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Right Atrial Dysfunction Is Prevalent in Pediatric Acute Respiratory Distress Syndrome and Reflects Pulmonary Hypertension and Right Ventricular Dysfunction

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IMPORTANCE: Right atrial (RA) dysfunction is associated with worse outcomes in some populations with pulmonary hypertension or respiratory failure but the prevalence and correlates of RA dysfunction in pediatric acute respiratory distress syndrome (PARDS) are unknown.

OBJECTIVES: The aim of this study was to evaluate RA function by characterizing the prevalence and pattern of RA dysfunction within the first 24 hours of PARDS onset. We hypothesized that RA dysfunction would be common and correlate with the presence of pulmonary hypertension and right ventricular (RV) systolic dysfunction.

DESIGN, SETTING, AND PARTICIPANTS: Retrospective, single-center cohort study at a tertiary care PICU of children (< 18 yr) with a clinically obtained echocardiogram within 24 hours following PARDS diagnosis and healthy controls without cardiopulmonary disease.

MAIN OUTCOMES AND MEASURES: Echocardiograms were evaluated for conventional and speckle-tracking (or strain) echocardiographic measures of RA and RV systolic function. Nonparametric summary statistics, comparisons, and correlational analyses were completed.

RESULTS: Ninety-two PARDS patients and 55 controls were included. Using a priori thresholds (> 2 SDs of control values), 49% ($n = 45$) of PARDS patients demonstrated RA dysfunction in at least one RA functional metric. The maximal RA strain during the reservoir phase was reduced in PARDS compared with controls (median 40.2% vs. 53.7%; $p < 0.001$). Patients with echocardiographic evidence of pulmonary hypertension had lower maximal RA strain during the reservoir phase (31.7%) compared with patients without (40.5%; $p < 0.05$). Patients with higher brain-type natriuretic peptide plasma concentrations had worse RA function. RA function significantly correlated with conventional and strain measures of RV systolic function.

CONCLUSIONS AND RELEVANCE: RA dysfunction is common within the first 24 hours of PARDS onset. RA dysfunction during the reservoir phase is associated with pulmonary hypertension and RV systolic dysfunction. Future studies investigating trajectories of RA function and their association with outcomes in PARDS patients are needed.

KEYWORDS: atrial function; echocardiography; pulmonary hypertension; respiratory distress syndrome; ventricular function

Acute respiratory distress syndrome (ARDS), a common cause of death in adult and PICUs, presents a unique challenge to the right heart (1–3). Disease states leading to ARDS, including pneumonia, aspiration, and COVID-19, and therapies such as invasive ventilation can cause acute right

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KEY POINTS

Question: We hypothesized that right atrial (RA) dysfunction as defined by speckle-tracking (or strain) echocardiography would be common in pediatric acute respiratory distress syndrome (PARDS) and correlate with the presence of pulmonary hypertension and right ventricular (RV) systolic dysfunction.

Findings: In this retrospective cohort study of clinically obtained echocardiograms within 24 hours of PARDS onset, RA dysfunction was common (49%) and dysfunction of the RA reservoir phase was associated with pulmonary hypertension and RV dysfunction.

Meaning: RA dysfunction identification through strain echocardiography is common within the first 24 hours of PARDS and may be a sensitive imaging biomarker for moderate-to-severe RV dysfunction.

ventricular (RV) systolic dysfunction through mechanisms that increase afterload to the right heart or cause direct myocardial injury. RV dysfunction may contribute to the high morbidity and mortality of ARDS (2–5).

ARDS similarly challenges the right atrium (RA) to maintain preload. A healthy RA stores venous blood during ventricular systole (the reservoir phase) before passively, then actively, emptying to fill the RV (the conduit phase and the active pump phase, respectively) (6). Elevated ventricular pressures and reduced ventricular compliance limit these processes by increasing RA pressure and limiting reservoir function (7). As such, prior studies have linked RA dysfunction with worse outcomes in chronic pulmonary hypertension (PH), bronchopulmonary dysplasia, and acute pulmonary embolism (6, 8–11). Although RV systolic dysfunction is associated with mortality and decreased probability of extubation in pediatric ARDS (PARDS) (4, 5), the effect of PARDS on RA function is unknown. Given the potential coupling between atrial and ventricular function, RA dysfunction may be prevalent in PARDS.

