Alveolar Dead Space Fraction Discriminates Mortality in Pediatric Acute Respiratory Distress Syndrome*

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Objectives: Physiologic dead space is associated with mortality in acute respiratory distress syndrome, but its measurement is cumbersome. Alveolar dead space fraction relies on the difference between arterial and end-tidal carbon dioxide (alveolar dead space fraction = \( \frac{\text{PetCO}_2 - \text{PACO}_2}{\text{PACO}_2} \)). We aimed to assess the relationship between alveolar dead space fraction and mortality in a cohort of children meeting criteria for acute respiratory distress syndrome (both the Berlin 2012 and the American-European Consensus Conference 1994 acute lung injury) and pediatric acute respiratory distress syndrome (as defined by the Pediatric Acute Lung Injury Consensus Conference in 2015).

Design: Secondary analysis of a prospective, observational cohort.

Setting: Tertiary care, university affiliated PICU.

Patients: Invasively ventilated children with pediatric acute respiratory distress syndrome.

*See also p. 165.

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Interventions: None.

Measurements and Main Results: Of the 283 children with pediatric acute respiratory distress syndrome, 266 had available Pet\(\text{CO}_2\). Alveolar dead space fraction was lower in survivors (median 0.13; interquartile range, 0.06–0.23) than nonsurvivors (0.31; 0.19–0.42; \(p < 0.001\)) at pediatric acute respiratory distress syndrome onset, but not 24 hours after (survivors 0.12 [0.06–0.18], nonsurvivors 0.14 [0.06–0.25], \(p = 0.430\)). Alveolar dead space fraction at pediatric acute respiratory distress syndrome onset discriminated mortality with an area under receiver operating characteristic curve of 0.76 (95% CI, 0.66–0.85; \(p < 0.001\)), better than either initial oxygenation index or Pet\(\text{O}_2/\text{FiO}_2\). In multivariate analysis, alveolar dead space fraction at pediatric acute respiratory distress syndrome onset was independently associated with mortality, after adjustment for severity of illness, immunocompromised status, and organ failures.

Conclusions: Alveolar dead space fraction at pediatric acute respiratory distress syndrome onset discriminates mortality and is independently associated with nonsurvival. Alveolar dead space fraction represents a single, useful, readily obtained clinical biomarker reflective of pulmonary and nonpulmonary variables associated with mortality. (Pediatr Crit Care Med 2016; 17:101–109)

Key Words: acute respiratory distress syndrome; alveolar dead space fraction; pediatric; pediatric acute respiratory distress syndrome

Measures of oxygenation, including Pet\(\text{O}_2/\text{FiO}_2\) (1, 2) and oxygenation index (OI) (3), are surrogates for intrapulmonary shunt and used to stratify the severity of acute respiratory distress syndrome (ARDS). However, degree of hypoxemia has an inconsistent association with mortality (4–6), and aberrations of pulmonary blood flow and microcirculation characteristic of ARDS (7, 8) are not entirely reflected by Pet\(\text{O}_2/\text{FiO}_2\) or OI. Physiologic dead space is the alveolar and anatomic components of ventilation not participating in gas exchange. Dead space is elevated in adult ARDS and correlated with risk of death (9). Dead space increases with decreasing pulmonary blood flow, including pericardiac arrest and other low cardiac output states, from pulmonary embolus, in pulmonary hypertension, and with alveolar overdistension. However,
measurement of physiologic dead space is cumbersome, requiring specialized equipment including a large-volume Douglas bag, metabolic cart or volumetric capnography, and is infrequently performed in routine care (10). The alveolar dead space fraction (AVDSf), which relies on the difference between the \( \text{PAO}_2 \) and the end-tidal \( \text{CO}_2 \) (Pet\( \text{CO}_2 \)), serves as a reasonable estimate of alveolar dead space (11–14). As most patients are ventilated with time-based capnography, AVDSf is readily obtainable. A single institution has reported in children with acute hypoxic respiratory failure (15), and in a separate population of intubated children (16), that elevated AVDSf early in the course of respiratory failure was associated with increased mortality.

Recently, we described a prospective observational study of pediatric ARDS (PARDS) with the aim of assessing the discriminative ability of traditional oxygenation-based metrics of severity (\( \text{PAO}_2/\text{FiO}_2 \) and OI) for survival (17). We did not assess dead space in that report. In the current study, we tested the hypothesis that AVDSf measured early in the course of PARDS was associated with mortality in this prospectively collected cohort.

