CORRESPONDENCE

Driving Pressure in COVID-19 Acute Respiratory Distress Syndrome Is Associated with Respiratory Distress Duration before Intubation

To the Editor:

The decision on the optimal time of invasive mechanical ventilation (IMV) onset in coronavirus disease (COVID-19) acute respiratory distress syndrome (ARDS) has been debated during the current pandemic (1, 2). Although affected by the availability of resources, timing of intubation may also affect the outcome for patients with COVID-19. In this study we investigate whether factors related to respiratory distress (RD) are associated with the driving pressure (DP) in patients with COVID-19 ARDS.

Methods

We prospectively enrolled all consecutive patients with COVID-19 ARDS who were admitted to the ICU of a tertiary hospital (April to December 2020). Patients were included if they were on IMV and had positive PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and ARDS. The local ethics committee (protocol number 53398/2020) approved the study with a waiver for informed consent. The primary outcome was the identification of predictors independently associated with patients' respiratory mechanics upon ICU admission.

In all patients, a lung protective protocol (V_T of 6–8 ml/kg of ideal body weight and proning [if $Pa_{O_2}/F_{I_{O_2}} < 150$ mm Hg]) was adopted. Positive end-expiratory pressure was set after a recruitment maneuver at the level of the lowest DP.

$Pa_{O_2}/F_{I_{O_2}}$, airway pressures, V_T, respiratory system compliance (V_T/DP) and elastance (Ers: DP/V_T/ideal body weight), Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment score, vasopressors, laboratory tests (on ICU admission), and COVID-19 treatment received before ICU admission were recorded.

RD before intubation was defined as the time (hours) spent with hypoxemia ($Pa_{O_2}/F_{I_{O_2}} < 150$ mm Hg, $Pa_{O_2}/F_{I_{O_2}} < 100$ mm Hg, $Pa_{O_2}/F_{I_{O_2}} < 50$ mm Hg) and tachypnea (respiratory rate [RR] >25/min and RR >30/min). $F_{I_{O_2}}$ values before intubation (oxygen delivery by face masks) were estimated on the basis of tables published in previous investigations (3), whereas in high-flow nasal cannula cases the value that was delivered by the device (myAirvo2, Fisher & Paykel Healthcare)

was recorded. The monitoring protocol of patients with COVID-19 ARDS before ICU admission included *1*) recordings of the RR, $F_{I_{O_2}}$, Sp_{O_2}, and other vital signs (i.e., arterial blood pressure, pulse rate, temperature, urine output) once every 3 hours; *2*) arterial blood gases once every 8 hours per protocol—unless the patients' condition required more frequent sampling (as decided by the attending physician); and *3*) continuous digital monitoring (arterial blood pressure, ECG, Sp_{O_2}, RR, hourly updates by the nursing staff) for all severe cases. During their ICU stay, patients had continuous digital monitoring of all clinical variables of interest (arterial blood pressure, ECG, Sp_{O_2}, RR, temperature), whereas arterial blood gases were measured once every 3 hours or more often.

The cutoff values for $Pa_{O_2}/F_{I_{O_2}}$ and RR used in the analysis were chosen on the basis of their frequency distribution and their clinical relevance (4).

The patients were classified in two groups according to the lowest DP achieved during the first 24 hours in ICU (after recruitment maneuvers and/or prone position): DP ≤ 14 cm H_2O and DP >14 cm H_2O (5). This cutoff value was chosen on the basis of its association with mortality (5, 6).

Data are presented as mean (SD). Variables significantly associated with DP (continuous variable) in univariate analysis were entered in multivariate analyses. The linear regression model was used. Analyses were performed using RD indices and repeated using its components (time with hypoxemia and time with tachypnea) separately. Ancillary analysis was performed using Ers as a dependent variable. Receiver operating characteristic analysis evaluated the diagnostic performance of RD indices and its components to identify patients with DP >14 cm H_2O. Two-tailed *P* values <0.05 were considered significant. SPSS version 26.0 was used (SPSS Inc.).

