SARS-CoV-2-induced Acute Respiratory Distress Syndrome: Pulmonary Mechanics and Gas Exchange Abnormalities

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In January 2020, the first cases of the novel coronavirus (SARS-CoV-2) infection were reported in Europe. Multiple outbreaks have since then led to a global pandemic, as well as massive medical, economic, and social repercussions (1,2).

SARS-CoV-2 pneumonia can develop into acute respiratory distress syndrome (ARDS) when mechanical ventilation (MV) is needed (3,4). ARDS produces abnormalities in gas exchange with a variable degree of shunt (5), high dead space ventilation (Vd/Vt) (6), diminished pulmonary compliance (7) and alterations to the pulmonary circulation (8). The cornerstone of ARDS management is to provide adequate gas exchange without further lung injury as a result of MV. To date, information regarding the characteristics of SARS-CoV-2-induced ARDS is not completely known. However, this information is crucial to better apply MV and facilitate organ support strategies. We therefore present the characteristics of gas exchange, pulmonary mechanics and ventilatory management of 50 patients with laboratory-confirmed SARS-CoV-2 infection, who developed ARDS and underwent invasive MV.

Methods

Descriptive analysis of 50 consecutive patients with laboratory-confirmed SARS-CoV-2 infection, who developed ARDS (9) and underwent invasive MV. These patients were admitted to the SARS-CoV-2-dedicated Intensive Care Units (ICU) at Hospital Clinic of Barcelona, Spain, between March 7th and March 25th, 2020.

Upon ICU admission, epidemiological characteristics, severity of SARS-CoV-2 infection with the acute physiology and chronic health evaluation II score (APACHE II), prognostic biomarkers of SARS-CoV-2 infection described elsewhere (4), time from hospital to ICU

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admission, time from ICU admission to intubation, oxygen therapy or noninvasive ventilation use and microbiology were investigated.

On the day that criteria for ARDS diagnosis were met (9) and invasive MV was needed, the following assessments were performed: impairment in oxygenation was analyzed with the PaO_2/FiO_2 ratio and abnormalities of CO_2 metabolism were studied with the ventilatory ratio (VR), a surrogate parameter of Vd/Vt (10).

Additionally, adjunctive therapies and MV parameters related with ventilation-induced lung injury (VILI) described elsewhere (11-15) were investigated.

Correlations of SARS-CoV-2 prognostic biomarkers (4), pulmonary mechanics and gas exchange data were performed. 28-day and hospital mortality, ventilator- and ICU-free days at day 28, hospital and ICU length of stay and need for tracheostomy were also evaluated (16). Finally, a sub-analysis assessing differences before and after prone position was performed. Additional detail on the method is provided in an online data supplement.

Results

By March 25th, 2020, 50 patients with laboratory-confirmed SARS-CoV-2 infection and ARDS had been admitted to our hospital. Table 1 shows the demographic and clinical characteristics of these patients. The median (IQR) age was 66 (57 - 74) years. Thirty-six patients (72%) were men. Upon ARDS diagnosis, forty-four percent of patients were initially classified as moderate, while 24 % were classified as mild and 32 % as severe. The outcomes of these patients are shown in Table 1. ICU and hospital length of stay were high, and tracheostomy was performed to 30 (60%) patients. Hospital mortality was 34%.

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Table 2 shows the results of gas exchange, pulmonary mechanics and variables associated with VILI upon ARDS diagnosis. Excluding baseline mechanical power (MP), other MV parameters associated with VILI were within normal range.

There was no correlation between PaO_2/FiO_2 and the static compliance of the respiratory system (Crs) (Figure 1A). Notwithstanding, a weak yet significant correlation was found between VR and both positive end-expiratory pressure (PEEP) and end-inspiratory plateau pressure (Figure 1C and 1D).However, D-dimer was not significantly correlated with VR (Figure 1B).

Eleven patients underwent prone position upon the day of ARDS diagnosis (Supplementary Table E1). On average, PaO_2/FiO_2 and Crs increased from supine to prone position by +59 (32 – 143; p= 0.002). Significant differences were also found in Crs between supine to prone position with an increase of +5.45 (4.32 – 18.25; p=0.015).