**METHODS**

**Study Design and Patient Selection**

This study was approved by the Children’s Hospital of Philadelphia’s (CHOP) Institutional Review Board, and requirement for informed consent waived. The cohort has been previously described in detail (17). Briefly, consecutive patients in the PICU were screened daily for eligibility between July 1, 2011, and June 30, 2014. Children (>1 mo and <18 yr) undergoing invasive mechanical ventilation meeting American-European Consensus Conference (AECC) criteria for acute lung injury (ALI; \( \text{PAO}_2/\text{FiO}_2 \) ≤ 300 on two consecutive arterial blood gas samples separated by ≥ 1 hr and bilateral parenchymal infiltrates) were included. Exclusion criteria were 1) respiratory failure exclusively from cardiac failure (determined by echocardiography) or fluid overload, 2) exacerbation of underlying chronic respiratory disease, 3) chronic ventilator dependence, 4) mixing cyanotic heart disease, 5) mechanical ventilation for greater than 7 days before \( \text{PAO}_2/\text{FiO}_2 \) ≤ 300, and 6) PARDS established outside of the CHOP PICU. Determination of bilateral infiltrates was made independently by a PICU attending and a pediatric radiologist blinded to clinical data; only cases agreed by both as consistent with AECC-defined ALI met inclusion (2). Determination of hydrostatic pulmonary edema (from either heart failure or anuric/oliguric renal failure) as the sole etiology of respiratory failure was made in consultation with the PICU attending using available data. As the study was initiated prior to 2012 Berlin updated definitions of ARDS (1), we did not specify a minimum positive end-expiratory pressure (PEEP); however, our institutional practice does not use PEEP less than 5 cm H\(_2\)O, and all patients therefore met the Berlin criteria. Similarly, as these data were collected prior to the 2015 Pediatric Acute Lung Injury Consensus Conference (PALICC) definitions of PARDS (3), children who met PARDS criteria by noninvasive (Sp\( \text{O}_2 \)) criteria were not enrolled; however, all children met PARDS criteria by invasive (O\( \text{I} \)) criteria.

**Data Collection and PARDS Management**

Demographics at admission, ventilator settings at PARDS onset and 24 hours after, and laboratory data and medications for the first 3 days of PARDS were recorded. We recorded first qualifying values (after initiation of ventilation) of \( \text{PAO}_2/\text{FiO}_2 \) and OI at PARDS diagnosis and 24 hours after diagnosis.

Absent a standardized ventilator protocol, our institutional practice is to initiate conventional ventilation with a minimum 5 cm H\(_2\)O of PEEP and attempt to wean \( \text{FiO}_2 \) to less than or equal to 0.60. There is no specific target \( \text{PAO}_2 \), but typically \( \text{PAO}_2 \) greater than or equal to 60 mm Hg is accepted as long as there is clinical stability. Inability to wean \( \text{FiO}_2 \) prompts PEEP escalation and subsequent efforts to wean \( \text{FiO}_2 \), attempting to maintain peak inspiratory pressures (PIPs) less than or equal to 35 cm H\(_2\)O. We exclusively use decelerating flow during conventional ventilation (either pressure control or pressure-regulated volume control). Persistently elevated PIP (≥ 35 cm H\(_2\)O), ongoing hypercarbia (\( \text{PACO}_2 \) ≥ 80), or oxygenation difficulties (inability to wean \( \text{FiO}_2 \) ≤ 0.60 despite increasing PEEP) prompted consideration for changing mode of ventilation or escalating to extracorporeal membrane oxygenation (ECMO). There was no standardization of ancillary therapies (inhaled nitric oxide [iNO], surfactant, neuromuscular blockade, prone positioning, and corticosteroids), which was left to the discretion of the attending physician.

**Calculation of AVDSf**

AVDSf was retrospectively abstracted from the medical records at PARDS onset and 24 hours after. We used the first qualifying arterial blood gas from which the initial \( \text{PAO}_2/\text{FiO}_2 \) and OI at PARDS diagnosis were calculated, and the blood gas 24 hours after PARDS diagnosis, to extract \( \text{PAO}_2 \). The Pet\( \text{CO}_2 \) value immediately preceding these blood gases was used for the following equation: AVDSf = (\( \text{PAO}_2 \) – Pet\( \text{CO}_2 \)) / \( \text{PAO}_2 \), with the requirement that the Pet\( \text{CO}_2 \) value used preceded the \( \text{PAO}_2 \) by no more than 30 minutes and that the endotracheal tube leak was less than 20%. This protocol has been used before to assess AVDSf with good reproducibility (15, 18).