Results

Eighty-five patients with COVID-19 were admitted in the ICU during the study period and were included (one patient was excluded because he was admitted because of hemorrhagic shock but did not present ARDS). Measurements (per patient/day) available for Sp_{O_2}, Pa_{O_2}, $F_{I_{O_2}}$, and RR were 24, 3, 24, and 8, respectively; no difference was found between the two groups (DP >14 cm H_2O and DP ≤ 14 cm H_2O) in terms of the number of assessments. Table 1 presents baseline characteristics of participants and variables associated with DP >14 cm H_2O.

Multiple linear regression analysis revealed that only $RD_{100/25}$ (time with $Pa_{O_2}/F_{I_{O_2}} < 100$ mm Hg and RR >25/min) was independently associated with DP ($R^2 = 0.265$, $P < 0.001$; $\beta = 0.044$, $P = 0.009$). When RD components (time with hypoxemia and time with tachypnea) were evaluated separately, only the duration (hours) with $Pa_{O_2}/F_{I_{O_2}} < 100$ mm Hg was independently associated with DP ($R^2 = 0.381$, $\beta = 0.044$, $P < 0.0001$). Figure 1 presents correlations of RD components with DP.

Ers at ICU admission was significantly correlated with both $RD_{100/25}$ (0.513, $P < 0.0001$) and $Pa_{O_2}/F_{I_{O_2}}$ (baseline values) ($r = -0.256$, $P = 0.019$), but it was independently associated only with $RD_{100/25}$ ($R^2 = 0.263$, $\beta = 0.017$, $P < 0.0001$).

Receiver operating characteristic analysis showed that duration of hypoxemia (expressed as either hours with $RD_{100/25}$ or hours with $Pa_{O_2}/F_{I_{O_2}} < 100$ mm Hg) could identify patients with DP >14 cm H_2O; specifically, $RD_{100/25}$ longer than 7 hours presented 83% sensitivity and 73% sensitivity to identify patients with DP >14 cm H_2O (area under