Discussion

SARS-CoV-2-induced ARDS produced an impairment in gas exchange and pulmonary mechanics comparable to prior cohorts of non-SARS-CoV-2 ARDS (10,13,17,18). As in other studies, VR was high and the most frequent presentation was moderate ARDS (10,17,19). On average, Crs in the SARS-CoV-2-induced ARDS cohort was also found to be comparable, but with remarkable heterogeneity (13,18). Other studies have reported similar (20), higher (21) or lower Crs (19,22,23) in SARS-CoV-2-induced ARDS. As Crs decreases alongside the collapse of alveolar units due to lung edema, several factors may provide explanation for such reported differences, including treatments, intubation strategies and the stage of the disease. In our cohort of early

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SARS-CoV-2-induced ARDS, the time from ICU admission to intubation was only 24 hours despite the use of high flow nasal cannula or noninvasive ventilation in some cases.

We found no correlation between Crs and PaO_2/FiO_2. Crs estimates the amount of aerated lung volume in ARDS (7). These results might therefore suggest that the proportion of non- or poorly aerated to well-aerated lung volume is not the only determinant for such degree of hypoxemia. This may not be specific to SARS-CoV-2-induced ARDS, as other factors apart from the amount of aerated lung tissue (i.e. lung perfusion) are largely known to influence pulmonary shunt (24). However, some authors have reported that lung perfusion in SARS-CoV-2-induced ARDS is more impaired than ARDS by other causes (21). We identified remarkable abnormal lung perfusion in CT scans performed in these patients (Supplementary Figure E1). We found no correlation between D-dimer and VR, suggesting that high Vd/Vt might not be related to a coagulation disorder (i.e. pulmonary microthrombosis). Nonetheless, as suggested by its association with VR, high end-inspiratory and end-expiratory pressures (i.e. mean airway pressures) could increase Vd/Vt if the lung is overdistended and perfusion is decreased. While driving pressure and end-inspiratory plateau pressure were within protective range, MP was found to be slightly high and might have promoted lung injury (25). In patients undergoing prone position, PaO_2/FiO_2 improvement was followed by an increase in Crs, suggesting recruitment and aeration of previously collapsed alveoli. In our study, mortality was similar to that reported in other studies of critically ill patients with SARS-CoV-2 pneumonia (3, 19).

This study presents some limitations. Four manual end-inspiratory and end-expiratory pauses could not be performed in all patients due to protection equipment shortages. However, all patients included had at least one end-inspiratory and end-expiratory pause done

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on the first day. These results cannot be extrapolated to late SARS-CoV-2-induced ARDS.

In summary, SARS-CoV-2-induced ARDS presents with an impairment in gas exchange and pulmonary mechanics comparable to prior ARDS cohorts. However, lung perfusion in SARS-CoV-2-induced ARDS warrants further investigation.

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Figure Legend:

Figure 1. Correlation between pulmonary mechanics and gas exchange abnormalities. A, Correlation between static compliance of the respiratory system and PaO_2/FiO_2. B, Correlation between ventilatory ratio and D-dimer concentration. C, Correlation between plateau pressure and ventilatory ratio. D, Correlation between PEEP and ventilatory ratio. Solid lines are the regression lines, while shaded bands display 95% confidence intervals. Crs, static compliance of the respiratory system; PaO_2/FiO_2 ratio between partial pressure of oxygen and fraction of inspired oxygen, PEEP, Positive end-expiratory pressure.

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Table 1. Characteristics of 50 SARS-CoV-2-induced ARDS.

Baseline characteristics	
Age, median (IQR), years	66 (57 – 74)
Male, n (%)	36 (72)
BMI, median (IQR), kg/m^2	27.68 (26.43 – 30.39)
Smoking status, n (%) *	
Never	23 (56)
Current	4 (10)
Former	14 (34)
Alcohol consumption habit, n (%)	6 (12)
APACHE II at ICU admission, median (IQR)	13 (11 – 18)
SOFA score upon ARDS diagnosis, median (IQR)	7 (6 – 9)
Time from hospital admission to ICU admission, median (IQR), days	2 (1 – 3.75)
Time from ICU admission to intubation, median (IQR), days	1 (0 – 1)
Co-infection, n (%)	2 (4)
Oxygen therapy and Noninvasive ventilation before intubation †, n (%)	
Venturi and Non-rebreathing oxygen mask	43 (93)
High-flow oxygen therapy	23 (50)
Noninvasive ventilation	5 (11)
ARDS severity, n (%)	
Mild	12 (24)
Moderate	22 (44)
Severe	16 (32)
Management factors, n (%)	