Echocardiography provides a convenient, noninvasive window into the myocardial function of the left and right heart (12, 13) and may be clinically useful in the care of children with PARDS (4, 5). Two-dimensional speckle-tracking, or strain, echocardiography quantifies myocardial deformation, is used to measure atrial and ventricular function, and has the potential to improve bedside assessments of cardiac function by acute care clinicians. Compared with the RV and its anterior anatomic location, the RA may be imaged more easily with echocardiography, especially in those with respiratory failure. The use of RA strain echocardiography as an imaging biomarker for PARDS severity and early RV systolic dysfunction may be both physiologically plausible and clinically feasible.

The aim of this study was to evaluate RA strain as an imaging biomarker of RV systolic dysfunction by characterizing the prevalence and pattern of RA dysfunction within the first 24 hours of PARDS onset. We hypothesized that RA strain during the reservoir phase, during the conduit phase, and during the active pump phase would be decreased in children with PARDS compared with controls, would correlate with measures of RV systolic function, and would be decreased in patients with PARDS-associated PH.

MATERIALS AND METHODS

Study Design and Patient Selection

This was a single-center retrospective analysis of a prospective PARDS cohort that has been previously described (14). Intubated children admitted to the PICU at the Children's Hospital of Philadelphia (CHOP) between July 1, 2013, and June 30, 2016, were eligible. Although recruitment into the prospective database was based on the American-European Consensus Conference ARDS criteria, all patients also fit the Berlin as well as the Pediatric Acute Lung Injury Consensus Conference (PALICC)-1 and PALICC-2 criteria (14–17). We included all patients who had a clinically performed echocardiogram within 24 hours of PARDS diagnosis with sufficient apical four chamber views for RA and RV strain measurements. The control cohort was constructed by including 55 otherwise healthy children of comparable age and sex who had outpatient echocardiograms with no signs of cardiovascular or pulmonary disease during the same time period (**Fig. 1**). Informed consent was waived by the CHOP Institutional Review Board (IRB 16-013536, "Echocardiographic Abnormalities in Pediatric ARDS and Associations with Outcomes," approved January 13, 2017). Study procedures were followed in

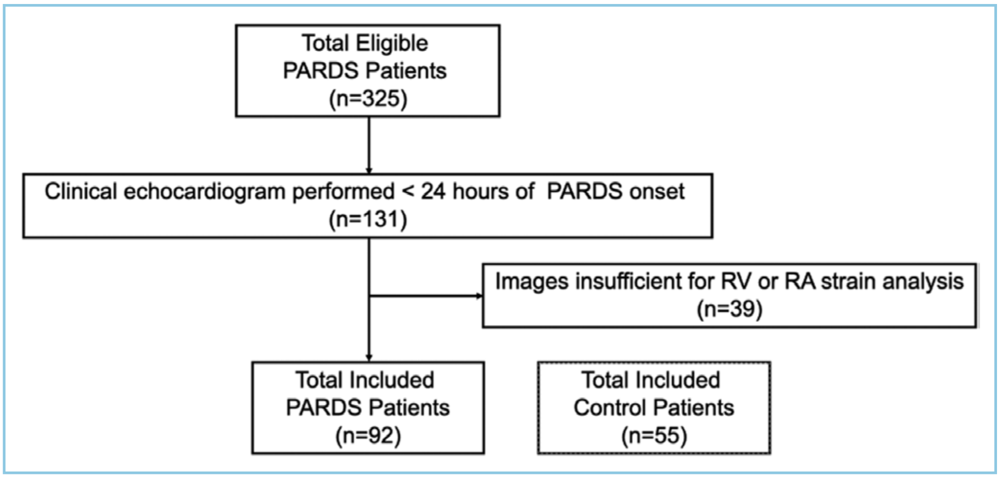

Figure 1. Study flow diagram. PARDS = pediatric acute respiratory distress syndrome, RA = right atrial, RV = right ventricular.

accordance with the ethical standards of the CHOP IRB and with the Helsinki Declaration of 1975.

