Echocardiographic parameters of right ventricular function predict mortality in acute respiratory distress syndrome: a pilot study

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Abstract: Right ventricular (RV) dysfunction in acute respiratory distress syndrome (ARDS) contributes to increased mortality. Our aim is to identify reproducible transthoracic echocardiography (TTE) parameters of RV dysfunction that can be used to predict outcomes in ARDS. We performed a retrospective single-center cohort pilot study measuring tricuspid annular plane systolic excursion (TAPSE), Tei index, RV-fractional area change (RV-FAC), pulmonary artery systolic pressure (PASP), and septal shift, reevaluated by an independent blinded cardiologist (JK). Thirty-eight patients were included. Patients were divided on the basis of 30-day survival. Thirty-day mortality was 47%. Survivors were younger than nonsurvivors. Survivors had a higher pH, $PaO_2 : FiO_2$ ratio, and TAPSE. Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score II (SAPS II), and Sequential Organ Failure Assessment (SOFA) scores were lower in survivors. TAPSE has the strongest association with increased 30-day mortality from date of TTE. Accordingly, TAPSE has a strong positive correlation with $PaO_2 : FiO_2$ ratios, and Tei index has a strong negative correlation with $PaO_2 : FiO_2$ ratios. Septal shift was associated with lower $PaO_2 : FiO_2$ ratios. Decrease in TAPSE, increase in Tei index, and septal shift were seen in the severe ARDS group. In multivariate logistic regression models, TAPSE maintained a significant association with mortality independent of age, pH, $PaO_2 : FiO_2$ ratios, positive end expiratory pressure, PCO_2, serum bicarbonate, plateau pressures, driving pressures, APACHE II, SAPS II, and SOFA scores. In conclusion, TAPSE and other TTE parameters should be used as novel predictive indicators for RV dysfunction in ARDS. These parameters can be used as surrogate noninvasive RV hemodynamic measurements to be manipulated to improve mortality in patients with ARDS and contributory RV dysfunction.

Keywords: pulmonary hypertension, tricuspid annular plane systolic excursion, transthoracic echocardiography.

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Acute respiratory distress syndrome (ARDS) is a life-threatening respiratory syndrome characterized by hypoxemia, noncardiogenic pulmonary edema, pulmonary inflammation, and decreased pulmonary compliance. Despite our best efforts, mortality rates associated with ARDS still remain between 30% and 40%.[1,2] Current management of ARDS is mainly supportive with mechanical ventilation and hemodynamic support.[3] Pulmonary hypertension and right ventricular (RV) dysfunction are independent predictors of mortality associated with poorer outcomes in patients with ARDS.[4-8] The increased lung mass in ARDS due to accumulation of inflammatory exudate in the alveolar space compresses not only the dependent alveoli but also the pulmonary vessels, leading to increased pulmonary vascular resistance.[9] In addition to direct compression, pulmonary endothelial cell dysfunction and microvascular thrombosis from systemic inflammatory response lead to development of pulmonary hypertension in ARDS.[10,11] Mechanical ventilator strategies in ARDS have mainly focused on oxygenation and lung recruitment. When increase in positive end expiratory pressure (PEEP) does not accompany significant recruitment, a high-PEEP strategy leads to over distention of alveoli and resultant increase in pulmonary vascular resistance and significant RV dysfunction.[12-14] High transpulmonary pressures are also associated with worsening RV dysfunction.[14] Hypercapnia, which is common in patients with ARDS secondary to a large amount of dead-space ventilation and low tidal volume strategy can worsen RV function in ARDS.[5,14,15] Thus, etiologies of pulmonary hypertension and RV dysfunction in ARDS are multifactorial, and many of these are at least partially modifiable to improve RV function in patients with ARDS.[14,16-18] Moreover, studies show that use of inhaled prostacyclins in patients with severe ARDS improves hemodynamic characteristics and oxygenation, but these studies were underpowered to look for mortality benefit.[19]

Modification of factors leading to RV dysfunction and the use of inhaled pulmonary vasodilators might provide an opportunity to decrease mortality associated with ARDS in the future. However, the majority of studies of pulmonary vascular hemodynamics or RV dysfunction in ARDS are done via invasive measures, including