**Other Equations and Definitions**

Metrics of oxygenation used were \( \text{PAO}_2/\text{FiO}_2 \) and OI ((mean airway pressure [mPaw] × \( \text{FiO}_2 \) × 100) / \( \text{PAO}_2 \)). The vasopressor score (19, 20) was calculated by the following equation: dopamine (\( \mu \text{g/kg/min} \) × 1 + dobutamine (\( \mu \text{g/kg/min} \) × 1 + epinephrine (\( \mu \text{g/kg/min} \) × 100 + norepinephrine (\( \mu \text{g/kg/min} \) × 100 + phenylephrine (\( \mu \text{g/kg/min} \) × 100 + milrinone (\( \mu \text{g/kg/min} \) × 10. Nonpulmonary organ failures at time of PARDS diagnosis were identified using the accepted definitions in children (21). The designation of “immunocompromised” required the presence of an immunocompromising diagnosis (oncologic, immunologic, rheumatologic, or transplant) and active immunosuppressive chemotherapy or a congenital immunodeficiency (17, 22). Severity of illness score used was the Pediatric Risk of Mortality (PRISM) III at 12 hours.

The primary reported outcome was PICU mortality. Ventilator-free days (VFD) at 28 days and duration of
mechanical ventilation were also recorded. All mention of “mechanical ventilation” in this study implies invasive ventilation, and noninvasive support was not counted toward VFD or total ventilator days. For VFD and duration of mechanical ventilation, the first day was initiation of invasive ventilation. Liberation from invasive ventilation for greater than 24 hours defined the duration of mechanical ventilation.

Patients requiring reintubation of invasive ventilation after 24 hours of extubation had the extra days counted toward total ventilator days. VFD was determined by subtracting total ventilator days from 28 in survivors. All patients with total ventilator days greater than or equal to 28 days and all PICU nonsurvivors were assigned VFD = 0. In some analyses, VFD was dichotomized to less than or equal to 14 days or greater than 14 days.

Statistical Analysis
All data were analyzed by using Stata 10.0 (StataCorp LP, College Station, TX). Data are expressed as percentages or as median (interquartile range). All variables were found to be non-normally distributed by the Shapiro-Wilk test. Differences between distributions of categorical variables were analyzed by Fisher exact test. Continuous variables were compared by using the Wilcoxon rank sum test. Area under the receiver operating characteristic (AUROC) curve was determined for testing the discriminative ability of AVDSf.

Multivariate logistic regression was performed to test for an independent association between AVDSf and mortality, separately for AVDSf at PARDS onset and at 24 hours. Variables with a univariate association with mortality (p < 0.10 in Table 1) were entered into a backward stepwise regression model, with a p value of less than 0.10 for retention in the model. Because of significant collinearity and overlap between the respiratory variables (Pao2/FiO2, OI, and PIP), only OI was modeled. Because of our primary hypothesis, AVDSf was always included in the model. After the first run, each variable was reintroduced into the model one at a time and retained in the final model if p value of less than 0.10. Model fit was assessed using Hosmer-Lemeshow statistics.

Since AVDSf may be modified by iNO use (selective pulmonary vasodilator, which may alter dead space), we explored the relationship between AVDSf at 24 hours, iNO exposure, and mortality testing an interaction term as additional independent variable in the backward stepwise regression model. Additionally, we constructed a propensity score for iNO use (for details, see supplementary text, Supplemental Digital Content 2).