Table 1. Baseline Characteristics

	DP $\leqslant 14$ cm H_2O ($n = 57$)	DP >14 cm H_2O ($n = 26$)	P Value
Age, yr	68.1 ± 12.2	68.1 ± 10.9	0.987
Sex, M, n (%)	37 (64.9)	19 (73.1)	0.468
BMI, kg/m^2	27.4 ± 0.8	27.5 ± 1.1	0.907
COPD, n (%)	4 (7.0)	3 (11.5)	0.429
Hypertension, n (%)	35 (61.4)	20 (76.9)	0.122
Diabetes mellitus, n (%)	23 (40.3)	6 (23.1)	0.06
Smoking, n (%)	21 (36.8)	5 (19.2)	0.081
COVID-19 symptoms' duration, d	9.5 ± 4.7	10.9 ± 5.5	0.23
Pa_{O_2}/Fi_{O_2} at hospital admission, mm Hg	237.8 ± 109.2	211.8 ± 121.9	0.335
Length of hospital stay before IMV, days	4.2 ± 0.5	7.9 ± 1.2	0.001
RD, h (n)			
RD$_{150/25}$	18.7 ± 19.2 (41)	67.2 ± 78.5 (23)	<0.0001
RD$_{150/30}$	5.2 ± 7.9 (28)	35.3 ± 49.8(23)	<0.0001
RD$_{100/25}$	9.3 ± 14.4 (33)	63.3 ± 72.5 (23)	<0.0001
RD$_{100/30}$	4.4 ± 7.5 (28)	36.9 ± 49.5 (23)	<0.0001
HFNC use*, h (n)	1.8 ± 7.2 (7)	40.8 ± 77.9 (11)	0.007
NIV use, h (n)	0.6 ± 3.7 (2)	2.2 ± 6.2 (4)	0.165
Intubation time (min before ICU admission)	29.8 ± 6.2	39.8 ± 12.3	0.423
IMV onset			
APACHE II†	14.5 ± 5.5	20.2 ± 8.1	<0.0001
SOFA	7.2 ± 1.8	8.7 ± 2.1	0.001
Pa_{O_2}/Fi_{O_2}, mm Hg (before intubation)	103.1 ± 41.5	61.1 ± 23.4	<0.0001
Pa_{O_2}/Fi_{O_2}, mm Hg (after intubation)	121.2 ± 45.2	95.4 ± 41.1	0.01
Ventilatory ratio	1.9 ± 0.6	2.7 ± 1.1	<0.0001
V$_T$, ml	462.3 ± 55.5	442.3 ± 54.7	0.131
V$_T$/IBW, ml/kg	7.1 ± 0.7	6.9 ± 0.8	0.360
RR (on IMV)	21.9 ± 3.1	25.1 ± 3.8	<0.001
Minute ventilation	10.2 ± 1.8	11 ± 1.8	0.048
DP, cm H_2O	11.5 ± 2.1	18.3 ± 3.6	<0.0001
Elastance, cm H_2O/ml/kg	1.6 ± 0.4	2.6 ± 0.7	<0.0001
PEEP, cm H_2O	11.6 ± 3.1	11.2 ± 2.9	0.581
Pplat, cm H_2O	23.2 ± 4.2	29.1 ± 4.9	<0.0001
Crs, ml/cm H_2O	41.8 ± 10.9	25.1 ± 6.4	<0.0001
Prone positioning	11 (19.3)	11 (42.3)	0.002
Noradrenaline, µg/kg/min	0.2 ± 0.3	0.6 ± 0.5	<0.0001
Vasopressin, n	0	5	0.001
CRP, mg/dl (<0.5)	8.8 ± 9.1	11.1 ± 10.6	0.327
D-dimers, ng/ml (<300)	$1,138.3 \pm 1,365.5$	$2,035.2 \pm 1,836.9$	0.015
Ferritin, ng/ml (24–336)	$1,710.9 \pm 3,231.8$	$4,862 \pm 12,785.3$	0.089
WBC $\times 10^6$/L (4,000–10,000)	$8,914.1 \pm 4,686.9$	$12,319.2 \pm 6,327.9$	0.008
Lymph $\times 10^6$/L (1,000–4,800)	678.8 ± 611.5	587.5 ± 292.3	0.472
Superinfections upon ICU admission			
Bloodstream infection	1 *C. albicans* 1 *S. maltophilia*	1 *A. baumannii*	
Lower respiratory tract infection	1 *S. aureus* (MSSA)		
Outcomes			
IMV duration, d	14.5 ± 8.0	11.2 ± 7.6	0.079
28-d survival, n (%)	29 (50.9)	6 (23.1)	0.01

Definition of abbreviations: *A. baumannii* = *Acinetobacter baumannii*; APACHE II = Acute Physiology and Chronic Health Evaluation II; BMI = body mass index; *C. albicans* = *Candida albicans*; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; CRP = C-reactive protein; Crs = respiratory system compliance; DP = driving pressure; elastance = respiratory system elastance; HFNC = high flow nasal cannula; IBW = ideal body weight; IMV = invasive mechanical ventilation; Lymph = lymphocytes; MSSA = methicillin-resistant *Staphylococcus aureus*; NIV = noninvasive ventilation; PEEP = positive end-expiratory pressure; Pplat = plateau pressure; RR = respiratory rate; RD = respiratory distress; *S. aureus* = *Staphylococcus aureus*; *S. maltophilia* = *Stenotrophomonas maltophilia*; SOFA = Sequential Organ Failure Assessment; WBC = white blood cells. Data are presented as mean ± SD unless otherwise noted.
*Note that three patients in the DP $\leqslant 14$ cm H_2O group and two in the DP > 14 cm H_2O group did not have Pa_{O_2}/Fi_{O_2} <150 mm Hg before admission. These patients were intubated because of tachypnea and tachycardia. All patients were admitted in the ICU after intubation.
†APACHE II score was calculated upon ICU admission.

the curve [AUC],0.855; 95% confidence interval [CI], 0.764–0.946), whereas Pa_{O_2}/Fi_{O_2} <100 mm Hg for more than 21.5 hours presented 83% sensitivity and 80% specificity (AUC, 0.916; 95% CI, 0.846–0.986) (Figure 1).