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pulmonary artery catheters and transesophageal echocardiography (TEE).[4-8] Because of a considerable decrease in the use of pulmonary artery catheters in the management of patients with ARDS and limited availability and expertise in TEE across most intensive care units (ICUs) in the United States, a more readily available screening test to detect RV dysfunction in ARDS is needed.[20-22] Transthoracic echocardiography (TTE) is a noninvasive and cost-effective screening modality to detect increased pulmonary vascular resistance and RV dysfunction in patients with ARDS. Novel indices for assessment of RV function, such as tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (RV-FAC), and Tei index add to the armamentarium for TTE assessment of RV function.[23] Earlier studies involving patients with ARDS that used TTE were limited to systolic pulmonary artery pressure (SPAP) and RV size and function assessment.[24] Another concern for the use of TTE for patients with ARDS is poor image quality because of lung artifact in ARDS, which can limit the utility of this test. A recent feasibility study involving patients with ARDS showed that it is possible to obtain TAPSE values in 96% of the population, whereas the feasibility for measurements that include RV end-diastolic area/left ventricular end-diastolic area and RV-FAC were 72% and 62%, respectively.[25] We therefore studied these objective parameters of RV function in ARDS and their ability to predict severity of ARDS ($PaO_2 : FiO_2$ ratio) and mortality in patients with ARDS.

METHODS

We performed a retrospective single-center cohort study from January 2013 to April 2015 involving patients admitted to the medical intensive care unit (ICU) at Rush University Medical Center in Chicago, Illinois. Patients were identified with the following inclusion criteria: age >18 years; *International Classification of Diseases, 9th Revision*, diagnosis of ARDS; and TTE performed during the first 2 weeks of ARDS. The exclusion criteria included significant mitral or aortic stenosis and/or insufficiency, known history of congestive heart failure, or underlying primary pulmonary parenchymal disease.

Baseline demographic characteristics, medical history, ventricular and valvular function by echocardiogram report, baseline blood chemistries and blood counts, arterial blood gases, ventilator modes, and ventilator settings on the day of TTE were collected. Thirty-day mortality from day of TTE and $PaO_2 : FiO_2$ ratios on day of echocardiogram was also collected. In addition to the initial TTE report by the on-call cardiologist, all TTE images were again independently reviewed by one blinded cardiologist (JK). TAPSE, Tei index, RV-FAC, SPAP, and septal shift were measured using American Society of Echocardiography 2010 Guidelines for Right Heart Assessment in Adults.[17]

Thirty-eight patients met the inclusion and exclusion criteria and were divided into two groups on the basis of 30-day mortality from day of TTE into survivors and nonsurvivors. Mean differences of age, sex, timing of TTE from day of ARDS onset, pH, $PaO_2 : FiO_2$ ratios, PCO_2, serum bicarbonate, plateau pressures, PEEP, driving pressures, Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score II (SAPS II), Sequential Organ Failure Assessment (SOFA) score, TAPSE, Tei index, RV-FAC, and SPAP between survivors and nonsurvivors were analyzed using independent samples Student *t*-test. TAPSE, Tei index, RV-FAC, and SPAP between mild, moderate, and severe ARDS groups, determined according to Berlin definition of ARDS, were analyzed using the ANOVA test.[26] Septal shift among these groups was compared using χ^2 test. Correlation between TAPSE, Tei index, RV-FAC, SPAP, and $PaO_2 : FiO_2$ ratios was evaluated using Pearson coefficients. Multivariate logistic regression model using a theoretical-hierarchical approach was used to assess the effect of covariates, namely age, sex, pH, $PaO_2 : FiO_2$ ratios, PCO_2, serum bicarbonate, plateau pressures, PEEP, driving pressures, APACHE II score, SAPS II score, and SOFA score on association of TAPSE with mortality.[27] Statistical analysis was performed with SPSS software (IBM).

RESULTS

Thirty-eight patients met inclusion and exclusion criteria. Of 38 patients included in the study, 18 died within 30 days of TTE and 20 survived (i.e., 30-day mortality from TTE date was 47%; 18 of 38 patients died). TTE images were adequate to assess for TAPSE in 82% (31 of 38), septal shift in 95% (36 of 38), Tei index in 68% (26 of 38), RV-FAC in 84% (32 of 38), and SPAP in 74% (28 of 38).