Data Collection and Definitions

We collected age, administrative sex, and family reported race and ethnicity for patients in both cohorts. For patients in the PARDS cohort, we also abstracted their first echocardiogram performed during that intensive care admission and other clinical data. PICU mortality was abstracted as well as ventilator-free days (VFDs) during the first 28 days, stratified into 0 days, 1–14 days, and greater than 14 days. We abstracted the mean airway pressure as well as the use of vasopressors and inhaled nitric oxide (iNO) closest to the start time of the clinical echocardiogram. Mean airway pressure (cm H_2O) was stratified into tertiles: 7–15, 16–20, and greater than 20. Over the first 24 hours, we identified worst PARDS severity by oxygenation index (OI), highest clinically obtained brain-type natriuretic peptide (BNP) plasma concentration (pg/mL), and percent fluid overload. OI was defined as mean airway pressure $\times$ FIO_2 $\times$ 100/PaO_2. PARDS severity was defined according to PALICC-2 categories (mild/moderate OI 4 to < 16, severe OI ≥16). Peak BNP was stratified into three categories: less than 200 pg/mL, 200–1200 pg/mL, and greater than 1200 pg/mL. Percent fluid overload was defined as the difference between daily total fluid input and output in milliliters, divided by the patient's weight in kilograms × 100. Fluid overload was then stratified a priori into the following categories: less than 100%, 100–120%, and greater than 120%.

Echocardiographic Measurements and Definitions

Echocardiograms were secondarily interpreted by an experienced sonographer (Y.W.) blinded to clinical outcome. Two-dimensional speckle-tracking echocardiography (2DSTE) was used to assess RA and RV size and function analyses using the best apical four-chamber view using TomTec atrial and RV packages (Cardiac Performance Analysis, Munich, Germany). For our analysis, the median frame rate for controls was 61 frames per second (interquartile range [IQR], 55–67) and 61 frames per second (IQR 54–61) for PARDS patients. Conventional metrics of RV systolic function were also measured.

RA strain measurements were performed twice and averaged. Several RA measures were used to characterize RA size and function in this study: RA end-diastolic volume (EDV), RA end-systolic volume (ESV), and RA ejection fraction (EF, measure of atrial systole), maximal RA strain during the reservoir phase (RASr), peak RA strain rate during the reservoir phase (pRASr), and peak RA strain rate during the conduit phase (pRASRcd) (18). ESV and EDV were transformed into *z* scores based on patient height, weight, and sex (19). Patient height was missing for one patient given the acuity of their presentation and deterioration, so median height for age and sex was imputed. We used RASr and pRASr to quantify the reservoir function and pRASRcd to quantify the conduit function. No patient in the PARDS cohort demonstrated an observable active pump phase separate from the conduit phase.

As there are limited normative values for RA functional metrics using 2D TomTec software in diverse populations (20), the normal limit of each RA metric for this study was defined as greater than 2 SDs from the internal control group mean. This approach produced the following thresholds: EF less than 46%; RASr less than 37%; pRASr less than 1.0; and pRASRcd greater than –1.1. For RA size metrics, we defined abnormal as a *z* score of EDV or ESV greater than 2.

The following echocardiographic indices of RV systolic function were also measured: qualitative function (normal or mildly, moderately, or severely diminished), tricuspid annular plane systolic excursion (TAPSE) *z* score, fractional area change (FAC), free wall strain (strain), and global longitudinal strain. TAPSE *z* score was calculated using an online resource (parameterz.blogspot.com). For this study, the presence of PH was defined as the presence of an abnormal septal position or tricuspid regurgitation greater than 2.8 m/s. No conventional measures of RV diastolic dysfunction were available in this dataset of clinically obtained echocardiograms.

Statistical Analyses

All analyses were conducted in R, Version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) (21). Descriptive statistics of both cohorts were calculated. We estimated the prevalence of RA dysfunction in patients with PARDS, defined as an abnormally low value in any of the RA functional metrics as defined above. We also report the percent of the cohort with an abnormal value in each size and functional metric to provide a broad sense of the estimated prevalence.

Next, we tested whether RA metrics depended on indicators of PARDS severity. The median and IQR for each RA continuous metric stratified by each clinical variable were calculated. Wilcoxon rank-sum or Kruskal-Wallis tests were then performed. We began by evaluating whether RA metrics differed between patients with PARDS and controls, and then explored whether clinical characteristics predicted differences in RA metrics within the PARDS cohort alone.

Finally, we examined whether RA strain was associated with RV dysfunction in PARDS patients. Spearman rho was used to estimate the relationships between continuous RA and RV echocardiographic metrics. There was one patient with missing TAPSE and one patient with missing RV FAC measurements due to image quality; complete case analysis was used for those estimates. Correlations were adjusted for multiple comparisons using the Holm closed-testing approach. Given the strong correlations found, we evaluated the sensitivity and specificity of any RA dysfunction in identifying moderate-to-severe RV qualitative dysfunction. Significance was defined as alpha less than 0.05.