RESULTS
AVDSf at PARDS Onset Is Associated With Mortality
Of the 283 children in the cohort, 266 (Table 1; and Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/PCC/A213) were on conventional ventilation with continuous PetCO2 monitoring allowing for calculation of AVDSf at PARDS onset (11 on high-frequency oscillatory ventilation [HFOV]; 6 on high-frequency percussive ventilation [HFPV]). By 24 hours after PARDS onset, this was reduced to 216 children (16 HFOV, 26 HFPV, 4 airway pressure release ventilation, 3 ECMO, and 1 dead). The PetCO2 value used was recorded 9 minutes (3–12 min) before the Paco2 was used. All patients had an endotracheal tube leak less than 15% (median, 0% [0–1%]), with 95% of patients having a leak less than or equal to 5%. PARDS onset occurred 10 hours (2–12 hr) after intubation. Of the 36 deaths from the cohort of 266 children, 17 had withdrawal of care for poor neurologic prognosis, 11 had multisystem organ failure, and 8 had refractory hypoxemia.

AVDSf was higher in nonsurvivors at PARDS onset (p < 0.001), but not 24 hours after PARDS onset (p = 0.430; Table 1 and Fig. 1A). AVDSf at PARDS onset discriminated survivors from nonsurvivors (Fig. 1B), with an AUROC of 0.76 (95% CI, 0.66–0.85; p < 0.001). AVDSf at PARDS onset discriminated survival better than either OI or Pao2/FiO2 at PARDS onset although the combination of AVDSf at PARDS onset with either OI or Pao2/FiO2 was not better than AVDSf alone (Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/PCC/A213).

AVDSf at PARDS onset correlated (all p < 0.05; Supplementary Table 3, Supplemental Digital Content 1, http://links.lww.com/PCC/A213) with severity of illness (PRISM III), cardiovascular status (nonpulmonary organ dysfunction and vasopressor score), and degree of hypoxemia (OI at PARDS onset and 24 hr after). Mortality was increased in the highest quartile of AVDSf at PARDS onset (Fig. 2; p < 0.001). Patients with AVDSf greater than or equal to 0.25 at PARDS onset had higher PRISM III scores, more nonpulmonary organ dysfunctions, worse respiratory indexes, higher vasopressor scores, more frequent use of iNO, longer duration of ventilation, and increased mortality (all p < 0.05; Supplementary Table 4, Supplemental Digital Content 1, http://links.lww.com/PCC/A213). Patients with AVDSf greater than or equal to 0.25 at PARDS onset had worse mortality in every PALICC oxygenation category (Supplementary Fig. 1, Supplemental Digital Content 3, http://links.lww.com/PCC/A215). A multivariate logistic regression model demonstrated that AVDSf at PARDS onset was independently associated with increased nonsurvival (adjusted odds ratio [OR], 1.10; 95% CI, 1.05–1.14; p < 0.001; Table 2). OI at PARDS onset was not independently associated with mortality after adjusting for other variables.

Effect of Transition to Alternative Ventilator Modes by 24 Hours
By 24 hours after PARDS onset, only 216 children of the original 266 remained on conventional ventilation, allowing calculation of AVDSf at this time point. The 50 children without calculable 24-hour AVDSf had a higher initial AVDSf (0.22 [0.10–0.33]) relative to the 216 who remained alive on conventional ventilation at 24 hours (0.15 [0.06–0.23]; p = 0.002). The mortality rate in these 50 patients (18%) was not significantly different relative to the 216 remaining on conventional ventilation (12.5%, Fisher exact p = 0.358).
To address whether the use of iNO impacted the performance of AVDSf 24 hours after PARDS onset, we separately examined the relationship between AVDSf, iNO use, and mortality. Of the initial cohort of 266 children, 91 (34%) were exposed to iNO (Supplementary Table 5, Supplemental Digital Content 1, http://links.lww.com/PCC/A213); of the 216 children on conventional ventilation 24 hours after PARDS onset, 56 (26%) had been exposed to iNO. The iNO cohort had more organ failures, worse respiratory indexes, higher vasopressor scores, longer duration of ventilation, and increased mortality.

After propensity score adjustment for iNO use (supplementary text, Supplemental Digital Content 2, http://links.lww.com/PCC/A214; and Supplementary Table 6, Supplemental Digital Content 1, http://links.lww.com/PCC/A213), use of iNO was no longer associated with mortality (adjusted OR for mortality, 1.17; 95% CI, 0.48–2.85; p = 0.731).