Significant differences between survivors and nonsurvivors were present in age, pH, TAPSE, $PaO_2 : FiO_2$ ratios, APACHE II, SAPS II, and SOFA scores, whereas there were no statistically significant differences in sex, timing of TTE from day of ARDS onset, PCO_2, serum bicarbonate, plateau pressures, PEEP, and driving pressures (Table 1). Survivors were younger than nonsurvivors (44.5 ± 7 vs. 57.5 ± 5.5). Survivors had a higher pH (7.38 ± 0.04 vs. 7.31 ± 0.05), higher $PaO_2 : FiO_2$ ratios (192.7 ± 50.43 vs. 122.31 ± 25.34), and higher TAPSE (19.12 ± 1.8 vs. 15 ± 1.77) as compared to nonsurvivors (Table 1). Survivors had lower APACHE II scores (20.9 ± 3.84 vs. 26.11 ± 3.39), lower SAPS II scores (45.3 ± 6.97 vs. 59.61 ± 9.23), and lower SOFA scores (9.65 ± 1.98 vs. 13.39 ± 2.203) compared with nonsurvivors (Table 1). A significant decrease in TAPSE and increase in Tei index were seen in the severe ARDS group compared with the mild ARDS group. Significant septal shift was seen in patients with moderate and severe ARDS compared with patients with mild ARDS. RV-FAC and SPAP did not differ significantly between all three ARDS severity groups (Table 3).

Of all echocardiographic parameters, TAPSE had a strong statistically significant association ($P = 0.004$) with increased 30-day mortality from date of TTE (Table 1). Tei index, RV-FAC, SPAP, and septal shift did not have a statistically significant association with mortality (Table 1). In addition, TAPSE had a strong positive correlation ($r = 0.52$, $P = 0.003$) with $PaO_2 : FiO_2$ ratios, and Tei index had a strong negative correlation ($r = -0.46$, $P = 0.018$) with $PaO_2 : FiO_2$ ratios (Table 2). Septal shift was significantly associated with lower $PaO_2 : FiO_2$ ratios, with $P = 0.025$, but was not associated with mortality (Tables 1, 2).

The association of TAPSE with mortality was further assessed with multivariate regression models using age, pH, $PaO_2 : FiO_2$ ratios, PEEP, PCO_2, serum bicarbonate, plateau pressures, driving pressures, APACHE II scores, SAPS II scores, and SOFA scores.

Table 1. Characteristics of patients with acute respiratory distress syndrome (ARDS) who survived versus those who died

Characteristic	No. of patients (n = 38)	Survivors (n = 20)	Nonsurvivors (n = 18)	P
Age, years	38	44.5 ± 7	57.5 ± 5.5	**0.007**
Female sex, %	38	50	50	1
Day of ARDS[a]	38	5.1 ± 1.7	4.9 ± 1.5	0.895
Arterial pH	38	7.38 ± 0.04	7.31 ± 0.05	**0.045**
PCO_2	38	47.4 ± 6.6	51.4 ± 8.9	0.47
Serum bicarbonate	38	24.85 ± 8.2	22.17 ± 6.6	0.281
$PaO_2 : FiO_2$ ratio	38	192.7 ± 50.43	122.31 ± 25.34	0.021
Plateau pressure	38	23.1 ± 15.25	24.89 ± 14	0.467
PEEP	38	8.7 ± 2.12	11.17 ± 1.55	0.08
Driving pressure	38	17.35 ± 3.29	17 ± 3.4	0.886
TAPSE	31	19.12 ± 1.8	15 ± 1.77	**0.004**
Tei index	26	0.31 ± 0.12	0.41 ± 0.05	0.16
RV-FAC	32	0.54 ± 0.12	0.60 ± 0.15	0.533
Septal shift	36	7/20 (35%)	8/16 (50%)	0.36
SPAP	28	48.86 ± 6.78	49.71 ± 6.01	0.854
APACHE II	38	20.9 ± 3.84	26.11 ± 3.39	**0.035**
SAPS II	38	45.3 ± 6.97	59.61 ± 9.23	**0.012**
SOFA	38	9.65 ± 1.98	13.39 ± 2.20	**0.012**

Note: Data are 95% confidence intervals (mean ± 1.96 × standard error), unless otherwise indicated. Boldface type indicates statistical significance. APACHE II: Acute Physiology and Chronic Health Evaluation II; NA: not applicable; PCO_2: partial pressure of carbon dioxide; PEEP: positive end expiratory pressure; RV-FAC: right ventricular–fractional area change; SAPS II: Simplified Acute Physiology Score II; SOFA: sequential organ failure assessment; SPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion.