RESULTS

The final cohort included 92 patients with PARDS and 55 controls. Both cohorts consisted of participants of comparable age (control median = 4.2 [IQR, 0.7–11.8], PARDS median = 4.4 [IQR, 1.3–10.6]), sex (control male n = 27 [49%], PARDS male n = 51 [55%]), and race and ethnicity (control non-Hispanic White n = 28 [51%], PARDS non-Hispanic White n = 41 [45%]) (**Table 1**). For the PARDS cohort, the median mean airway pressure was 17 cm H_2O (IQR, 15–22 cm H_2O), 30% were on iNO, and 55% were on vasoactive infusions. PICU mortality was 28% with a median time-to-death of 6 days (IQR, 3.25–10.25 d) (Table 1).

Using our a priori defined thresholds, 62% of patients with PARDS demonstrated an abnormal RA EDV, 56% abnormal RA ESV, 24% abnormal RA EF, 46% abnormal RASr, 10% abnormal pRASr, and 14% abnormal pRASRcd. In sum, 49% (n = 45) of PARDS patients demonstrated RA dysfunction defined as an abnormal value in at least one of the functional metrics.

The magnitude of RASr was reduced in patients with PARDS (median = 40.2% [IQR 28.4–53.3]) compared with controls (median=53.7% [IQR, 48.6–62.1%]; p < 0.001) as well as pRASRcd (PARDS median = −1.83 [IQR, −2.36 to −1.30], control median = −2.15 [IQR, −2.43 to −1.88]; p = 0.017). No significant differences between PARDS patients and controls were found across other RA functional metrics. PARDS patients with echocardiographic evidence of PH had lower median RASr (31.7%) compared with those without (40.5%), as well as elevated median EDV and ESV *z* scores (p < 0.05; **Fig. 2**). PARDS patients with higher BNP had higher RA EDV and lower RA EF, RASr, and pRASRr (Fig. 2). RA EDV and ESV were lower among nonsurvivors compared with survivors and those who required an inotrope or vasopressor compared with those who did not. Other PARDS clinical characteristics and outcomes, including PARDS severity, VFDs, percent fluid overload, iNO use, and mean airway pressure were not associated with differences in measured RA function (**Supplementary Table S1**, http://links.lww.com/CCX/B485).

RA strain functional metrics significantly correlated with all RV systolic function variables. Better RA strain was positively correlated with markers of better RV systolic function (p < 0.05; **Table 2**). However, higher RA ESV were only associated with a higher TAPSE,

TABLE 1.
Cohort Characteristics

Variables	Controls ($n = 55$)	PARDS Cohort ($n = 92$)
Age, median (interquartile range)	4.2 (0.7–11.8)	4.4 (1.3–10.6)
Sex, *n* (%)		
Male	27 (49)	51 (57)
Female	28 (51)	39 (43)
Race and ethnicity, *n* (%)		
Non-Hispanic Black or African American	10 (18)	31 (34)
Non-Hispanic White	28 (51)	41 (45)
Hispanic or Latino	5 (9)	10 (11)
Other or unknown	12 (22)	10 (11)
Comorbidity, *n* (%)		
Liquid malignancy		17 (32)
Prematurity		11 (20)
Stem cell transplant		11 (21)
Genetic syndrome		10 (19)
Cerebral palsy		8 (15)
Hematological condition		7 (13)
Pediatric intensive care unit mortality, *n* (%)		
Survivors		66 (72)
Nonsurvivors		26 (28)
PARDS severity, *n* (%)		
Mild/moderate		46 (48)
Severe		48 (52)

PARDS = pediatric acute respiratory distress syndrome.

and RA EDV was not associated with any RV function metrics. The presence of any RA dysfunction was 100% sensitive and 62% specific for moderate-to-severe RV qualitative dysfunction.

