

OPEN

Systolic Strain by Speckle-Tracking Echocardiography Is a Feasible and Sensitive Measure of Right Ventricular Dysfunction in Acute Respiratory Failure Patients on Mechanical Ventilation

OBJECTIVES: Right ventricular (RV) dysfunction is common in acute respiratory failure and associated with worse outcomes, but it can be difficult to detect in the ICU setting. Speckle-tracking echocardiography (STE) can identify early changes in RV systolic function and be quantified as systolic strain. We measured the feasibility of RV global longitudinal systolic strain (RV GLS) in respiratory failure patients and its association with clinical outcomes.

DESIGN: Retrospective cohort.

SETTING: Two tertiary hospital medical ICUs in Providence, RI, from March 2015 to January 2018.

PATIENTS: Two hundred twenty-three patients with acute respiratory failure requiring mechanical ventilation (MV) with available echocardiograms.

MEASUREMENTS AND MAIN RESULTS: Clinical data were extracted from medical records. RV GLS was measured via STE (TOMTEC, Chicago, IL), along with standard echocardiographic measurements by two independent readers blinded to outcomes. The average age was 65 years (range, 21–90 yr), 121 (54%) were men, and the most common etiology of respiratory failure was pneumonia ($n = 83$, 37%). The average RV GLS was -16% ($SD \pm 7$). The intraobserver correlation coefficients were 0.78 and 0.94, whereas the interobserver correlation coefficient was 0.61 for RV GLS. In the majority of echocardiograms ($n = 178$, 80%), all wall segments were tracked appropriately by operator visual inspection. Worse RV GLS was associated with greater hospital mortality (odds ratio, 1.03; 95% CI, 1.00–1.07; $p = 0.03$), such that every 1% decrement in RV GLS was associated with up to a 7% increase in the risk of death. RV GLS was 90% sensitive for the detection of RV dysfunction compared with tricuspid annular plane systolic excursion.

CONCLUSIONS: The measurement of RV GLS by STE in subjects on MV is feasible, reproducible, and sensitive for the detection of RV dysfunction. RV GLS may predict poor outcomes in acute respiratory failure.

KEY WORDS: respiratory failure, right ventricle echocardiography, right ventricular function, speckle-tracking echocardiography, strain

Severe forms of acute respiratory failure (ARF) including acute respiratory distress syndrome (ARDS) may be caused by various insults and disease processes. Despite this heterogeneity, the development of pulmonary vascular and right ventricular (RV) dysfunction in ARF is common and consistently associated with poor outcomes (1–4). The cardiopulmonary interaction in ARF is understudied and was identified as a critical research gap in a 2018

James Simmons, MD¹

Philip Haines, MD, MPH, MS²

Jonathan Extein, MD¹

Zubair Bashir, MD³

Jason Aliotta, MD¹

Corey E. Ventetuolo, MD, MS^{1,4}

Copyright © 2022 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of the Society of Critical Care Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/CCE.0000000000000619

American Thoracic Society Research Statement (5). Prone positioning reduces mortality in ARDS and has received considerable attention in the management of COVID-associated ARF (6–8). Acute cor pulmonale occurs in as many as 50% of patients with severe ARDS, and proning reduces RV enlargement and septal dyskinesia (9), suggesting proning may provide a benefit via direct cardiac effects. These observations imply that the detection of RV dysfunction in ARF may shed light on cardiac contributions, track with prognosis, and ultimately direct management to optimize heart-lung function in respiratory failure patients.

The identification of RV dysfunction in the ICU has historically been difficult. Invasive hemodynamic monitoring has been shown in clinical trials to carry risks without benefit, and hemodynamics do not capture RV contractile or morphologic changes (10, 11). Advanced RV imaging has not been widely adopted because of issues with feasibility and reliability in the ICU (5, 12, 13). Speckle-tracking echocardiography (STE) for the measurement of strain is an easily added software algorithm to standard echocardiographic windows obtained frequently at the bedside in the ICU. STE measures the change in the length of the myocardium of interest throughout the cardiac cycle (termed strain imaging), in order to provide a quantifiable measure of contractility. Strain is dimensionless and is typically reported as the percent change in length of myocardium from fully relaxed to fully contracted, so myocardium with worse contractility (i.e., decreased percent change in length of myocardium) will have a lower absolute strain measurement. However, strain is reported as a negative value because it measures a decrease in the length of myocardium, so a less negative (or more positive) strain value is consistent with worse contractility. Since RV longitudinal strain is most affected by subendocardial perfusion (the myocardium at highest risk in low flow or oxygen deficient states), STE may have high sensitivity to detect early RV myocardial damage and dysfunction (14–17). STE has been studied in several ICU settings and is now recommended for comprehensive assessment of RV dysfunction (18–25), but there are little data on the feasibility and reliability of STE measurements by critical care providers and trainees in the ICU setting. Although a single study demonstrated poor RV systolic strain is associated with mortality in COVID-associated ARF, this is a unique phenotype with significant cardiopulmonary

involvement that has not been fully elucidated (3, 26–28). To our knowledge, no study has carefully evaluated the feasibility and reliability of strain measurements in the ICU, nor whether RV contractile changes detected with STE predicts outcomes in non-COVID ARF.

We sought to measure RV global longitudinal systolic strain (RV GLS) in subjects with ARF requiring mechanical ventilation (MV) who had an available standard transthoracic echocardiogram during their time on MV. We hypothesized that RV GLS would be feasible to measure from stored standard transthoracic echocardiogram images and be reliable, and that worse (less negative) RV GLS would be associated with worse outcomes. We also speculated that RV GLS would have comparable performance to a widely accepted standard echocardiographic measurement of RV contractility (tricuspid annular plane systolic excursion [TAPSE]) (29–31).

