LETTER TO THE EDITOR

Abnormal Right Ventricular Free Wall Strain Prior to Prone Ventilation May Be Associated With Worse Outcome of Patients With COVID-19–Associated Acute Respiratory Distress Syndrome

ABSTRACT: We investigated the effect of prone ventilation on right ventricular (RV) function of intubated patients with COVID-19–associated acute respiratory distress syndrome by measuring both conventional RV functional variables (namely, tricuspid annular peak systolic velocity, tricuspid annular plane systolic excursion, and fractional area change) and right ventricular free wall strain (RVFWS) using transthoracic speckle-tracking echocardiography at baseline (before prone positioning), 18 hours after prone positioning, and 1 hour after supine repositioning. We found that transthoracic echocardiography was feasible in a considerable proportion (nine patients, 75% of our cohort) of patients undergoing prone ventilation. Also, abnormal as opposed to normal RVFWS values (in the absence of conventional variables of RV dysfunction) at baseline were associated with higher mortality (100% vs 20%; \( p = 0.048 \)). Finally, we found that, among patients without acute cor pulmonale or conventional markers of RV dysfunction, one session of prone ventilation may not affect right myocardial strain.

KEY WORDS: acute respiratory failure; COVID-19; critical care; intensive care unit; mechanical ventilation

To the Editor:

Since the beginning of the pandemic, studies demonstrated the beneficial effect of prone ventilation on respiratory variables and outcomes of intubated patients with COVID-19 (1). Furthermore, before the pandemic, studies had demonstrated the beneficial effect of prone ventilation among patients with acute respiratory distress syndrome (ARDS) who had acute cor pulmonale (2) or abnormal conventional variables of right ventricular (RV) function (3). Although a few recent studies reported on advanced RV functional evaluation of critically ill patients with COVID-19 (4, 5), data on its feasibility and association with outcomes specifically among patients undergoing prone ventilation are scarce. Such data would be interesting because, although prone ventilation is actively used for many patients with COVID-19–associated ARDS, its effects on hemodynamics (including on RV function) may not be well understood. Therefore, we attempted to investigate the effect of prone ventilation on RV function of intubated patients with COVID-19–associated ARDS by measuring both conventional RV functional variables and right ventricular free wall strain (RVFWS) using 2D transthoracic speckle-tracking echocardiography.

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Adult (≥ 18 yr old) patients with ARDS associated with laboratory-confirmed COVID-19 hospitalized in the academic ICU of a tertiary hospital (Evangelismos Hospital, Athens, Greece) were included in this cohort. The Institutional Review Board at Evangelismos Hospital (116/31-03-2021) approved of the data collection and waived the need of informed consent. Transthoracic echocardiography was performed as part of standard care at three time points; namely, at baseline (immediately before prone positioning), 18 hours after prone positioning (i.e., while the patient was undergoing prone ventilation), and 1 hour after supine repositioning. These time points were selected to ensure that hemodynamic changes induced by the postural change have been stabilized (3). To reduce variability, all patients were evaluated during the first session (which lasted 18 hr) of prone ventilation after their intubation.

Images were acquired by in cine-loop format from several consecutive beats and analyzed offline (EchoPAC Version 204; GE Healthcare, Chicago, IL). A RV-focused view was used to generate all strain measurements in accordance to current published recommendations (6). Tricuspid annular peak systolic velocity (S′ velocity), tricuspid annular plane systolic excursion (TAPSE), and fractional area change (FAC) were considered as conventional variables of RV function. Values of less than 9.5 cm/s, less than 1.7 cm, and less than 35% for S′ velocity, TAPSE, and FAC, respectively, were considered as indicative of RV dysfunction, in accordance with relevant published guidelines (6). To facilitate interpretation of results, RVFWS values are presented as absolute values with larger numbers signifying better cardiac function and smaller numbers signifying poorer cardiac function. RVFWS was evaluated according to the cutoff derived by a meta-analysis of relevant studies, with a lower normal limit of 23.7% (7). Images were acquired by one cardiologist (P.T.) and analyzed independently by two cardiologists (P.T., A.K.) with more than 5 years of experience in performing advanced level echocardiography in critically ill patients.

Statistical analyses were performed using SPSS software Version 22.0 (IBM, Armonk, NY). Continuous variables are presented as median and interquartile range. Mann-Whitney rank-sum test was used to compare continuous variables. Categorical variables are presented as n (%). chi-square or Fisher exact test was used to compare categorical variables. A mixed-design analysis of variance was used to compare RVFWS mean values with three time points as a within-subjects factor and the aforementioned patients’ classification as a between-subjects factor. Variability and reproducibility of the strain analyses were assessed using a two-way mixed intraclass correlation coefficient model. All statistical tests were two-tailed and statistical significance was defined as p value of less than 0.05.