For nonsurvivors, AVDSf at 24 hours was lower than at PARDS onset in both cohorts exposed and not exposed to iNO (Fig. 3). In neither cohort did AVDSf at 24 hours discriminate between survivors and nonsurvivors in univariate analysis (both p > 0.05; Fig. 4). Because 50 patients (35 of whom were

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n = 266)</th>
<th>Survived (n = 230)</th>
<th>Died (n = 36)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>4.2 (1.4–12.8)</td>
<td>3.8 (1.4–11.9)</td>
<td>6.8 (2.1–15.2)</td>
<td>0.059</td>
</tr>
<tr>
<td>Pediatric Risk of Mortality III at 12 hr</td>
<td>10 (5–17)</td>
<td>9 (5–15)</td>
<td>18 (11.5–30)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cause of PARDS</td>
<td>0.599</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious pneumonia</td>
<td>153 (57.5)</td>
<td>135 (59)</td>
<td>18 (50)</td>
<td></td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>24 (9)</td>
<td>20 (9)</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>50 (19)</td>
<td>44 (19)</td>
<td>6 (17)</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>21 (8)</td>
<td>16 (7)</td>
<td>5 (14)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>18 (6.5)</td>
<td>15 (6)</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td>Immunocompromised (%)</td>
<td>52 (20)</td>
<td>33 (14)</td>
<td>19 (53)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nonpulmonary organ dysfunctions at PARDS onset</td>
<td>1.5 (1–3)</td>
<td>1 (1–2)</td>
<td>3 (2–4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PARDs onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P/O_{2}/FIO_{2} )</td>
<td>158 (112–210)</td>
<td>160 (118–210)</td>
<td>130 (80–198)</td>
<td>0.030</td>
</tr>
<tr>
<td>OI</td>
<td>10 (7–15.4)</td>
<td>9.7 (7.1–14.2)</td>
<td>12.8 (6.5–24.8)</td>
<td>0.049</td>
</tr>
<tr>
<td>PEEP (cm H(_2)O)</td>
<td>10 (8–12)</td>
<td>10 (8–12)</td>
<td>10 (8–11)</td>
<td>0.989</td>
</tr>
<tr>
<td>Peak inflating pressure (cm H(_2)O)</td>
<td>30 (25–35)</td>
<td>30 (25–35)</td>
<td>31 (28–38)</td>
<td>0.089</td>
</tr>
<tr>
<td>Tidal volume (mL/kg)</td>
<td>7.5 (6.7–7.3)</td>
<td>7.5 (6.7–8.3)</td>
<td>7.7 (6.7–8.3)</td>
<td>0.566</td>
</tr>
<tr>
<td>AVDSf</td>
<td>0.16 (0.07–0.25)</td>
<td>0.13 (0.06–0.23)</td>
<td>0.31 (0.19–0.42)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n = 216, 27 died)</th>
<th>Survived (n = 216)</th>
<th>Died (n = 27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P/O_{2}/FIO_{2} )</td>
<td>231 (175–282)</td>
<td>236 (184–285)</td>
<td>175 (131–233)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>OI</td>
<td>6.3 (4.8–9)</td>
<td>6.1 (4.7–8.3)</td>
<td>8.9 (6.2–12.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PEEP (cm H(_2)O)</td>
<td>10 (8–10)</td>
<td>10 (8–10)</td>
<td>10 (8–12)</td>
<td>0.178</td>
</tr>
<tr>
<td>Peak inflating pressure (cm H(_2)O)</td>
<td>27 (24–32)</td>
<td>27 (24–31)</td>
<td>30 (26–35)</td>
<td>0.025</td>
</tr>
<tr>
<td>Tidal volume (mL/kg)</td>
<td>7.6 (6.5–8.1)</td>
<td>7.4 (6.6–8.2)</td>
<td>7.1 (6.3–7.9)</td>
<td>0.480</td>
</tr>
<tr>
<td>AVDSf</td>
<td>0.12 (0.06–0.18)</td>
<td>0.12 (0.06–0.18)</td>
<td>0.14 (0.06–0.25)</td>
<td>0.430</td>
</tr>
<tr>
<td>Use of inhaled nitric oxide (%)</td>
<td>91 (34)</td>
<td>72 (31)</td>
<td>19 (53)</td>
<td>0.012</td>
</tr>
<tr>
<td>First 72 hr of PARDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum vasopressor score</td>
<td>10 (3–19)</td>
<td>8 (3–17)</td>
<td>14 (6–27.5)</td>
<td>0.029</td>
</tr>
<tr>
<td>Fluid balance (mL/kg)</td>
<td>95 (37–179)</td>
<td>93 (37–172)</td>
<td>120 (56–264)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

PARDS = pediatric acute respiratory distress syndrome, OI = oxygenation index, PEEP = positive end-expiratory pressure, AVDSf = alveolar dead space fraction.