MATERIALS AND METHODS

Study Sample

We performed a retrospective study of adult patients with ARF who underwent transthoracic echocardiography while on MV in the medical ICU of two hospitals (Rhode Island Hospital and The Miriam Hospital, Providence, RI) between May 2015 and January 2018. Subjects were identified by selecting ICU patients on MV for ARF during this time period, then compared with a list of all echocardiograms performed during the same study period. As we were interested in the study of isolated RV dysfunction, patients were excluded if they had left ventricular ejection fraction (LVEF) less than 40%, more than moderate aortic or mitral valve disease, prosthetic heart valves, or cardiac tamponade. We also excluded patients with echocardiographic images of insufficient quality to perform STE, those who were pregnant, or who were intubated for reasons other than ARF (e.g., airway protection). The Lifespan institutional review boards of both Rhode Island Hospital and The Miriam Hospital approved this study (approval reference 201018 45CFR), and no informed consent was required.

Clinical Variables

Clinical data were collected from the electronic medical record of each subject, including demographics,

prior medical history, illness severity scores, duration of MV, length of stay, and hospital survival. All clinical data used to calculate illness severity (Acute Physiology and Chronic Health Evaluation [APACHE] II) were collected at the time closest to the performance of and within 12 hours of the echocardiogram.

Strain and Echocardiography Measurements

STE (TOMTEC, Chicago, IL) was retroactively applied by two trained and blinded investigators (J.E.S., a pulmonary critical care fellow at the time of the study, trained by P.H., a cardiologist with expertise in cardiac imaging) to standard 2D echocardiograms to determine the RV GLS of the four-chamber and subcostal views. These values were averaged to determine the RV GLS if multiple views were available. In order to measure STE, investigators used still images from the cardiac cycle to demarcate their region of interest (ROI) for strain analysis (i.e., RV) within the software. The software analyzes the ROI through the cardiac cycles available within the image collection, and then the investigator visually inspected the tracking quality. If tracking appeared inaccurate with the STE given, appeared inconsistent throughout the cycle, or did not encompass the ROI, then the investigator redrew the ROI and reran the analysis. Once the best tracking analysis was determined for a given ROI, the RV GLS was recorded, whereas the speckle-tracking quality by visual inspection was reported as a tracking feasibility score (TFS) as follows: 3 (all segments tracking appropriately), 2 (all segments but one tracking appropriately), or 1 (more than one segment not tracking appropriately) (32). The RV GLS assesses the RV in its entirety and includes the free wall and the septal wall. Average RV longitudinal free-wall strain (average RV FWS) was measured by averaging the strain measurements of the three free-wall segments alone. The TOMTEC software provided an estimation of GLS accuracy that was collected. An illustrative example from a study subject of RV GLS determination is displayed in **Figure 1**. Standard echocardiographic measurements were measured de novo by investigators blinded to the original echocardiogram report (GE Healthcare Centricity Cardio Imaging Version 5.0 and Cardio Workflow Version 6.0). TAPSE measurements were measured for this study in those subjects with an apical four-chamber view via M-mode cursor placement at site of the lateral tricuspid annulus,

after which the peak excursion of the tricuspid annulus from the end of diastole to the end of systole was measured in millimeters. Variables that were part of the exclusion criteria (e.g., LVEF, valvular disease, and presence and degree of pericardial effusion) were extracted from the original echocardiogram report and not repeated. Other standard echocardiographic measurements that were repeated for this study (e.g., left atrial volume, right ventricular fractional area of change [RV FAC], and right ventricular systolic pressure [RVSP]) were measured per the American Society of Echocardiography guidelines when views were available and appropriate. Investigators repeated STE and echocardiographic measurements on a randomly determined sample of 10% of the total studies to calculate intra- and interclass correlations.

Statistical Analysis

Continuous data were summarized as median (interquartile range [IQR]), and categorical data were reported as frequency and percentages. ICU and in-hospital mortalities were regressed on RV GLS (and average RV FWS, RV FAC, and TAPSE, respectively) using multivariable Cox hazard regression. We selected covariates known to be associated with RV function and ICU outcome: sex, presence of chronic lung disease, illness severity (APACHE II score), and LVEF in order to account for the impact of occult left ventricular (LV) dysfunction on the RV. The sensitivity and specificity of RV GLS to identify RV dysfunction was calculated using the measured TAPSE for a given subject, with RV dysfunction defined as a TAPSE less than 18 mm. Concordance was measured using the intraclass correlation coefficient. 95% CIs were estimated. *p* values of less than 0.05 were considered significant. All analyses were conducted using the SAS Software 9.4 (SAS, Cary, NC).

RESULTS

We screened 1,951 patients to identify 348 subjects with ARF requiring MV and an available echocardiogram during the study period. Table 1 summarizes the baseline characteristics for the total cohort ($n = 348$) and the study sample ($n = 223$). We excluded 125 subjects (36%) because of predetermined exclusion criteria; 223 subjects had RV STE analyzed (**Figure 2**). The final study sample had a median age of 65 years old (IQR, 56–74 yr old), and