[a] Timing of transthoracic echocardiography from day of ARDS onset.

TAPSE maintained statistically significant association independent of these factors (Table 4).

DISCUSSION

ARDS is a major cause of morbidity and mortality in patients hospitalized in the ICU. Although lung protective ventilator management has improved survival in ARDS, mortality and morbidity from ARDS remains unacceptably high.[28] Pulmonary hypertension and RV dysfunction have a definite association with poorer outcomes in patients with ARDS.[4-8] However, to this date there is no consensus on the best predictive model for identification of pulmonary hypertension and RV dysfunction in ARDS.

Table 2. Correlation of transthoracic echocardiography (TTE) parameters with $PaO_2 : FiO_2$ ratios

TTE parameter	Correlation coefficient	Present	Absent	P
TAPSE	0.52	. . .	. . .	**0.003**
Tei index	−0.46	. . .	. . .	**0.018**
RV-FAC	−0.05	. . .	. . .	0.77
SPAP	−0.11	. . .	. . .	0.58
Septal shift[a] (range)	. . .	118 (93–143)	185 (131–238)	**0.025**

Note: RV-FAC: right ventricular–fractional area change; SPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion. Boldface type indicates statistical significance.

[a] Data for 36 of 38 patients.

Table 3. Transthoracic echocardiography (TTE) parameters according to severity of acute respiratory distress syndrome (ARDS)

TTE parameter	Mild ARDS	Moderate ARDS	Severe ARDS	*P*
TAPSE	20.28 ± 3.63	18.25 ± 1.95	14.36 ± 2.68	0.007
Tei index	0.18 ± 0.17	0.39 ± 0.09	0.46 ± 0.10	0.003
RV-FAC	0.73 ± 0.30	0.56 ± 0.15	0.51 ± 0.17	0.31
SPAP	51.4 ± 26.54	48.74 ± 5.66	49.00 ± 7.69	0.915
Septal shift, no. of patients	0/7	8/16	7/13	0.044

Note: Data are mean ± 1.96 × standard error, unless otherwise indicated. RV-FAC: right ventricular–fractional area change; SPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion.

Traditionally, TTE has not been used to screen or evaluate for RV dysfunction in ARDS because of concern for inferior image quality in patients with ARDS. However, Fichet et al.[25] showed, in a preliminary study, that TTE yielded good to excellent image quality in 78% of patients, and TAPSE could be assessed in 96% of patients. Indeed, in our study, we were able to obtain good to excellent images in 74% of patients (28 of 38 patients), and TAPSE could be obtained in 82% of patients. This finding supports the feasibility of using TTE to assess RV dysfunction in ARDS.

Our study further explores the utility of various TTE parameters in assessing RV dysfunction in ARDS and its association with $PaO_2 : FiO_2$ ratios, severity of ARDS, and mortality. We found that patients with ARDS who died within 30 days of their TTE had a significantly lower TAPSE score (15 ± 1.77 vs. 19.12 ± 1.8) compared with patients who survived. Moreover, this association persisted even after adjustment for age, sex, PEEP, driving pressure, plateau pressure, pH, PCO_2, serum bicarbonate, APACHE II scores, SAPS II scores, and SOFA scores. This suggests that low TAPSE is an independent predictor of mortality in ARDS even after adjusting for severity of illness and other factors that could affect mortality. In a study involving 750 patients with various cardiac conditions by Tamborini et al.,[29] a TAPSE value of <17 mm had very high specificity for RV dysfunction but very low sensitivity.[23] This is in line with our findings that nonsurvivors had an average TAPSE value of <17 mm (upper limit of 95% confidence interval: 16.77 mm). Because most patients with ARDS have normal right heart function before onset of ARDS, even mild decreases in TAPSE might be an indicator of early RV dysfunction. A cutoff of <17 mm might allow for early identification of these patients. Our study also shows that low TAPSE score, high Tei index, and septal shift are associated with lower $PaO_2 : FiO_2$ ratios and increased severity of ARDS (Tables 2, 3). Although high Tei index and septal shift are not associated with mortality, they are suggestive of worse RV function, which leads to lower PaO_2:FiO_2 ratios and increased severity of ARDS (Tables 2, 3).