Discussion

This study demonstrates that *1*) DP was above 14 cm H_2O in 32.6% of patients with COVID-19 ARDS; *2*) DP and Ers were independently associated with the duration of RD; and *3*) duration of Pa_{O_2}/Fi_{O_2} <100
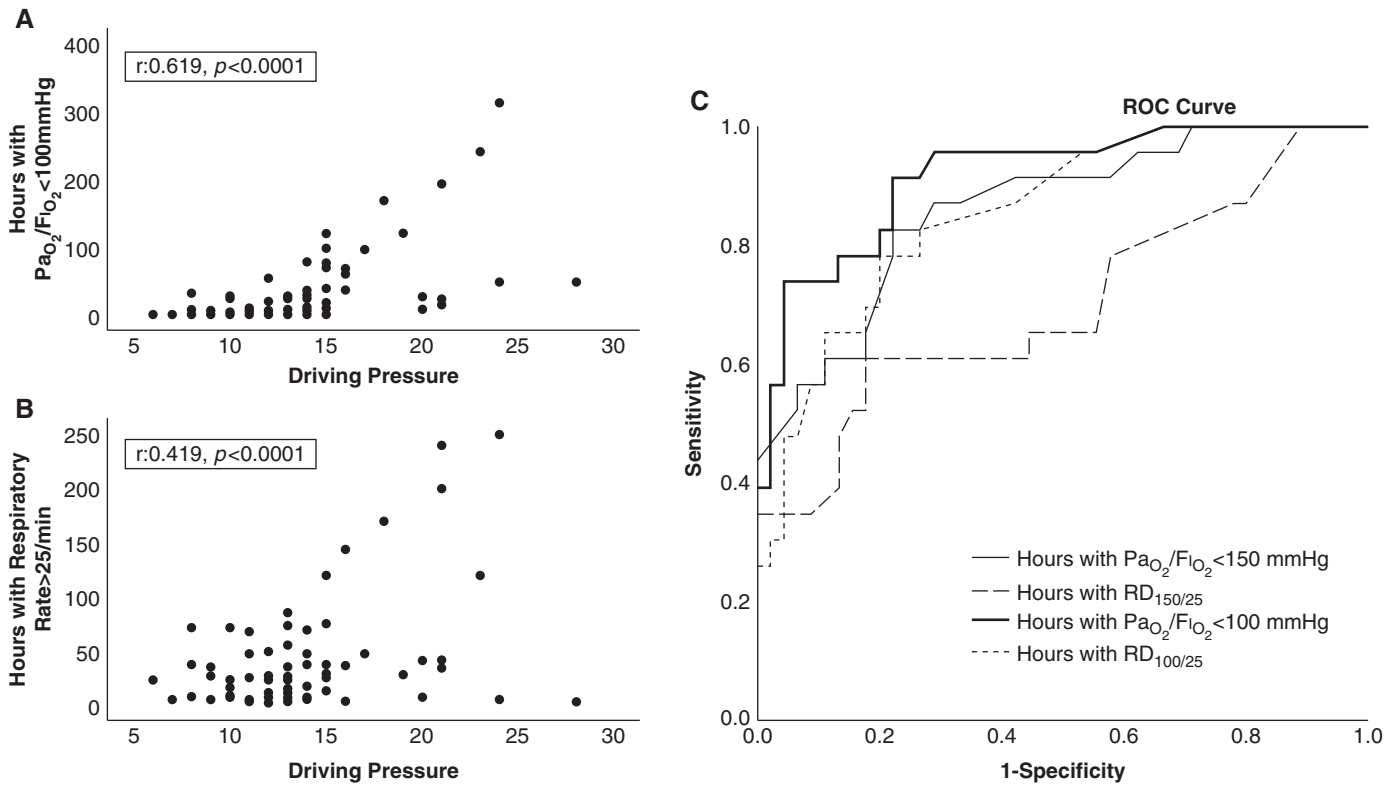
Figure 1. (*A*) Pearson correlation between hours with $Pa_{O_2}/F_{I_{O_2}} <100$ mm Hg and driving pressure ($r = 0.619$, $P < 0.0001$). (*B*) Pearson correlation between hours with respiratory distress (RD)$_{100/25}$ and driving pressure ($r = 0.518$, $P < 0.0001$). (*C*) ROC analysis of factors associated with driving pressure >14 cm H_2O. The solid bold line depicts hours with $Pa_{O_2}/F_{I_{O_2}} <100$ mm Hg (area under the curve [AUC], 0.916; 95% confidence interval [CI], 0.846–0.986; $P < 0.0001$). The solid line depicts hours with $Pa_{O_2}/F_{I_{O_2}} <150$ mm Hg (AUC, 0.861; 95% CI, 0.768–0.954; $P < 0.0001$). The dotted line depicts hours with RD$_{100/25}$ (AUC, 0.855; 95% CI, 0.764–0.946; $P < 0.0001$). The dashed line depicts hours with RD$_{150/25}$ (AUC, 0.700; 95% CI, 0.557–0.842; $P < 0.0001$). ROC = receiver operating characteristic.