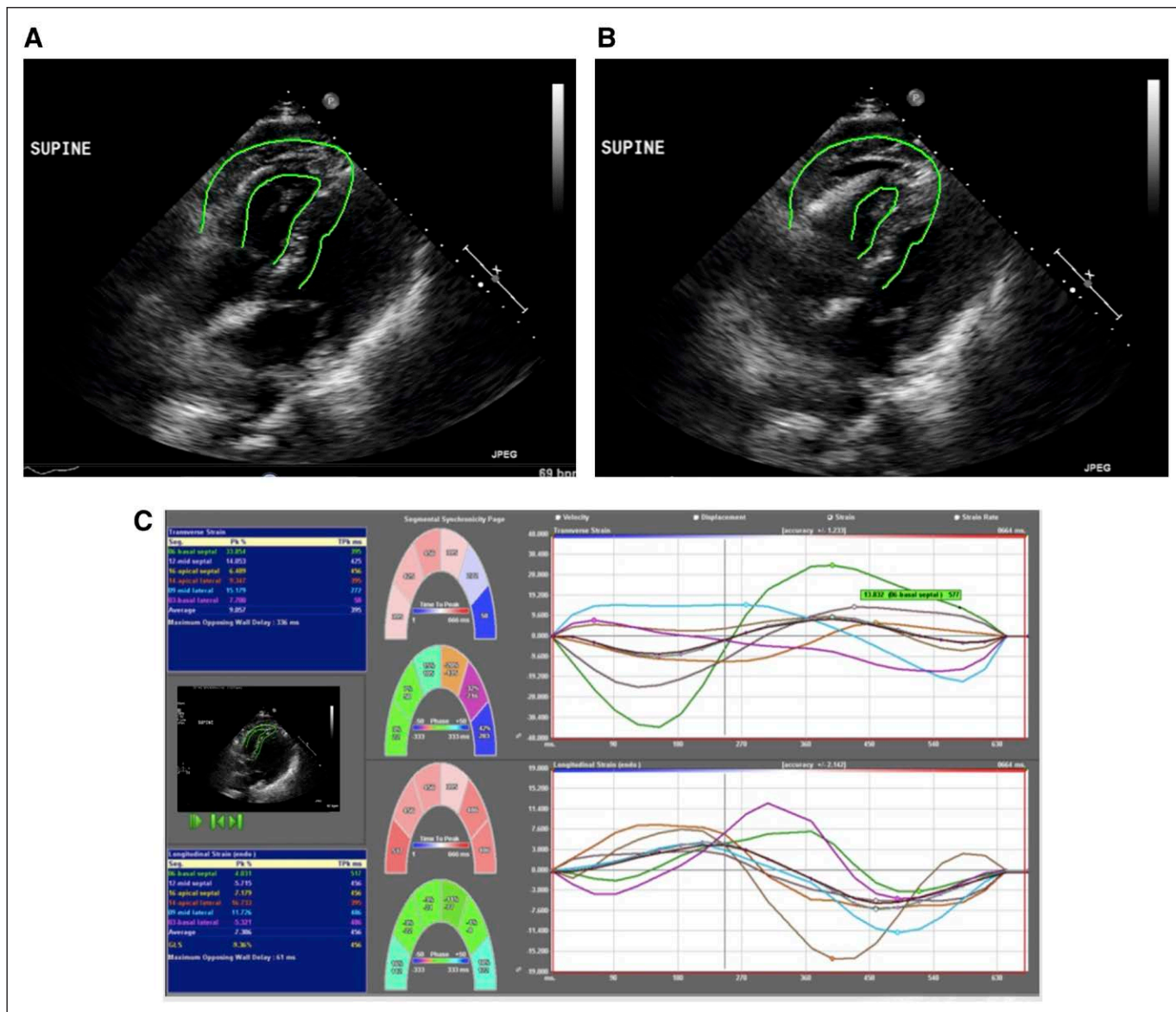


Figure 1. Illustrative example of strain measurement from a study subject. **A**, Investigator marked region of interest (ROI) of the right ventricle in the four-chamber view during relaxation using the TOMTEC speckle-tracking echocardiography software. **B**, Software-generated ROI at maximal contraction of the myocardium. The software-generated ROI is created for all images of the entire cardiac cycle to calculate strain; only two points in time are shown here. Strain software can differentiate active movement from passive movement, so the ROI can include nonmyocardial tissue without affecting strain measurement if tracking appropriately. **C**, Representative example of the output data in graphical and numerical form, which can be global or stratified into individual cardiac segments. Global longitudinal strain is reported in *bottom left table* as percent change (GLS).

54 % were men. The most common etiology of ARF was pneumonia ($n = 83, 37\%$; mean RV GLS, -16% ; IQR, -21% to -10%), followed by cardiac arrest ($n = 46, 21\%$; mean RV GLS, -16% ; IQR, -20% to -11%); 21 subjects (9%) had ARDS by Berlin criteria. The average RV GLS was -16% (IQR, -21% to -11%); additional echocardiographic measures for the population included are summarized in Table 2.

The intraobserver correlation coefficients were 0.78 and 0.94 for each reader for RV GLS, whereas

the interobserver correlation coefficient was 0.61 (Table 3). For all other reread standard echocardiography and strain measurements, the intraclass and interclass correlations were between 0.46 and 0.99. In most echocardiograms ($n = 178, 80\%$), all wall segments were tracked appropriately by operator visual inspection (TFS = 3). An additional 35 echocardiograms (16%) had all but one wall segment appropriately tracked (TFS = 2), and the average TFS was 2.75.