Twelve patients with COVID-19–associated ARDS were assessed for transthoracic RV speckle-tracking echocardiography by an experienced cardiologist, who was present during their first prone session after intubation. In three of them, acquisition of images was not feasible. Thus, echocardiography was feasible in nine patients (75% of cohort). Table 1 summarizes the baseline characteristics, physiologic variables, and outcome of included patients. Hemodynamic variables, such as mean arterial pressure, heart rate, and norepinephrine intake, were not different between patients with abnormal RVFWS versus normal RVFWS values at baseline. No inotropes were administered. With regard to RV function, at baseline, no patient had acute cor pulmonale, that is, RV enlargement and/or septal dyskinesia were absent. Also, at baseline, no patient had abnormal S′ velocity, TAPSE, and FAC values. However, four patients had abnormal RVFWS values, whereas the remaining five patients had normal RVFWS values. Patients with abnormal RVFWS (even in the absence of conventional variables of RV dysfunction) at baseline had higher mortality than those with normal RVFWS values (100% vs 20%; p = 0.048).

Table 2 depicts the values of both conventional RV functional variables (namely, S′ velocity, TAPSE, and FAC) and RVFWS of included patients at the three time points, along with physiologic variables that may affect RV function. All patients responded to prone ventilation in terms of oxygenation. There was no significant effect of time (i.e., prone ventilation) on RVFWS (F[2,14] = 0.042; p = 0.959). Reproducibility of RVFWS measurements was good with an intraclass correlation coefficient of 0.827. Figure 1 demonstrates the lack of association between prone ventilation and RVFWS values among patients with or without RV strain at baseline.

Our observational study provides three interesting findings. First, our study shows that not only transthoracic echocardiography is feasible
| Variable | Patients With Abnormal Baseline Right Ventricular Free Wall Strain Values (n = 4) | Patients With Normal Baseline Right Ventricular Free Wall Strain Values (n = 5) | p |
|----------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------|----|
| Characteristics |                                                                                      |                                                                                |    |
| Age, yr   | 61.0 (42.2–82.7)                                                                 | 62.0 (57.0–69.5)                                                               | 1.000 |
| Female sex | 1 (25.0)                                                                      | 1 (20.0)                                                                       | 1.000 |
| Race      |                                                                                      |                                                                                |    |
| Caucasian | 4 (100.0)                                                                      | 4 (80.0)                                                                       |    |
| African   | 0 (0.0)                                                                         | 1 (20.0)                                                                       |    |
| Comorbidity |                                                                                      |                                                                                |    |
| Chronic kidney disease | 0 (0.0)                                                                         | 0 (0.0)                                                                       | 1.000 |
| Chronic lung disease | 0 (0.0)                                                                        | 0 (0.0)                                                                       | 1.000 |
| Heart condition | 0 (0.0)                                                                         | 0 (0.0)                                                                       | 1.000 |
| Hypertension | 1 (25.0)                                                                        | 3 (60.0)                                                                       | 0.524 |
| Liver disease | 0 (0.0)                                                                         | 0 (0.0)                                                                       | 1.000 |
| Diabetes mellitus | 1 (25.0)                                                                         | 1 (20.0)                                                                       | 1.000 |
| Malignancy | 0 (0.0)                                                                         | 0 (0.0)                                                                       | 1.000 |
| Days from symptom onset to intubation  | 10.0 (4.7–14.5)                                                                  | 14.0 (4.0–18.0)                                                                | 0.806 |
| Days from intubation to prone positioning | 3.5 (0.7–5.5)                                                                    | 1.0 (1.0–2.5)                                                                  | 0.260 |
| Physiologic variables |                                                                                       |                                                                                |    |
| Sequential Organ Failure Assessment score | 6.5 (4.5–7.7)                                                                    | 7.0 (5.5–9.0)                                                                  | 0.457 |
| Mean arterial pressure, mm Hg | 77.5 (64.0–113.5)                                                                | 80.0 (66.0–87.0)                                                               | 0.902 |
| Heart rate, beats/min | 80.0 (70.0–83.7)                                                                 | 77.0 (52.5–87.0)                                                               | 0.624 |
| Norepinephrine intake, µg/kg/min | 0.02 (0.00–0.11)                                                                 | 0.10 (0.06–0.40)                                                               | 0.142 |
| Ventilation mode |                                                                                       |                                                                                |    |
| Volume control | 3 (75.0)                                                                         | 5 (100.0)                                                                       | 0.444 |
| Pressure control | 1 (25.0)                                                                         | 0 (0.0)                                                                         |    |
| Respiratory rate, beats/min | 26.0 (21.2–29.2)                                                                  | 30.0 (21.5–31.5)                                                               | 0.459 |
| Tidal volume, mL | 460.0 (405.0–537.5)                                                              | 450.0 (390.0–470.0)                                                            | 0.539 |
| Positive end-expiratory pressure external, cm H₂O | 14.5 (12.5–15.0)                                                                  | 12.0 (10.0–13.0)                                                                | 0.058 |
| Plateau pressure, cm H₂O | 28.0 (25.2–30.7)                                                                  | 29.0 (25.5–31.5)                                                                | 0.901 |
| Driving pressure, cm H₂O | 13.0 (10.0–21.2)                                                                  | 17.0 (15.0–17.5)                                                                | 0.215 |
| PacO₂/FIO₂ | 77.0 (68.5–118.0)                                                                 | 144.7 (116.3–240.8)                                                            | 0.050 |
| PacO₂, mm Hg | 50.0 (43.6–56.5)                                                                  | 48.7 (38.4–58.4)                                                                | 0.806 |
| pH | 7.35 (7.32–7.42)                                                                  | 7.28 (7.24–7.40)                                                                | 0.221 |
| Outcome |                                                                                      |                                                                                |    |
| Mortality | 4 (100.0)                                                                        | 1 (20.0)                                                                       | **0.048** |