DISCUSSION

RA dysfunction was prevalent within 24 hours of PARDS diagnosis with significant reductions in RA reservoir (RASr) and conduit (pRAScd) phases compared with controls in this retrospective cohort study involving clinically performed echocardiograms. We also observed a significant reduction in RA reservoir function in patients with PARDS-associated PH, a strong association with RA dysfunction and BNP elevation, and a high correlation between RA function and contemporaneous RV systolic function. RA volume was associated with mortality and inotrope/vasopressor requirement, but not with RV systolic function. The strong sensitivity of RA dysfunction in identifying moderate-to-severe RV systolic dysfunction alongside these findings underscores its potential for an imaging biomarker in PARDS when RV imaging is difficult to acquire.

To the best of our knowledge, this is the first study to investigate RA function in children with PARDS. We observed decreased reservoir (RASr) and conduit (pRASRcd) functions in PARDS patients when compared with controls, with almost half of PARDS patients demonstrating some RA dysfunction within the first 24 hours of PARDS onset. Physiologically, this reduction in RA reservoir and conduit function could be related to increased RV filling pressure resulting in RA hypertension as well as impaired RA

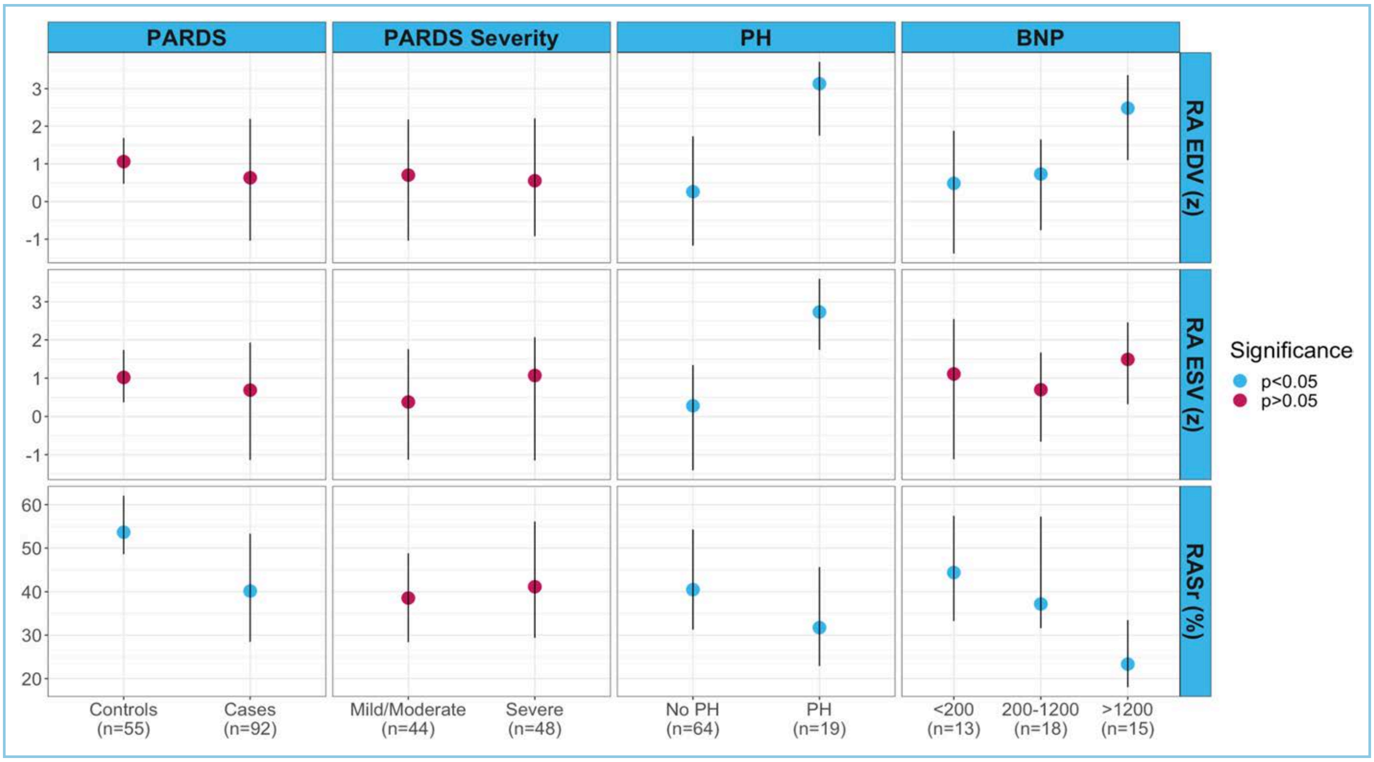

Figure 2. Comparison of maximal right atrial (RA) strain during the reservoir phase (RASr), RA end-diastolic volume (RA EDV) *z* scores, and RA end-systolic volume (RA ESV) *z* scores between: 1) control patients vs. pediatric acute respiratory distress syndrome (PARDS) patients; 2) PARDS severity; 3) PARDS patients with and without echocardiographic evidence of pulmonary hypertension (PH); and 4) PARDS patients with different brain-type natriuretic peptide (BNP, pg/dL) plasma concentrations. Values are reported as median with interquartile ranges with blue dots indicating $p < 0.05$ on Wilcoxon rank-sum test or Kruskal-Wallis test as indicated.

filling and emptying, which may threaten the preload necessary to maintain adequate cardiac output. In a sheep model investigating these RA functions, Gaynor et al (7) showed that cardiac output was inversely related to the early conduit-to-reservoir ratio. Their study showed a shift toward reservoir function with partial pulmonary artery occlusion. As the RV-RA pressure gradient at the time of maximum RA volume increased, the RA functioned more as a conduit resulting in increased conduit-to-reservoir ratio and lower cardiac output. While their invasive hemodynamic measurements are not directly translatable to the noninvasive measures of RA function in our study