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Prone position	11 (22)
Neuromuscular blockade use	24 (48)
Recruitment maneuvers	18 (36)
Vasopressor use	16 (32)
Corticosteroid therapy	18 (36)
Laboratory findings ‡ , median (IQR)	
Hemoglobin, g/dL	12.80 (11.83 – 13.40)
White blood cell count, $\times 10^9$/L	8.11 (6.26 – 11.42)
Lymphocyte count, $\times 10^9$/L	0.60 (0.40 – 0.90)
Platelet count, $\times 10^9$/L	219 (174– 274)
Creatinine, mg/mL	0.98 (0.77 – 1.45)
Sodium, mEq/L	138 (136 – 140)
Potassium, mEq/L	3.90 (3.60 – 4.30)
Aspartate aminotransferase, U/L	65 (48– 82)
Alanine aminotransferase, U/L	45 (28 – 76)
Total bilirubin, mg/dL	0.50 (0.40 – 0.90)
Gamma-glutamyltransferase, U/L	54 (36 – 105)
Lactate, mmol/L	1.33 (1 – 1.59)
Alkaline phosphatase, U/L	67 (53 – 86)
Lactate dehydrogenase, U/L	442 (386 – 541)
Albumin, g/L	36 (33 – 38)
D-dimer, ng/mL	1100 (800 – 3800)
Ferritin, ng/mL	1436.50 (951.25 – 2149.25)
Procalcitonin, ng/mL	0.27 (0.17 – 0.97)

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C-reactive protein, mg/dL	15.68 (9.64 – 27.03)
Outcomes§	
Hospital mortality, n (%)	15 (34)
Mortality at day 28, n (%)	10 (20)
Ventilator-free days at day 28, median (IQR), days	9 (0 – 16)
ICU-free days at day 28, median (IQR), days	0 (0 – 9)
Hospital length of stay, median (IQR), days	36 (24 – 44)
ICU length of stay, median (IQR), days	26 (17 – 34)
Tracheostomy, n (%)	30 (60)

* Missing data from nine patients. † Missing data from four patients. ‡ Laboratory findings upon ARDS diagnosis. § Six patients were still in the hospital after follow-up ending. APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; SOFA, sequential organ failure assessment.

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Table 2. Gas exchange, pulmonary mechanics and ventilation-induced lung injury of 50 SARS-CoV-2-induced ARDS patients upon ARDS diagnosis.

Arterial blood gas, median (IQR)	
pH	7.31 (7.28 – 7.37)
$PaCO_2$, mmHg	47 (42.9 – 53.4)
PaO_2, mmHg	107 (88.5 – 133.6)
PaO2/FiO2	174 (128– 232)
Ventilatory ratio*	1.93 (1.55 – 2.23)
Ventilator settings, pulmonary mechanics and other variables associated with VILI, median (IQR)	
Tidal volume/PBW, mL/Kg	6.78 (6.30 – 7.32)
Respiratory rate, breaths/min	22 (20 – 23)
PEEP, cmH_2O	13 (11 – 14)
FiO_2, %	62 (53– 76)
Peak inspiratory pressure, cmH_2O	32 (29 – 34)
End-inspiratory plateau pressure, cmH_2O	23 (21 – 25)
Driving pressure, cmH_2O †	11 (9 – 13)
Mechanical power, J/min ‡	22.32 (18.49 – 28.10)
Crs, $mL*cmH_2O^{-1}$ §	40.13 (32.88 – 51.68)

* Ventilatory ratio is defined as [minute ventilation (ml/min) × PaCO2 (mm Hg)]/(predicted body weight × 100 × 37.5). † Driving pressure is the difference between plateau pressure and PEEP. ‡ Mechanical power was calculated following previously published formulae (11) § Static compliance of the respiratory system is the ratio of tidal volume to driving pressure. Crs, Static compliance of the respiratory system; FiO_2, fraction of inspired oxygen, IQR, interquartile range; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PEEP, Positive end-expiratory pressure; PBW, predicted body weight; VILI, ventilation-induced lung injury.