TABLE 1.
Baseline Characteristics of Screened and Speckle-Tracking Echocardiogram Performed Subjects

Variables	Total Cohort	Speckle-Tracking Echocardiography Performed
Number of subjects	348	223
Age, yr	65 (55–74)	65 (56–74)
Male sex, <i>n</i> (%)	194 (56)	121 (54)
Documented smoking history, <i>n</i> (%)	192 (55)	126 (57)
Body mass index, kg/m ²	29 (25–36)	30 (25–37)
Chronic lung disease, <i>n</i> (%)	134 (39)	92 (41)
Chronic obstructive lung disease	99 (28)	71 (32)
Asthma	24 (7)	13 (6)
Interstitial lung disease	9 (3)	5 (2)
Cystic fibrosis/bronchiectasis	2 (1)	1 (1)
Pulmonary hypertension	16 (5)	12 (5)
Obstructive sleep apnea	35 (10)	22 (10)
Primary lung cancer	12 (3)	9 (4)
Chronic cardiac disease, ^a <i>n</i> (%)	250 (72)	159 (71)
Chronic renal disease, ^b <i>n</i> (%)	44 (13)	31 (14)
Shock requiring pressors, <i>n</i> (%)	258 (74)	162 (72)
Number of pressors used	2 (1–2)	2 (1–2)
Inotropes, <i>n</i> (%)	35 (10)	11 (5)
Extracorporeal membrane oxygenation, <i>n</i> (%)	12 (3)	6 (3)
Extubated, <i>n</i> (%)	227 (65)	147 (66)
Acute Physiology and Chronic Health Evaluation II score	22 (17–27)	22 (18–27)
Etiology of acute respiratory failure, <i>n</i> (%)		
Pneumonia	116 (33)	83 (37)
Cardiac arrest	83 (24)	46 (21)
Aspiration	43 (12)	29 (13)
Pulmonary edema	61 (18)	34 (15)
Acute exacerbation of chronic obstructive pulmonary disease	8 (2)	6 (3)
Acute respiratory distress syndrome diagnosed	32 (9)	21 (9)
Outcomes		
Duration of mechanical ventilation, d	3 (2,9)	3 (5,23)
Inhospital survival time, d	24 (7–63)	24 (19–39)
ICU length of stay, d	7 (4–15)	8 (6–10)
Hospital length of stay, d	17 (10–27)	19 (15–20)

Data are presented as median (interquartile range) or *n* (%).

^aChronic cardiac disease = prior history of myocardial infarction, coronary artery disease, hypertension, less than moderate valvular heart disease, left ventricle diastolic dysfunction or heart failure with preserved ejection fraction, chronic pericardial disease, and chronic arrhythmias.

^bChronic kidney disease = > stage III or on chronic hemodialysis.

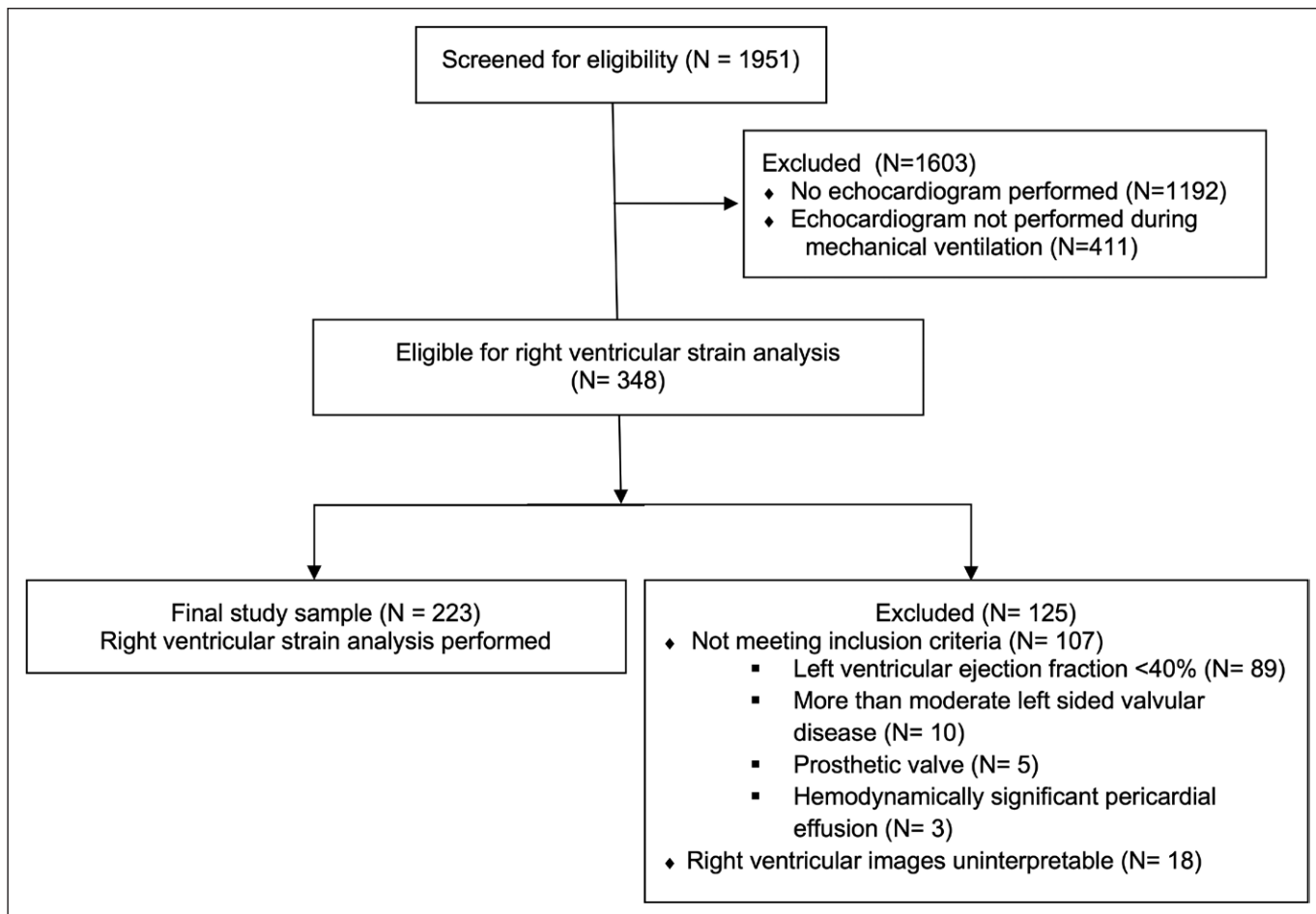


Figure 2. Flowchart of study population.