mm Hg longer than 21.5 hours was the most significant factor predicting DP >14 cm H_2O.

To our knowledge, this is the first study to evaluate differences between patients with COVID-19 ARDS according to DP and factors that are associated with DP. We chose DP as it represents the distending pressure applied to the lung during a tidal inflation. Moreover, DP reflects respiratory compliance and provides useful information when a lung protective ventilation protocol is adopted (5, 6). In this respect, we found it reasonable to target and analyze patients according to the best DP that could be achieved during the first 24 hours of ICU admission.

The factors that best correlated to DP >14 cm H_2O were the duration of hypoxemia ($Pa_{O_2}/F_{I_{O_2}} <100$ mm Hg) and its combination with tachypnea, the RD$_{100/25}$. Baseline characteristics and infection duration did not have any impact. One explanation could be the increased disease severity leading to decreased compliance and tachypnea and hypoxemia. On the other hand, prolonged RD may further compound the lung injury induced by COVID-19 pathology. Our observation is in line with clinical data suggesting that vigorous, spontaneous ventilatory efforts for extended periods can exacerbate the lung damage (7), inducing a secondary insult (patient self-induced lung injury) (1). Experimental data show that in cases of acute lung injury, spontaneous breathing may provoke increased volumetric strain and heterogeneity in lung units (8).

Hypoxemia duration correlated with respiratory mechanics. The majority of patients with DP ≤ 14 cm H_2O presented hypoxemia and tachypnea, yet for a significantly shorter time interval than patients with DP >14 cm H_2O. A duration of $Pa_{O_2}/F_{I_{O_2}} <100$ mm Hg longer than 21.5 hours or RD$_{100/25}$ longer than 7 hours predicted a DP >14 cm H_2O. These findings could help identify thresholds for the degree and duration of hypoxemia/increased work of breathing to decide the optimal time for intubation in COVID-19 ARDS (1, 2, 9).

Moreover, patients with DP >14 cm H_2O presented advanced multiorgan involvement in terms of APACHE II, Sequential Organ Failure Assessment scores, and vasopressors compared with patients with earlier IMV initiation.