of children with PARDS, we also observed decreased RA reservoir function in patients with echocardiogram evidence of PARDS-associated PH. However, we did observe a similar RA conduit function, which may increase the conduit-to-reservoir ratio and mechanistically may be a marker of or contribute to lower cardiac output. Future studies should investigate how the reservoir and conduit phases of RA function change over time in PARDS and whether it may be an early marker of patients at risk of developing PARDS-associated PH.

Preserving cardiac output in PARDS is vital as the majority of patients who die with PARDS do so from multiple organ dysfunction syndrome (1, 22). RV dysfunction in the setting of PARDS and PH may be a rate-limiting step for preserving adequate cardiac output. It is unclear whether RA dysfunction is simply a result of RV hemodynamic changes or independently contributes to RV function. Better delineation of the causal relationships of RA and RV dysfunction may provide insight to new avenues for improving cardiac output during PARDS, and thus improving outcomes.

We found that RA dysfunction was associated with a higher BNP, but only decreased RA ESV and EDV were associated with an inotrope or vasopressor requirement and mortality. The presence of ventricular stretching in PARDS may drive both RA dysfunction and BNP elevation. However, this relationship may also indicate inflammation or pulmonary vascular dysfunction (23, 24). In our study, total body fluid overload in the first 24 hours was not associated with

TABLE 2.
Spearman Correlations Between Right Atrial and Right Ventricular Systolic Function With 95% Bootstrapped CIs

RA Variables	RV Fractional Area Change	RV Global Longitudinal Strain	RV Free Wall Strain	Tricuspid Annular Plane Systolic Excursion z Score	RV Qualitative Function
RA end-diastolic volume	−0.18 (−0.37 to 0.02)	0.14 (−0.07 to 0.33)	0.11 (−0.10 to 0.31)	0.07 (−0.14 to 0.27)	0.13 (−0.08 to 0.33)
RA end-systolic volume	−0.05 (−0.26 to 0.15)	−0.02 (−0.22 to 0.19)	−0.05 (−0.25 to 0.16)	0.28 (0.08–0.46)[a]	−0.05 (−0.26 to 0.15)
RA ejection fraction	0.36 (0.16–0.52)[a]	−0.35 (−0.52 to −0.16)[a]	−0.35 (−0.52 to −0.16)[a]	0.37 (0.17–0.53)[a]	−0.52 (−0.65 to −0.35)[a]
Maximal RA strain during the reservoir phase	0.47 (0.29–0.61)[a]	−0.48 (−0.62 to −0.30)[a]	−0.47 (−0.62 to −0.30)[a]	0.53 (0.37–0.66)[a]	−0.63 (−0.74 to −0.48)[a]
Peak RA strain rate during the reservoir phase	0.46 (0.28–0.61)[a]	−0.44 (−0.60 to −0.26)[a]	−0.48 (−0.62 to −0.30)[a]	0.45 (0.27–0.60)[a]	−0.62 (−0.73 to −0.48)[a]
Peak RA strain rate during the conduit phase	−0.34 (−0.51 to −0.14)[a]	0.32 (0.12–0.49)[a]	0.36 (0.17–0.52)[a]	−0.39 (−0.55 to −0.20)[a]	0.57 (0.42–0.70)[a]