A worse RV GLS (less negative) was associated with a significant increase in in-hospital mortality (hazard ratio [HR], 1.03; 95% CI, 1.00–1.07; $p = 0.049$) after adjustment for sex, presence of chronic lung disease, illness severity (APACHE II score), and LVEF, such that every 1% change in RV GLS was associated with up to a 7% increase in the risk of death (Table 4). We failed to detect an association between RV GLS and ICU mortality (Table 4) and duration of MV (data not shown). Average RV FWS was not associated with clinical outcomes, even after adjustment (data not shown).

Finally, we compared RV GLS with TAPSE, as a widely accepted measure to detect RV dysfunction on standard 2D echocardiograms, and RV FAC, another common measure of RV systolic function. Among subjects with cardiac windows to successfully measure RV GLS, TAPSE was measured in 168 subjects (75%), whereas RV FAC could only be measured in 161 subjects (72%). RV FAC was abnormal (defined as RV FAC less than 35%) in 21 subjects (13% of those measured). In multivariable Cox hazard

regression models, a 1-mm increase in TAPSE was associated with a 6% reduction in hospital mortality (HR, 0.94; CI, 0.89–0.99; $p = 0.02$) and ICU mortality ($p = 0.01$), whereas RV FAC was not associated with hospital or ICU mortality in this population, even after adjustment (Table 4). Finally, compared with TAPSE less than 18 mm as an established standard for RV dysfunction, RV GLS was highly sensitive for the detection of RV dysfunction (90%) but poorly specific (20%).

DISCUSSION

We have shown that the measurement of RV GLS is feasible and reasonably reliable—even when measured by a trainee on images not specifically obtained for STE—in critically ill patients on MV. A worse (less negative) RV GLS was associated with a significant increase in in-hospital mortality after adjustment for clinically relevant factors. When compared with TAPSE as one widely accepted clinical standard to detect RV dysfunction, RV GLS was found to be highly sensitive.

TABLE 2.
Study Sample Strain and Echocardiogram Measurements

Echocardiogram Variables	Values
RV GLS (<i>n</i> = 223)	
Average RV GLS, all views, %	−16 (−21 to −11)
Subcostal view, when applicable (<i>n</i> = 170), %	−18 (−24 to −17)
Four-chamber view, when applicable (<i>n</i> = 207), %	−16 (−20 to −11)
Right ventricle free wall strain, %	−20 (−25 to −14)
Tracking feasibility score = 3, <i>n</i> (%)	178 (80)
Average RV GLS accuracy	± 3.75 (3.15–4.47)
Traditional echocardiographic parameters	
Left ventricle ejection fraction, %	60 (55–65)
Left sided valve dysfunction identified, <i>n</i> (%)	77 (35)
Diastolic function, <i>n</i> (%)	
Diastolic dysfunction present on report	53 (24)
Indeterminate diastolic dysfunction on report	16 (7)
Septal flattening, <i>n</i> (%)	14 (6)
Atrial fibrillation at time of echocardiogram, <i>n</i> (%)	14 (6)
Mitral valve E-wave Vmax, m/s	0.86 (0.68–0.10)
E', m/s	0.075 (0.062–0.096)
Left atrial volume, mL	57 (40–77)
Left atrial index	28 (21–38)
Right atrial volume, mL	45 (32–62)
Tricuspid annular plane systolic excursion, mm (<i>n</i> = 168)	18 (15–22)
Right ventricle basal diameter, mm	39 (34–44)
Right atrial pressure, mm Hg	8 (8–15)
Right ventricular systolic pressure, mm Hg	39 (32–48)
Right ventricular fractional area change (<i>n</i> = 161), %	51 (42–60)

RV GLS = right ventricular global longitudinal strain.

Data are presented as median (interquartile range) or *n* (%).

Not all subjects were able to have every traditional echocardiographic parameter measured due to differences in included views and their quality.

To our knowledge, this is the only study to feasibly measure RV GLS in a large, heterogeneous population of patients with respiratory failure requiring MV, which may make our results more generalizable.

Reliability estimates for the measurement of RV GLS were fair to good within and across readers, though it is notable that agreement was better for more established echocardiographic parameters, including TAPSE. The average TFS of 2.75 and percentage of studies with TFS of 3 (80%) for strain are similar to those reported for nine different software packages when previously compared head-to-head (32), suggesting tracking

limitations are more software-dependent than operator-dependent. Newer versions of the TOMTEC software that was used in this study may provide more consistent measurements of RV GLS. Notably, RV GLS was measurable more often than FAC and TAPSE, and only 18 of eligible subjects (5%) had uninterpretable (or missing) RV images and were excluded from strain measurement. This number may have been improved in a prospective study where even suboptimal views are kept for strain measurements. Our findings are in-line with other recent studies demonstrating it is feasible to measure cardiac strain in the setting of respiratory

TABLE 3.
Intraclass and Interclass Correlation Coefficients for Echocardiographic and Strain Measurements

Measured Variables	Intraclass Correlation Coefficient, Reader 1 ^a	Intraclass Correlation Coefficient, Reader 2 ^b	Interclass Correlation Coefficient
Echocardiographic variables			
E' septum, LV	0.99	0.97	0.99
E' lateral wall, LV	0.99	0.99	0.99
E' average	0.99	0.98	0.99
MV E-wave Vmax	0.99	0.99	0.99
MV A-wave Vmax	0.99	0.99	0.99
LA volume	0.97	0.92	0.80
LA index volume	0.97	0.82	0.78
Right atrium volume	0.72	0.94	0.87
Right ventricular systolic pressure	0.97	0.79	0.91
Right ventricular fractional area of change	0.87	0.78	0.67
Tricuspid annular plane systolic excursion	0.99	0.86	0.75
Strain variables			
LV average GLS	0.85	0.85	0.80
Strain left ventricular ejection fraction	0.94	0.97	0.94
RV average GLS	0.94	0.78	0.61
RV strain rate	0.72	0.95	0.96
RV free wall strain	0.66	0.80	0.46

GLS = global longitudinal strain, LA = left atrium, LV = left ventricle, MV = mitral valve, RV = right ventricle.