Limitations of the study are its single-center and observational character. Therefore, the association of RD with a DP >14 cm H_2O does not necessarily imply causality. Second, intrathoracic pressure swings were not directly evaluated; yet, esophageal pressure monitoring is not always feasible, especially in conscious patients with RD, and the interpretation of measurements is not always straightforward and simple (10). RD was arbitrarily defined as it has never been definitely quantified. One might certainly argue that the optimal time for intubation/ICU admission may also impact outcomes. Such decisions during a pandemic depend on clinical assessment, end-of-life issues, and resources/bed availability. We acknowledge that these parameters were not assessed and could be the scope of a future study.

Conclusions

In the present study, RD and hypoxemia duration in patients with COVID-19 ARDS were significantly associated with a DP >14 cm H_2O on ICU admission. ∎

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References

1. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. *JAMA* 2020;323:2329–2330.
2. Tobin MJ, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19. *Ann Intensive Care* 2020;10:78.
3. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, *et al.*; EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009;302:2323–2329.
4. Darreau C, Martino F, Saint-Martin M, Jacquier S, Hamel JF, Nay MA, *et al.* Use, timing and factors associated with tracheal intubation in septic shock: a prospective multicentric observational study. *Ann Intensive Care* 2020; 10:62.
5. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, *et al.* Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747–755.
6. Goligher EC, Costa ELV, Yarnell CJ, Brochard LJ, Stewart TE, Tomlinson G, *et al.* Effect of lowering Vt on mortality in acute respiratory distress syndrome varies with respiratory system elastance. *Am J Respir Crit Care Med* 2021;203:1378-1385.
7. Hurtado DE, Erranz B, Lillo F, Sarabia-Vallejos M, Iturrieta P, Morales F, *et al.* Progression of regional lung strain and heterogeneity in lung injury: assessing the evolution under spontaneous breathing and mechanical ventilation. *Ann Intensive Care* 2020;10:107.
8. Retamal J, Bergamini BC, Carvalho AR, Bozza FA, Borzone G, Borges JB, *et al.* Non-lobar atelectasis generates inflammation and structural alveolar injury in the surrounding healthy tissue during mechanical ventilation. *Crit Care* 2014;18:505.
9. Hernandez-Romieu AC, Adelman MW, Hockstein MA, Robichaux CJ, Edwards JA, Fazio JC, *et al.*; Emory COVID-19 Quality and Clinical Research Collaborative. Timing of intubation and mortality among critically ill coronavirus disease 2019 patients: a single-center cohort study. *Crit Care Med* 2020;48:e1045–e1053.
10. Gulati G, Novero A, Loring SH, Talmor D. Pleural pressure and optimal positive end-expiratory pressure based on esophageal pressure versus chest wall elastance: incompatible results. *Crit Care Med* 2013;41:1951–1957.

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Pulmonary Artery Enlargement Is Associated with Exacerbations and Mortality in Ever-Smokers with Preserved Ratio Impaired Spirometry

To the Editor:

The subset of ever-smokers with a FEV_1 to FVC ratio >0.7 and a FEV_1 <80% predicted have been classified as preserved ratio impaired spirometry (PRISm), exhibiting respiratory symptoms similar to patients with chronic obstructive pulmonary disease (COPD), progression of airway and lung parenchymal disease, and increased risk for acute respiratory events (1). The prevalence of PRISm is estimated to be as high as 24% in ever-smokers (2). Despite similar classification based on these criteria, PRISm remains a poorly characterized group with variable clinical phenotypes and disease courses (3).

In moderate to severe COPD, the ratio of the diameters of the pulmonary artery (PA) and aorta (A) as measured on nongated, thoracic computed tomography (CT) is associated with increased risk for severe respiratory exacerbations and death (4, 5). We hypothesized that pulmonary vascular disease, indicated by PA enlargement, will be associated with increased symptom severity, risk for acute respiratory exacerbations, and mortality within PRISm. Some of the results from this study were previously reported in the form of an abstract (6).

Methods

The study population includes participants in COPDGene (the Genetic Epidemiology of COPD Study) who completed comprehensive clinical history, quality of life questionnaires including St. George's Respiratory Questionnaire (SGRQ), pre- and post-bronchodilator spirometry, and