RA = right atrial, RV = right ventricular.
[a] $p < 0.05$.

concurrent echocardiographic RA dysfunction. RA pressure estimation by noninvasive means, including through speckle-tracking echocardiography, does not correlate well with invasive RA pressure measurements in adult or pediatric patients with chronic PH (6, 8). However, acute changes in volume during hemodialysis does have effects on RA reservoir and conduit phases (25). Future studies should investigate how RA function changes may reflect volume status during critical illness. It is interesting that the lower RA EDV and ESV were associated with an inotrope or vasopressor requirement and mortality but that elevations in these variables were associated with PH and BNP. One possible explanation is that lower RA EDV and ESV is a marker of lower preload from a combination of factors such as intravascular volume depletion, low systemic vascular resistance, or positive pressure ventilation. Another possible explanation is that these children had smaller or less compliant right atria at baseline, and thus had less reserve. Regardless, these results highlight the need to incorporate both volume and functional metrics into an assessment of RA function in PARDS.

The association between RA and RV systolic function renders RA strain a potentially sensitive imaging biomarker for early RV systolic dysfunction. In one recent study, reduced RA function by speckle-tracking echocardiography was observed in adult patients with acute pulmonary embolism compared with normal controls (9). While our study was limited to the first 24 hours following PARDS onset, there is interdependence between the RA and RV, as evidenced by the strong correlations between all echocardiographic metrics in the study. Demonstration of any RA dysfunction was very sensitive for qualitatively moderate-to-severe RV systolic dysfunction in our study. Given that there are sometimes challenges to echocardiogram imaging of the RV in PARDS, identifying the absence of RA dysfunction may help reassure clinicians against RV dysfunction, whereas its presence may prompt further investigation. Furthermore, this finding allows clinicians to incorporate RA strain with other measures, such as a flattened interventricular septum, increased tricuspid regurgitation, RV systolic, and diastolic functional metrics to generate a comprehensive assessment of RV function. Future work is needed to better characterize the utility of RA function in clinical practice and its association with RV diastolic dysfunction.

There are several limitations to this study. This is a single-center retrospective cohort study and results may not generalize. Although PARDS severity of illness and mortality is relatively high in this retrospective cohort, the clinical characteristics are similar to what has been described worldwide (21). We did not include central venous pressure (CVP) in our analysis, as only 15% ($n = 14$) of patients had a CVP documented within 1 hour of echocardiogram using a central venous catheter. We were limited by the images of the clinically performed echocardiograms that were not standardized and performed on PARDS patients who may have limited sonographic windows due to positive pressure ventilation, critical illness, or associated air leak. Thus, we were unable to assess conventional measures of RV diastolic function or the RA active pump phase in PARDS patients because the appropriate images were not available. Comparison of RA functional and size metrics measured with 2DSTE with TomTec was based on a limited population of internal controls as there are no currently published normative values. Some of the 2DSTE analyses were performed on echocardiograms with a low frame rate or high heart rate, both of which have been associated with increased variability of strain measurements. As such, the control values and thresholds that we reported may not be applicable to other populations. In addition, echocardiograms were obtained for clinical purposes using undefined criteria, likely introducing some confounding by indication. Similarly, children with PARDS who demonstrated critical and rapidly progressive illness as well as those with mild illness may not have received echocardiograms. PARDS is a heterogeneous disease process, and our relatively small sample size limited our ability to evaluate RA dysfunction among more homogenous strata. It is possible that RA dysfunction is associated with worse outcomes, including mortality or VFD, only in certain patients with PARDS.

CONCLUSIONS

RA dysfunction identification through RA strain measurement is feasible and may be a sensitive imaging biomarker for moderate-to-severe RV dysfunction in PARDS. RA reservoir and conduit dysfunction were common in PARDS and worse in PARDS patients compared with controls. RA reservoir function was worse in patients with PARDS-associated PH and may be valuable in the longitudinal follow-up of these patients, especially when imaging of the RV is challenging. Lower RA EDV and ESV were associated with survival and concurrent inotrope or vasopressor administration. Future studies in PARDS patients should examine trajectories of RA dysfunction in relation to RV systolic and diastolic dysfunction, clinical factors, and outcomes.

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