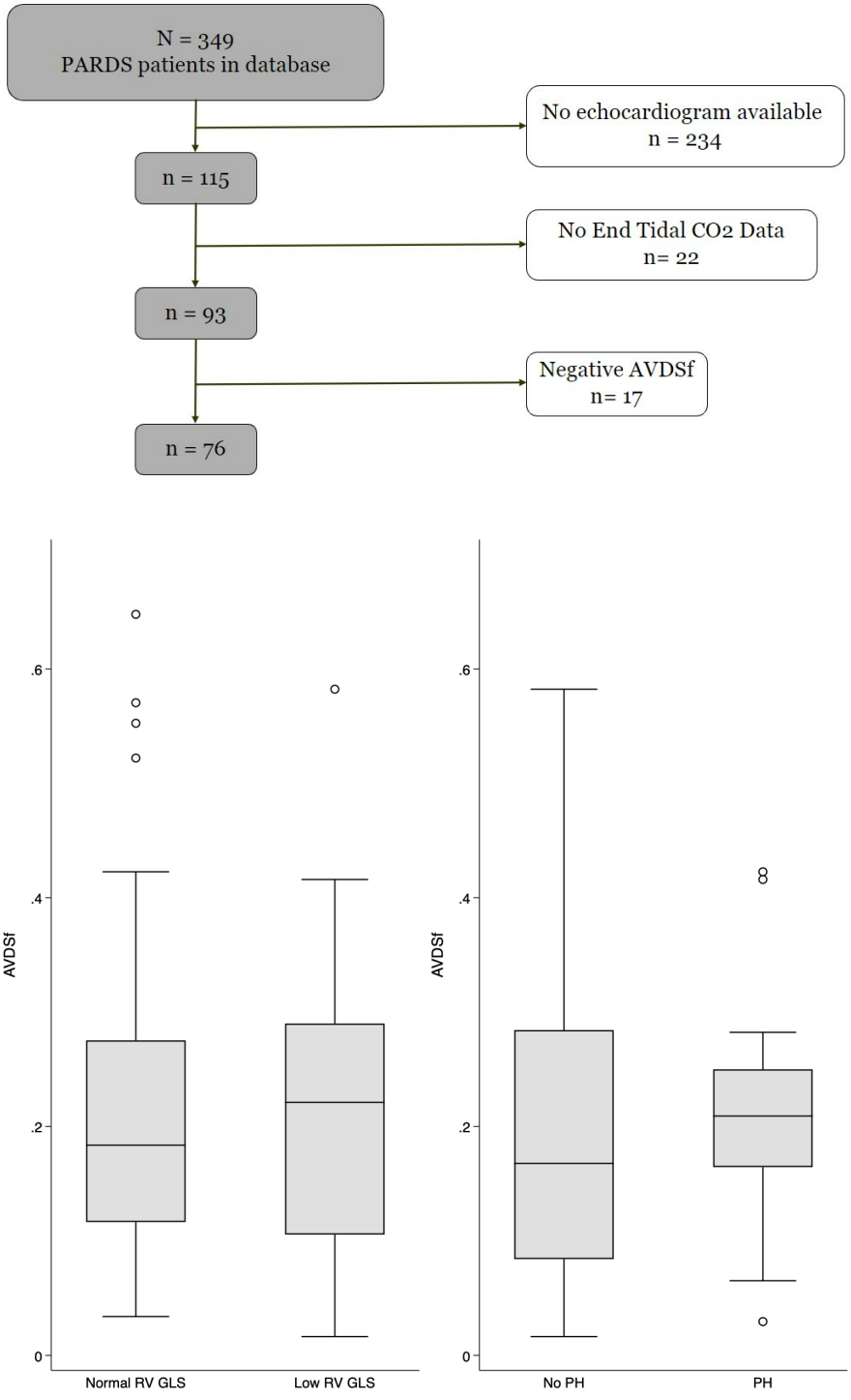

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