Heart condition included congestive heart failure, coronary artery disease, and cardiomyopathies.
Mortality was censored at day 28 following intubation.
Data are presented as median (interquartile range) or n (%). Boldface value indicates statistical significance.
### TABLE 2.
Right Ventricular Echocardiographic Findings and Physiologic Variables of Included Patients at Three Time Points

| Variable                        | Patients With Abnormal Baseline RVFWS Values (n = 4) | Patients With Normal Baseline RVFWS Values\(^a\) (n = 5) | p     |
|---------------------------------|------------------------------------------------------|--------------------------------------------------------|-------|
| **Baseline (before prone positioning)** |                                                      |                                                       |       |
| RVFWS, %                        | 20.3 (17.1–22.1)                                     | 26.2 (24.1–32.8)                                      | 0.014 |
| TAPSE, mm                       | 24.5 (22.5–26.5)                                     | 25.0 (21.0–27.0)                                      | 1.000 |
| S’ velocity, cm/s               | 13.0 (11.2–14.7)                                     | 16.0 (11.5–18.5)                                      | 0.176 |
| FAC\(^b\), %                    | 41.7 (38.5–52.5)                                     | 44.0 (42.5–50.0)                                      | 0.462 |
| Mean arterial pressure, mm Hg   | 77.5 (64.0–113.5)                                    | 80.0 (66.0–87.0)                                      | 0.902 |
| Heart rate, beats/min           | 80.0 (70.0–83.7)                                     | 77.0 (52.5–87.0)                                      | 0.624 |
| Norepinephrine intake, µg/kg/min| 0.02 (0.00–0.11)                                     | 0.10 (0.06–0.40)                                      | 0.142 |
| PEEPext, cm H\(_2\)O            | 14.5 (12.5–15.0)                                     | 12.0 (10.0–13.0)                                      | 0.058 |
| Paco\(_2\), mm Hg              | 50.0 (43.6–56.5)                                     | 48.7 (38.4–58.4)                                      | 0.806 |
| pH                              | 7.35 (7.32–7.42)                                     | 7.28 (7.24–7.40)                                      | 0.221 |
| **18 hr after prone positioning** |                                                      |                                                       |       |
| RVFWS, %                        | 23.1 (15.7–24.1)                                     | 26.3 (21.8–30.2)                                      | 0.142 |
| TAPSE, mm                       | 27.5 (24.7–29.5)                                     | 26.0 (20.5–28.0)                                      | 0.268 |
| S’ velocity, cm/s               | 13.5 (13.0–15.5)                                     | 20.0 (10.5–21.5)                                      | 0.623 |
| Mean arterial pressure, mm Hg   | 89.5 (78.5–98.2)                                     | 90.0 (73.0–100.0)                                     | 1.000 |
| Heart rate, beats/min           | 67.5 (58.5–75.0)                                     | 79.0 (62.0–90.5)                                      | 0.325 |
| Norepinephrine intake, µg/kg/min| 0.01 (0.00–0.21)                                     | 0.12 (0.05–0.35)                                      | 0.140 |
| PEEPext, cm H\(_2\)O            | 14.0 (12.5–14.7)                                     | 12.0 (9.5–13.0)                                       | 0.076 |
| Paco\(_2\),FiO\(_2\)            | 263.1 (165.9–334.2)                                  | 193.3 (149.9–275.2)                                  | 0.462 |
| Paco\(_2\), mm Hg              | 54.1 (39.9–67.3)                                     | 57.9 (43.3–70.0)                                      | 0.624 |
| pH                              | 7.39 (7.29–7.46)                                     | 7.32 (7.20–7.37)                                      | 0.221 |
| **One hr after supine repositioning** |                                                  |                                                       |       |
| RVFWS, %                        | 22.2 (13.4–28.8)                                     | 26.8 (19.7–29.3)                                      | 0.624 |
| TAPSE, mm                       | 22.5 (21.2–24.5)                                     | 24.0 (20.5–25.0)                                      | 0.900 |
| S’ velocity, cm/s               | 14.0 (11.7–18.2)                                     | 13.0 (11.5–19.0)                                      | 0.901 |
| FAC\(^b\), %                    | 41.5 (36.2–48.6)                                     | 43.0 (41.0–54.5)                                      | 0.462 |
| Mean arterial pressure, mm Hg   | 86.0 (76.7–101.2)                                    | 83.0 (77.5–89.5)                                      | 0.624 |
| Heart rate, beats/min           | 68.5 (63.5–79.5)                                     | 75.0 (65.6–77.5)                                      | 0.806 |
| Norepinephrine intake, µg/kg/min| 0.00 (0.00–0.21)                                     | 0.12 (0.04–0.31)                                      | 0.135 |
| PEEPext, cm H\(_2\)O            | 13.0 (12.0–14.7)                                     | 10.0 (9.5–13.0)                                       | 0.102 |
| Paco\(_2\),FiO\(_2\)            | 267.4 (153.4–314.1)                                  | 180.2 (139.4–222.8)                                  | 0.221 |
| Paco\(_2\), mm Hg              | 52.5 (39.2–66.1)                                     | 44.6 (40.7–54.9)                                      | 0.806 |
| pH                              | 7.41 (7.34–7.46)                                     | 7.39 (7.25–7.41)                                      | 0.327 |