^aReader 1 was a pulmonary and critical care fellow, except for RV fractional area of change, read by internal medicine hospitalist.

^bReader 2 is a cardiologist.

TABLE 4.
Association of Right Ventricular Global Longitudinal Strain, Tricuspid Annular Plane Systolic Excursion, and Right Ventricular Fractional Area of Change With Clinical Outcomes

Measurement	Unadjusted HR	p	Adjusted HR ^a	p
Right ventricular global longitudinal strain				
Hospital mortality	1.02 (0.99–1.05)	0.15	1.03 (1.00–1.07)	0.05
ICU mortality	1.02 (0.98–1.05)	0.37	1.04 (0.99–1.08)	0.10
Right ventricular fractional area of change				
Hospital mortality	1.00 (0.98–1.02)	0.94	1.01 (0.99–1.03)	0.48
ICU mortality	1.00 (0.97–1.02)	0.72	1.00 (0.97–1.03)	0.91
Tricuspid annular plane systolic excursion				
Hospital mortality	0.92 (0.88–0.97)	< 0.001	0.94 (0.89–0.99)	0.02
ICU mortality	0.92 (0.86–0.97)	0.01	0.91 (0.85–0.97)	0.01

HR = hazard ratio.

^aAdjusted for sex, chronic lung disease, illness severity (Acute Physiology and Chronic Health Evaluation II), and left ventricular ejection fraction.

Data presented as hazard ratio (95% CI).

failure and supports clinician uptake of this still infrequently used technology (24).

The association with in-hospital mortality after multivariable adjustment suggests that the deleterious effects of RV dysfunction during respiratory failure contribute to the recovery process and that RV GLS is likely a marker of global illness severity. Our findings differ somewhat from a prior study by Lemarié et al (24), which found no association between RV GLS and mortality or duration of MV in patients with ARDS. We included a larger number of subjects (223 compared with 48) with a wide variety of types of respiratory failure and did not exclude patients with chronic respiratory failure or chronic RV failure, increasing generalizability. Neither our nor the study by Lemarié et al (24) included a nonventilated comparator group, so the contribution of MV itself to RV dysfunction may be underestimated. In fact, only a small portion of subjects ($n = 31$, 14%) had a normal RV GLS (defined as more negative than -25%) in our study. RV GLS in healthy individuals ranges from -24.2 to -26.7 and is somewhat dependent on the software used and sex (33). Normative values for RV GLS in intubated patients with preserved RV function are unknown at this time. Based on our results and others, it is possible that MV itself affects RV contractility to the point that different RV GLS reference values may be appropriate, but further investigation is needed (24, 26, 33).

Subjects with abnormal RV GLS tended to have worse parameters of both RV and LV function (lower LVEF, more diastolic dysfunction, higher incidence of clinical pulmonary edema, and higher RVSP). We excluded those with measurable LV systolic dysfunction (defined as LVEF less than 40%); there is a likely important (and expected) contribution of subclinical LV systolic and diastolic dysfunction to RV function that has been identified in other studies (34). Although 21% of the study population had suffered a cardiac arrest and may therefore have been more prone to LV dysfunction, cardiac arrest subjects had a mean RV GLS of -16% (IQR, -20% to -11%), which was similar to that of subjects with pneumonia (mean RV GLS, -16% ; IQR, -21% to -10%). Collectively, these findings suggest that RV GLS may serve as an integrated measurement of biventricular, cardiopulmonary function in patients with otherwise normal LV systolic function and no significant left-sided valvular disease. Other factors that we did not account for but that may contribute to RV GLS include

patient positioning and body habitus, supportive therapies (e.g., vasopressors, inotropes, and volume management), pacing, timing of echocardiogram relative to course of illness, and degree of subclinical LV systolic and diastolic dysfunction.

Though standardization of RV strain measurements is improving, there is still debate about which structural components of the RV are most clinically consequential, since the free wall function is classically thought to be the main determinant of systolic function. Our results show that measuring the average of the 3 RV free wall segments generally leads to a more negative RV GLS (-20% ; IQR, -25 to -14) when compared with the RV chamber as a whole, both by four-chamber view (average RV GLS, -16% ; IQR, -20 to -11) and subcostal view (average RV GLS, -18% ; IQR, -24 to -7). These differences may be explained by the addition of septal segments that are more dependent on LV strain or by loss of signal when multiple segments' strain is averaged instead of measuring the entire subendocardium as a single unit. There is still much debate in the literature about what standardized measure of RV strain provides the most clinically useful information.

TAPSE had stronger associations with clinical outcomes than RV GLS in this population. Although RV GLS was sensitive for the identification of RV dysfunction, it was poorly specific. TAPSE is angle-dependent (and load-dependent) and measures only the displacement of a single segment, different from GLS that is angle-independent and measures multiple segments; these differences suggest RV GLS should be able to detect RV dysfunction in the context of a normal TAPSE (35). In our cohort, there was a very high prevalence of RV dysfunction, which inherently impacts performance characteristics. TAPSE and RV FAC themselves are not direct measures of global RV function, and therefore, identification of true negatives or false positives of RV dysfunction is based on assumptions that may not be valid. The true specificity may be higher or lower than that reported here. Future studies should include patients who have less severe respiratory failure and incorporate cardiac MRI or 3D echo, although these are difficult to perform in critically ill patients on MV, less well established, and not widely available. RV FAC measurements could not be measured in over a quarter of subjects and would qualify the majority of these subjects (87%) as normal if the standard cutoff of greater than 35% was applied, suggesting that RV FAC is not a sufficiently

sensitive (or obtainable) measure of RV dysfunction in this population.