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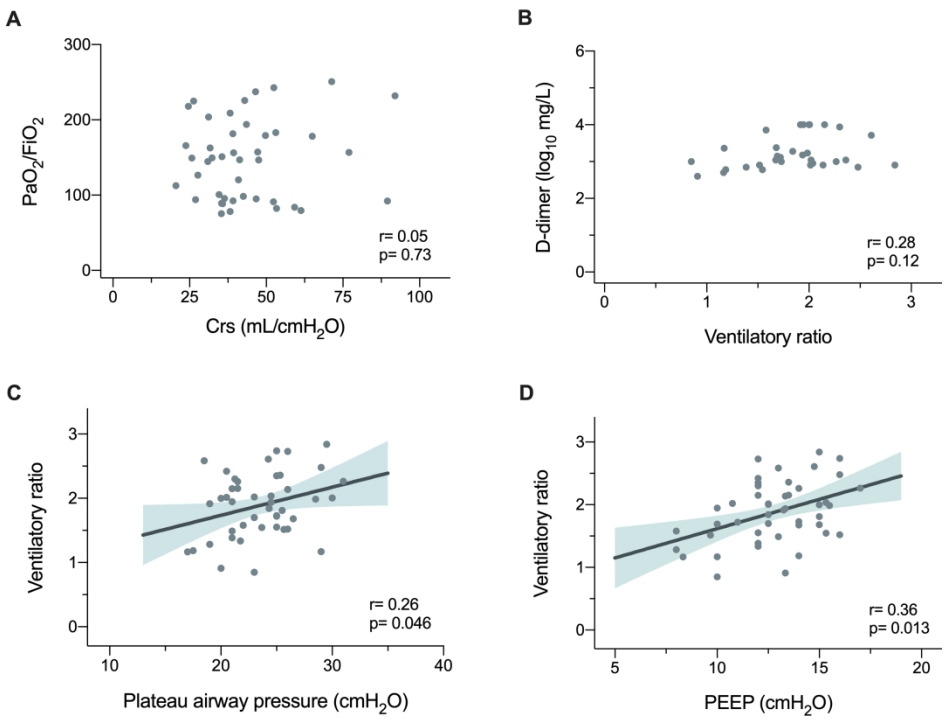

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Supplementary methods

Measurements

Follow-up finished May 9th. Data collected from daily electronic ICU records was registered on electronic worksheets by researchers. Respiratory mechanics and gas exchange variables were recorded every 6 hours on the first day of ARDS diagnosis. Mean values of all measurements gathered in supine or prone position during the first day are reported. Ventilatory ratio and mechanical power were calculated following previously published formulae (1, 2). End-inspiratory and end-expiratory occlusions were performed to calculate intrinsic and total positive end-expiratory pressure (PEEP), as well as end-inspiratory plateau pressure. Patient-ventilator asynchronies were monitored to avoid measurements during these periods.

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Statistical analysis

Categorical variables were reported as number (%), while continuous variables were reported as median [interquartile range (IQR); 25 th - 75 th percentile], due to the small sample size. Paired samples were compared with nonparametric Wilcoxon signed-rank test due to the small sample size. Spearman's correlation analyses were performed to determine associations between continuous variables. A two-sided p value ≤ 0.05 was considered statistically significant. Data was processed with IBM SPSS Statistic for Windows, version 22.0 (IBM Corporation, Armonk, NY, USA).

Bias

During the study period, a local triage protocol was used to assess eligibility for ICU admission according to age, prior performance of daily living activities, presence of neoplastic disease and other severe chronic comorbidities, and the severity of organ dysfunction caused by SARS-CoV-2 infection. Patients less likely to survive were not admitted and this may have therefore influenced the outcomes and severity of the cohort (i.e. less severity, better survival).

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Local protocol

Local treatment guidelines recommended treatment with lopinavir/ritonavir; hydroxychloroquine; azithromycin; corticosteroids; tocilizumab and antimicrobials for bacterial co-infection. Anakinra and other immunomodulatory therapies were used for refractory disease.

Ventilatory management of SARS-CoV-2-induced ARDS was based on a local protocol: ventilation with tidal volumes less than 6mL/kg, Driving pressure <15 cmH_2O, inspiratory plateau pressure <28 cmH_2O, and early prone position when PaO_2/FiO_2 <150. PEEP titration was based on the lower PEEP /FiO_2 ARDS network table and by best compliance. Judicious use of recruitment maneuvers and neuromuscular blockade was advised in cases of severe hypoxemia and patient-ventilator asynchronies, respectively.