\(^a\)One patient had abnormal S’ velocity but normal TAPSE, FAC, and RVFWS at baseline.

\(^b\)FAC was calculated only at baseline and at final supine positions. Measurements were made independently by two experienced cardiologists and the mean of their measurements was used.

Data are presented as median (interquartile range) or n (%). Boldface value indicates statistical significance.

FAC = fractional area change, PEEPext = positive end-expiratory pressure external, RVFWS = right ventricular free wall strain, S’ velocity = tricuspid annular peak systolic velocity, TAPSE = tricuspid annular plane systolic excursion.
in a considerable proportion (75% in our cohort) of patients with ARDS undergoing prone ventilation (a finding in line with previous observations) (8) but also acquisition of images allow for assessing RVFWS. Second and importantly, abnormal as opposed to normal RVFWS values (in the absence of conventional variables of RV dysfunction) at baseline may be associated with worse prognosis of patients with COVID-19–associated ARDS. Interestingly, this was the case despite the fact that patients with abnormal RVFWS values did not require higher doses of norepinephrine and they did not have worse hemodynamic variables (such as mean arterial pressure, heart rate, $S'$ velocity, TAPSE, and FAC) than those with normal RVFWS values at baseline; that is, their RV dysfunction was subclinical. Finally, our study suggests that, among patients without acute cor pulmonale or conventional markers of RV dysfunction at baseline, one session of prone ventilation may not affect right myocardial strain. Potential explanations of the latter finding may include a true lack of significant
effect of prone ventilation among patients with subtle or no RV dysfunction at baseline, a need for more prone sessions to improve cardiac function, or a need for a larger cohort to reveal a difference. Taken together, the impact of prone ventilation might be speculative in this instance, given the small size of our cohort. That being said, our cohort may justify the execution of larger in-depth studies, which will take advantage of state-of-art echocardiographic techniques to shed more light on the apparently not so simple effect (9) of prone ventilation of RV function.

REFERENCES

1. Mathews KS, Soh H, Shaefi S, et al: Prone positioning and survival in mechanically ventilated patients with coronavirus disease 2019-related respiratory failure. Crit Care Med 2021; 49:1026–1037
2. Vieillard-Baron A, Charron C, Caille V, et al: Prone positioning unloads the right ventricle in severe ARDS. Chest 2007; 132:1440–1446
3. Joziwick M, Teboul JL, Anguel N, et al: Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2013; 188:1428–1433
4. Bleakley C, Singh S, Garfield B, et al: Right ventricular dysfunction in critically ill COVID-19 ARDS. Int J Cardiol 2021; 327:251–258
5. 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
6. Lang RM, Badano LP, Mor-Avi V, et al: Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015; 28:1–39.e14
7. Badano LP, Kolias 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
8. Gibson LE, Di Fenza R, Berra L, et al: Transthoracic echocardiography in prone patients with acute respiratory distress syndrome: A feasibility study. Crit Care Explor 2020; 2:e0179
9. Albert RK, Hubmayr RD: The hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome remain to be defined. Am J Respir Crit Care Med 2014; 189:1567