Our study demonstrates TAPSE is also a feasible and reliable bedside measure of clinically important RV dysfunction in respiratory failure patients, although the “gold standard” of RV function assessment in the ICU remains debatable. A recent study by Vieillard-Baron et al (36) demonstrated the limited clinical utility of TAPSE to identify RV failure (defined by RV size and central venous pressure) and predict fluid responsiveness of septic shock patients on MV. In addition to differences in the two study populations, Vieillard-Baron et al (36) did not examine associations between TAPSE and clinical outcomes, making direct comparisons with our study difficult. Of the 223 subjects with measurable RV GLS, 55 (25%) did not have windows to measure TAPSE, so RV GLS may have additional value in patients with limited views.

There were some limitations, including that this was a retrospective study from a single institution, albeit two hospitals and ICUs were included. We did not repeat echocardiograms to improve or adjust image quality in patients that would otherwise have been included, and the majority of patients with ARF on MV did not have coincident echocardiograms performed, which may have created selection bias. Similarly, the retrospective nature of this study limited our ability to ensure that certain views used for traditional echocardiographic measurements (e.g., S' wave, RV FAC, and TAPSE) could not be obtained, though it is standard practice in our hospitals that echocardiogram technicians assess multiple potential windows, approaches, and patient positions to obtain them. Of the patients with echocardiograms performed while on MV, 64% met our inclusion criteria; we believe our study population encompasses most patients in ARF on MV. We did not include a comparator group of patients on MV without ARF, nor did we have baseline echocardiograms for the study population. We believe our findings suggest echocardiograms should be considered in more patients while on MV given the minimal risk and common findings of overt LV disease and subclinical RV dysfunction. Future studies should include repeated measurements of RV GLS to fully assess accuracy and precision and to determine if therapeutic interventions or changes in clinical status track with changes to RV GLS. Newer STE software may improve myocardial tracking and precision of measurements.

Colinearity may have also contributed to our findings. Although TAPSE derived from transthoracic echocardiograms was chosen as the gold standard for this study, more advanced imaging techniques including transesophageal echocardiograms may be preferable to the reference standard in ICU patients.

CONCLUSIONS

The measurement of RV GLS is feasible and reasonably reliable in critically ill patients on MV. A worse (less negative) RV GLS was associated with a significant increase in in-hospital mortality after adjustment for clinically relevant factors for critically ill patients. When compared with the ability of TAPSE to detect RV dysfunction, RV GLS was found to be highly sensitive and could be measured in several patients whose images did not provide appropriate views for TAPSE, though TAPSE had stronger associations with clinical outcomes in this population.

ACKNOWLEDGMENTS

This article has been reviewed by all investigators for scientific content and consistency of data interpretation. Significant comments have been incorporated prior to submission for publication. We thank the other investigators, the staff, and the patients that were included in this study.

- 1 Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Alpert Medical School of Brown University, Providence, RI.
- 2 Department of Medicine, Division of Cardiology, Alpert Medical School of Brown University, Providence, RI.
- 3 Department of Medicine, Alpert Medical School of Brown University, Providence, RI.
- 4 Department of Health Services, Policy and Practice, Brown School of Public Health, Providence, RI.

Dr. Simmons helped in study concept and design, data analysis and interpretation, drafting, and revision of article. Dr. Haines helped in echocardiographic and strain data collection and analysis, and revision of article. Dr. Aliotta contributed to data collection and revision of article. Dr. Extein helped in data collection and revision of article. Dr. Bashir helped in echocardiographic data collection and revision of article. Dr. Ventetuolo helped in study concept and design, data analysis and interpretation, drafting, and revision of article.

Supported, in part, by the National Institutes of Health (Dr. Ventetuolo: R01 HL141268).

Dr. Haines has served as an education consultant for Philips Healthcare. Dr. Ventetuolo has received grant funding to her institution from United Therapeutics and has served as a consultant

for Acceleron Pharma and Altavant Sciences. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: corey_ventetuolo@brown.edu