Data reported as median (interquartile range) for continuous variables, and as number (percentage) for categorical.

Effect of iNO

To address whether the use of iNO impacted the performance of AVDSf 24 hours after PARDS onset, we separately examined the relationship between AVDSf, iNO use, and mortality. Of the initial cohort of 266 children, 91 (34%) were exposed to iNO (Supplementary Table 5, Supplemental Digital Content 1, http://links.lww.com/PCC/A213); of the 216 children on conventional ventilation 24 hours after PARDS onset, 56 (26%) had been exposed to iNO. The iNO cohort had more organ failures, worse respiratory indexes, higher vasopressor scores, longer duration of ventilation, and increased mortality.
exposed to iNO) did not have AVDSf available 24 hours after PARDS (because of transition to alternative ventilator modes), repeating the above analyses while excluding these 50 patients produced similar results (Supplementary Fig. 2, Supplemental Digital Content 4, http://links.lww.com/PCC/A216).

When repeating the multivariate regression testing for independent associations with mortality (Table 3), AVDSf at 24 hours retained an association only when the interaction term between AVDSf at 24 hours and use of iNO was modeled. This suggests that the association between mortality and AVDSf at 24 hours was modified by the use of iNO and that AVDSf at 24 hours was independently associated with mortality only in the cohort not exposed to iNO (adjusted OR, 1.07; 95% CI, 1.00–1.14; \( p = 0.040 \)).

**DISCUSSION**

AVDSf at PARDS onset was independently associated with mortality and discriminated mortality better than initial OI or \( Pao_2/Fio_2 \). AVDSf at 24 hours retained independent association only in those not exposed to iNO. AVDSf likely reflects decreased pulmonary blood flow associated with low cardiac output, explaining the correlation with PRISM III, number of nonpulmonary organ failures, and vasopressor score. It also reflects the degree of pulmonary injury, adding information to oxygenation metrics. Lack of utility of AVDSf 24 hours after PARDS onset seems to be explained by both transition of the sickest children to alternative modes of ventilation (in which AVDSf could not be calculated) and high iNO usage. As AVDSf is readily obtained and clinically relevant, it may assist with risk stratification and prognostication in both clinical and research settings.

Metrics of oxygenation have an inconsistent relationship with mortality in adults with ARDS (4–6) and are dependent on ventilator settings (6, 23), degree of venous admixture (24), and \( Fio_2 \) (25, 26). Although children have a somewhat more reproducible relationship between oxygenation defect and mortality (17, 27, 28), several other variables not included in definitions of PARDS, such as nonpulmonary organ failures and immunocompromised status (17, 29), substantially affect mortality and length of ventilation. The imprecision of the definition makes risk stratification and prognostication of ARDS problematic. In children, this is compounded by the fact that neither the 1994 AECC (2) nor the 2012 Berlin (1) definitions included a discussion on pediatrics. Absent specific considerations, children have typically been diagnosed according to adult definitions of ARDS. To address the distinct epidemiology and outcomes of children (17, 27–29), PALICC was convened to propose pediatric-specific definitions for PARDS (3). The PALICC group determined that the primary risk stratification mechanism of the 2015 PARDS definitions should remain oxygenation, with severity categories defined by OI rather than by \( Pao_2/Fio_2 \). As there was only a single report of children with heterogeneous respiratory failure associating AVDSf with mortality (15), AVDSf was considered but ultimately not included in the final PALICC definition. Our data support using dead space measurements in future definitions of PARDS.

Increased physiologic dead space, derived from metabolic monitoring and using the Enghoff modification of the Bohr equation, was an independent predictor of mortality in adult ARDS (9). Dead space fraction was considered when developing the 2012 Berlin definition but ultimately not included, in part, because of infrequency of measurement (1). Accurate
measurements of expired CO₂ have historically been performed by using a Douglas bag, collecting up to 60 L of exhaled gas to determine expired CO₂. More recent approximations include calculations derived from metabolic carts and volumetric capnographs. All of these techniques are limited by requiring specialized equipment and thus are not consistently performed during routine PICU care. This may be addressed by a more easily obtained surrogate of alveolar dead space, such as AVDSf. Furthermore, it is likely that fluctuations in alveolar dead space, rather than anatomic, are responsible for the association between dead space and mortality. As such, alveolar dead space as measured by AVDSf may actually be more sensitive to perturbations in physiology (14, 30).