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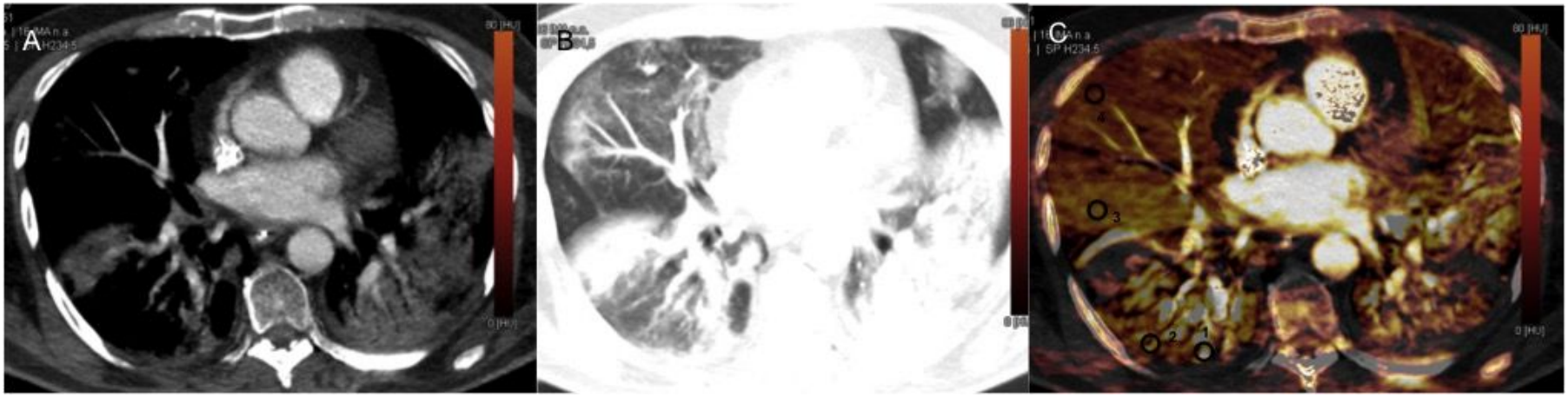
Supplementary Figure E1. Chest CT scan showing inhomogeneous perfusion of the lungs.



69-year-old male presenting with laboratory-confirmed SARS-CoV-2 infection and ARDS. A, Chest Dual Energy-CT scan in mediastinal window without evidence of the presence of pulmonary arteries thrombi. B, Chest Dual Energy-CT scan in lung window that showed consolidation in both lower lobes and ground-glass opacities with a gravitational gradient. C, Chest Dual Energy-CT scan with iodine map reconstruction that showed an inhomogeneous perfusion of the lung with elevated enhancement in the right lower lobe consolidation, areas of normal perfusion, and areas of hypoperfusion. We performed 4 ROIs that demonstrate irregular enhancement of the lung (ROI 1: 4.0 mg / ml of iodine density, ROI 2: 2.1 mg / ml; ROI 3: 3.0 mg / ml; ROI 4: 1.5 mg / ml). ARDS, acute respiratory distress syndrome; ROI, region of interest.

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Supplementary Table E1. Ventilator settings, gas exchange and pulmonary mechanics before and after prone positioning upon ARDS diagnosis.

	Supine position* N=11, median (IQR)	**Prone position*** N=11, median (IQR)	**P value**†
Tidal volume/PBW, mL/Kg	6.06 (5.54 – 6.57)	6.66 (6.02 – 6.90)	0.25
Respiratory rate, breaths/min	22 (20 – 23)	23 (21 – 25)	0.41
PEEP, cmH_2O	15 (14 – 17)	15 (14 - 16)	0.53
FiO_2, %	90 (70 – 100)	60 (45 – 80)	0.063
Peak inspiratory pressure, cmH_2O	37 (36 – 39)	34 (29 – 36)	0.055
End-inspiratory plateau pressure, cmH_2O	26 (25 – 29)	26 (23 – 29)	0.094
Driving pressure, cmH_2O ‡	11 (11 – 14)	11 (9 – 12)	0.19
Ventilatory ratio §	1.84 (1.63 – 2.13)	2.05 (1.79 – 2.19)	0.52
Crs, $mL*cmH_2O^{-1}$ ‖	36.36 (33.18 – 38.46)	41.82 (37.5 – 56.71)	**0.016**
$PaCO_2$, mmHg	56 (50.9 – 58.7)	51 (41.8 – 58.4)	0.32
PaO_2, mmHg	85 (76 – 93.9)	91 (82.7 – 135.7)	0.11
PaO_2/FiO_2	108 (86 – 143)	202 (176 – 232)	**0.002**

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* Supine position measurements were performed just before prone positioning, while prone position measurements were taken after prone positioning. † For paired difference tests between before (supine) and after prone positioning (prone), nonparametric Wilcoxon signed-rank test was used. ‡ Driving pressure is the difference between positive end-inspiratory plateau pressure and PEEP. § Ventilatory ratio is defined as [minute ventilation (ml/min) × PaCO2 (mm Hg)]/ (predicted body weight × 100 × 37.5). ‖ Static compliance of the respiratory system is the ratio of tidal volume to driving pressure. Crs, Static compliance of the respiratory system; FiO_2, fraction of inspired oxygen, IQR, interquartile range; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PBW, predicted body weight; PEEP, Positive end-expiratory pressure.

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