REFERENCES

1. Bull TM, Clark B, McFann K, et al; National Institutes of Health/ National Heart, Lung, and Blood Institute ARDS Network: Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. *Am J Respir Crit Care Med* 2010; 182:1123–1128
2. Biteker FS, Başaran Ö, Sözen H, et al: Prognostic value of transthoracic echocardiography and biomarkers of cardiac dysfunction in community-acquired pneumonia. *Clin Microbiol Infect* 2016; 22:1006.e1001–1006.e1006
3. Creel-Bulos C, Hockstein M, Amin N, et al: Acute cor pulmonale in critically ill patients with Covid-19. *N Engl J Med* 2020; 382:e70
4. Singanayagam A, Schembri S, Chalmers JD: Predictors of mortality in hospitalized adults with acute exacerbation of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2013; 10:81–89
5. Lahm T, Douglas IS, Archer SL, et al; American Thoracic Society Assembly on Pulmonary Circulation: Assessment of right ventricular function in the research setting: Knowledge gaps and pathways forward. An official American Thoracic Society research statement. *Am J Respir Crit Care Med* 2018; 198:e15–e43
6. Guérin C, Reignier J, Richard JC, et al; PROSEVA Study Group: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368:2159–2168
7. Scholten EL, Beitler JR, Prisk GK, et al: Treatment of ARDS with prone positioning. *Chest* 2017; 151:215–224
8. Elharrar X, Trigui Y, Dols AM, et al: Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. *JAMA* 2020; 323:2336–2338
9. Vieillard-Baron A, Charron C, Caille V, et al: Prone positioning unloads the right ventricle in severe ARDS. *Chest* 2007; 132:1440–1446
10. Wheeler AP, Bernard GR, Hite RD, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006; 354:2213–2224
11. Richard C, Warszawski J, Anguel N, et al; French Pulmonary Artery Catheter Study Group: Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2003; 290:2713–2720
12. Foale R, Nihoyannopoulos P, McKenna W, et al: Echocardiographic measurement of the normal adult right ventricle. *Br Heart J* 1986; 56:33–44
13. Perk G, Tunick PA, Kronzon I: Non-Doppler two-dimensional strain imaging by echocardiography—from technical considerations to clinical applications. *J Am Soc Echocardiogr* 2007; 20:234–243
14. Algranati D, Kassab GS, Lanir Y: Why is the subendocardium more vulnerable to ischemia? A new paradigm. *Am J Physiol Heart Circ Physiol* 2011; 300:H1090–H1100
15. Frangogiannis NG: Pathophysiology of myocardial infarction. *Compr Physiol* 2015; 5:1841–1875
16. Lowe JE, Cummings RG, Adams DH, et al: Evidence that ischemic cell death begins in the subendocardium independent of variations in collateral flow or wall tension. *Circulation* 1983; 68:190–202
17. Beyhoffer N, Brix S, Kintscher U, et al: Application of speckle-tracking echocardiography in an experimental model of isolated subendocardial damage. *J Am Soc Echocardiogr* 2017; 30:1239–1250.e1232
18. Garcia-Montilla R, Imam F, Miao M, et al: Optimal right heart filling pressure in acute respiratory distress syndrome determined by strain echocardiography. *Echocardiography* 2017; 34:851–861
19. Orde SR, Pulido JN, Masaki M, et al: Outcome prediction in sepsis: Speckle tracking echocardiography based assessment of myocardial function. *Crit Care* 2014; 18:R149
20. Hestenes SM, Halvorsen PS, Skulstad H, et al: Advantages of strain echocardiography in assessment of myocardial function in severe sepsis: An experimental study. *Crit Care Med* 2014; 42:e432–e440
21. De Geer L, Engvall J, Oscarsson A: Strain echocardiography in septic shock - a comparison with systolic and diastolic function parameters, cardiac biomarkers and outcome. *Crit Care* 2015; 19:122
22. Platz E, Hassanein AH, Shah A, et al: Regional right ventricular strain pattern in patients with acute pulmonary embolism. *Echocardiography* 2012; 29:464–470
23. Sugiura E, Dohi K, Onishi K, et al: Reversible right ventricular regional non-uniformity quantified by speckle-tracking strain imaging in patients with acute pulmonary thromboembolism. *J Am Soc Echocardiogr* 2009; 22:1353–1359
24. Lemarié J, Maigrat CH, Kimmoun A, et al: Feasibility, reproducibility and diagnostic usefulness of right ventricular strain by 2-dimensional speckle-tracking echocardiography in ARDS patients: the ARD strain study. *Ann Intensive Care* 2020; 10:24
25. Badano LP, Koliás TJ, Muraru D, et al; Industry representatives; Reviewers: This document was reviewed by members of the 2016–2018 EACVI Scientific Documents Committee: Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: A consensus document of the EACVI/ ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging* 2018; 19:591–600
26. Li Y, Li H, Zhu S, et al: Prognostic value of right ventricular longitudinal strain in patients with COVID-19. *JACC Cardiovasc Imaging* 2020; 13:2287–2299
27. Poor HD, Rurak K, Howell D, et al: Cardiac index is associated with oxygenation in COVID-19 acute respiratory distress syndrome. *Pulm Circ* 2021; 11:20458940211019626
28. Reynolds AS, Lee AG, Renz J, et al: Pulmonary vascular dilatation detected by automated transcranial Doppler in COVID-19 pneumonia. *Am J Respir Crit Care Med* 2020; 202:1037–1039

29. Kaul S, Tei C, Hopkins JM, et al: Assessment of right ventricular function using two-dimensional echocardiography. *Am Heart J* 1984; 107:526–531
30. Rudski LG, Lai WW, Schiller NB, et al: Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23:685–713
31. Ueti OM, Camargo EE, Ueti A de A, et al: Assessment of right ventricular function with Doppler echocardiographic indices derived from tricuspid annular motion: Comparison with radio-nuclide angiography. *Heart* 2002; 88:244–248
32. Farsalinos KE, Daraban AM, Ünlü S, et al: Head-to-head comparison of global longitudinal strain measurements among nine different vendors: The EACVI/ASE inter-vendor comparison study. *J Am Soc Echocardiogr* 2015; 28:1171–1181, e2
33. Lee JH, Park JH: Strain analysis of the right ventricle using two-dimensional echocardiography. *J Cardiovasc Imaging* 2018; 26:111–124
34. Brand A, Bathe M, Oertelt-Prigione S, et al: Right heart function in impaired left ventricular diastolic function: 2D speckle tracking echocardiography-based and Doppler tissue imaging-based analysis of right atrial and ventricular function. *Echocardiography* 2018; 35:47–55
35. Aloia E, Cameli M, D'Ascenzi F, et al: TAPSE: An old but useful tool in different diseases. *Int J Cardiol* 2016; 225:177–183
36. Vieillard-Baron A, Prigent A, Repessé X, et al: Right ventricular failure in septic shock: Characterization, incidence and impact on fluid responsiveness. *Crit Care* 2020; 24:630