In patients with ARDS with normal baseline cardiac function, RV dysfunction is mainly due to direct compression of pulmonary arteries, pulmonary endothelial cell dysfunction, pulmonary vascular remodeling, micro thrombi, mechanical ventilation strategies (PEEP and transpulmonary pressures), and metabolic disturbances, such as hypercapnia and acidosis.[9,11-14,18,30,31] We looked for some of these readily available factors that could have affected RV function in our patients. In our study, we found that nonsurvivors had a statistically significant lower pH compared with survivors (7.31 ± 0.05 vs. 7.38 ± 0.04). However, we did not find a statistically significant difference in driving pressure, plateau pressures, hypercapnia, and PEEP between survivors and nonsurvivors. A small sample size may have limited the ability of our study to evaluate a difference among these parameters. A statistical difference in pH suggests that patients with ARDS may have improved outcomes with near normal pH. Acidosis is a known etiology for inducing RV dysfunction.[15,31]

There are some other limitations to our study. Because it is a retrospective study, we could establish an association only with low TAPSE and increased mortality but not causality. Due to the small sample size of our study, it is possible that we did not detect a statistically significant association of other TTE parameters and mortality. Additionally, we might not have detected a difference in PEEP, PCO_2, bicarbonate, driving pressure, and plateau pressures

Table 4. Final logistic regression model

	Unstandardized coefficients		Standardized coefficients		
Model	B	Standard error	*β*	*t*	*P*
1 (Constant)	−.477	.348	. . .	−1.369	0.182
TAPSE	.061	.019	.501	3.118	**0.004**

Note: Dependent variable was mortality. TAPSE: tricuspid annular plane systolic excursion. Boldface type indicates statistical significance.

between survivors and nonsurvivors. TAPSE was also collinear with many of the other potential predictors. Because of this collinearity and TAPSE's strong predictive relationship with mortality, other possibly useful predictors may have been eliminated from the model. But this is also a function of the small sample size.

Our study also observed higher than expected mortality (18 [47%] of 38 patients died). Due to the retrospective nature of our study and small sample size, we can only speculate regarding the factors that led to a high mortality rate. A few likely reasons are that we were only looking at a select subset of patients with ARDS who were more ill at presentation. First, only patients who received an echocardiogram in the first week of ARDS were included in the study, whereas many patients with mild ARDS might not have received TTE as part of their workup. Second, our hospital is a large tertiary care referral center in Chicago with expertise in salvage modes for ARDS, which could have led us to select a sicker population of patients. Third, a large number of our patients (55%) had evidence of RV dysfunction on echocardiogram, which by itself could have led to higher mortality. We did not elicit any overt preexisting history of pulmonary hypertension in our ARDS population; however, potentially preexisting pulmonary vascular disease with concomitant development of ARDS may explain the increased mortality. The higher mortality seen should be studied as a prospective model of ARDS with preexisting pulmonary vascular disease.

Nevertheless, our study does provide an important association of low TAPSE (<17 mm) and mortality and paves the pathway for future studies of RV dysfunction in ARDS using TAPSE and other TTE parameters as initial tests. This subpopulation of ARDS patients can be managed with RV protective measures, namely limiting plateau pressures, driving pressures, acidosis, and hypercapnia as well as using prone position ventilation, prostaglandins, and perhaps other pulmonary vasodilators.[14,15,17-19,31,32] Future studies should incorporate the use of TAPSE to identify RV dysfunction early in ARDS and perhaps to target improvement in TAPSE with RV-protective measures prospectively to look for further reduction in mortality associated with ARDS.

CONCLUSION

Low TAPSE (<17 mm) is an independent predictor of mortality in patients with ARDS. Lower TAPSE, higher Tei index, and septal shift are associated with increased severity of ARDS. TAPSE can be used to predict mortality in ARDS with resultant RV dysfunction. Implementation of protective RV measures may be a key in improving ARDS survival in these patients.

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