AVDSf has been associated with mortality in a cohort of 95 mechanically ventilated children with acute hypoxemic respiratory failure (15), and in a larger cohort of intubated children (16), both from the same institution. The AVDSf value reported in those studies used the first 24-hour period of ventilation in which all necessary variables were available and demonstrated an AUROC for mortality of 0.74 in both studies. We confirm this finding in this larger cohort meeting both the Berlin 2012 definition of ARDS and the PALICC 2015 definition of PARD5, but limited to the initial AVDSf at PARD5 onset, and report a comparable AUROC of 0.76. We also demonstrate the association of elevated initial AVDSf with markers of both pulmonary (as reflected by OI) and nonpulmonary (nonpulmonary organ failure, vasopressor score) morbidity. As alveolar dead space is increased with low cardiac output, it is not surprising that AVDSf correlates with other surrogates of low cardiac output states, including vasopressor score and nonpulmonary organ dysfunction. However, the independent association of AVDSf after controlling for surrogates of intrapulmonary shunt (OI) and cardiac output (vasopressor score) suggests that AVDSf may be characterizing additional risk, possibly related to aberrations in pulmonary microcirculation or pulmonary microthrombi.

The lack of utility after 24 hours in the cohort of children exposed to iNO is consistent with AVDSf as a reflection of pulmonary microcirculation. As such, the utility of AVDSf for risk stratification may not lie in its specificity to pulmonary physiology; rather, AVDSf at PARD5 onset is a single, useful, readily obtained clinical biomarker reflective of multiple pulmonary and nonpulmonary variables associated with mortality, including oxygenation, cardiovascular status, and organ failures. In our study, it is notable that initial AVDSf greater than or equal to 0.25 identified children at higher risk of mortality, even if the initial OI stratified them as mild or moderate PARD5 (Supplementary Fig. 1, Supplemental Digital Content 3, http://links.lww.com/PCC/A215). Early identification and

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Risk of Mortality III</td>
<td>1.05</td>
<td>1.00–1.10</td>
<td>0.045</td>
</tr>
<tr>
<td>Immunocompromised (yes)</td>
<td>5.77</td>
<td>2.03–16.38</td>
<td>0.001</td>
</tr>
<tr>
<td>Nonpulmonary organ dysfunctions</td>
<td>1.94</td>
<td>1.25–3.01</td>
<td>0.003</td>
</tr>
<tr>
<td>Alveolar dead space fraction at pediatric acute respiratory distress syndrome onset (per every increase by 0.01)</td>
<td>1.10</td>
<td>1.05–1.14</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Figure 3.** Alveolar dead space fraction (AVDSf) at pediatric acute respiratory distress syndrome (PARD5) onset and at 24 hr in patients (A) not exposed and (B) exposed to inhaled nitric oxide (iNO).
risk stratification of PARDS patients at high risk for mortality, whether for pulmonary or nonpulmonary organ failure, may allow for earlier application of interventions, which have not proven successful in heterogeneous PARDS cohorts, with lower overall mortality risk. Future clinical trials stratifying by AVDSf may successfully identify a detectable signal by limiting interventions to sicker patients with higher baseline mortality risk. This concept is especially appealing for interventions that may favorably impact ventilation/perfusion ratios, such as prone positioning or iNO.

Kallet et al (31) demonstrated that physiologic dead space retains prognostic significance up to 6 days after ARDS onset in 59 adults. In our cohort, AVDSf at PARDS onset was able to discriminate mortality and was independently associated with nonsurvival. However, AVDSf 24 hours after did not discriminate mortality and was only independently associated with nonsurvival in the cohort of children not exposed to iNO. We speculate that iNO, as has been demonstrated before in a sheep acid aspiration model (14), improved alveolar dead space by passively redistributing pulmonary blood flow toward areas with excess ventilation and deficient perfusion. As iNO therapy directly acted to reduce the alveolar dead space, the 24-hour AVDSf value was improved irrespective of mortality risk and thus prognostic value was lost.

Alternatively, it is possible that our analysis 24 hours after PARDS onset is underpowered for mortality, limited by the unavailability of PetCO2 in 50 patients with a higher mortality rate (18%) relative to the 216 remaining on conventional ventilation (12.5%, p = 0.358). Presumably, the patients who remained on conventional ventilation at 24 hours did not escalate to alternative ventilator modes because they were less ill or because they had a favorable response to ongoing therapy, including iNO. Therefore,

### TABLE 3. Multivariate Logistic Regression of Variables Associated With Mortality (Testing Alveolar Dead Space Fraction 24 Hours After Pediatric Acute Respiratory Distress Syndrome Onset)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Risk of Mortality III</td>
<td>1.08</td>
<td>1.02–1.15</td>
<td>0.014</td>
</tr>
<tr>
<td>Immunocompromised (yes)</td>
<td>3.25</td>
<td>1.07–9.84</td>
<td>0.037</td>
</tr>
<tr>
<td>Oxygenation index 24 hr after PARDS onset</td>
<td>1.13</td>
<td>1.03–1.25</td>
<td>0.013</td>
</tr>
<tr>
<td>Interaction (AVDSf at 24 hr × use of iNO)</td>
<td>0.93</td>
<td>0.87–0.99</td>
<td>0.050</td>
</tr>
<tr>
<td>AVDSf 24 hr after PARDS onset (per every increase by 0.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iNO use (no)</td>
<td>1.07</td>
<td>1.00–1.14</td>
<td>0.049</td>
</tr>
<tr>
<td>iNO use (yes)</td>
<td>0.99</td>
<td>0.92–1.07</td>
<td>0.830</td>
</tr>
</tbody>
</table>

PARDS = pediatric acute respiratory distress syndrome, AVDSf = alveolar dead space fraction, iNO = inhaled nitric oxide.
the patients exposed to iNO for whom AVDSf was available at 24 hours may have selected for a population with a favorable iNO response on conventional ventilation and lower mortality. However, the independent association of 24-hour AVDSf with mortality in the cohort not exposed to iNO (Table 3) suggests direct modification of the prognostic utility of AVDSf by iNO.

AVDSf appears to be more consistent with a marker for severity of injury, rather than a therapeutic target. In both children exposed and not exposed to iNO, there was no evident relationship between the degree of AVDSf improvement and mortality. Furthermore, in the cohort exposed to iNO, the AVDSf improved more than did the AVDSf in the cohort not exposed to iNO; nevertheless, mortality was nearly double in the cohort exposed to iNO. However, given the observational nature of this study, we are limited in the inferences we can draw. A future prospective physiologic study may clarify whether targeting specific AVDSf values can improve the outcomes in PARDS. Echocardiographic monitoring and extrapolated pulmonary artery pressures in such a study may allow dissection of the underlying mechanism underlying AVDSf, including the role of pulmonary vascular resistance.

Our study has limitations. The study was conducted at a single center, and although demographics and severity of illness are comparable to other PARDS cohorts, mortality rate, ventilator practices, and usage of ancillary therapies (including iNO) may not allow translation to other PICUs. Also, as we restricted enrollment to patients undergoing invasive ventilation with arterial access, and required two consecutive Pao2/Fio2 less than or equal to 300, we selected only a fraction of patients with respiratory failure, likely biased toward those with greater disease severity. However, our eligibility criteria were similar to many PARDS trials. We did not assess AVDSf beyond 24 hours after PARDS onset in patients, and the utility of AVDSf over time in PARDS deserves further study. The heterogeneity of our population and the low mortality rate may have affected the utility of AVDSf at 24 hours. The AVDSf was derived retrospectively and may not be an accurate calculation, as ETCO2 may have changed by the time the corresponding blood gas was drawn. However, the ETCO2 value used was only 9 minutes before the Paco2 used for calculation, and this method has been used to derive AVDSf in previous studies (15, 18). These concerns are best addressed via a prospective study, with alveolar dead space assessed by both AVDSf and volumetric capnography.

CONCLUSIONS

AVDSf at PARDS onset discriminates mortality and is independently associated with nonsurvival. For those who remained on conventional ventilation at 24 hours, the independent association with mortality is only evident in the cohort unexposed to iNO. AVDSf represents a single, useful, readily obtained clinical biomarker reflective of multiple pulmonary and nonpulmonary variables associated with mortality, including oxygenation, cardiovascular status, and organ failures.

REFERENCES


