Respiratory Mechanics of COVID-19 *vs.* Non-COVID-19 Associated Acute Respiratory Distress Syndrome

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To the Editor:

Most of patients admitted to the intensive care unit with a severe presentation of coronavirus disease 2019 (COVID-19) fulfill the acute respiratory distress syndrome (ARDS) criteria (1) and require invasive mechanical ventilation (2). In such patients, knowledge of respiratory mechanics and potential for lung recruitability may provide valuable information to guide ventilator's settings adjustments. Some authors have regularly reported from their clinical experience that the key feature of COVID-19 respiratory mechanics would be an uncommon association of severe hypoxemia and preserved respiratory system compliance, altogether with poor recruitability (3–5). However, dramatic decrease in respiratory system compliance has been reported as well in SARS-CoV-2 related ARDS (6). Gattinoni *et al.* recently proposed to reconciliate these different observations, hypothesizing that the different phenotypes may result from interactions between the time course and severity of the disease and the patient's ventilatory response, with an early L phenotype (low lung elastance, low recruitability), and a late H phenotype (high lung elastance, high recruitability) (5). However, physiological description of COVID-19 associated ARDS and its comparison to non COVID-19 classical ARDS remain scarce in the literature.

The aim of the present study is to describe the respiratory mechanics and lung recruitability of COVID-19 associated ARDS patients, to compare it to that of non-COVID-19 ARDS, and to explore their possible relation with COVID-19 phenotypes.

Methods

This is an ancillary report of an ongoing prospective monocentric observational study on respiratory mechanics in patients with ARDS, conducted in the Henri Mondor University Hospital medical ICU, Créteil, France (IRB 2018-A00867-48). Inclusion criteria were age > 18 years and presence of ARDS according to the Berlin definition (7). Exclusion criteria were intubation for more than 24 hours prior to ICU admission. All consecutive COVID-19 patients included in this study are reported here and compared to consecutive non-COVID-19 patients previously enrolled. Written informed consent was waived due to the observational nature of the study. The ventilator was set by the attending physician. During the first 48 hours of invasive mechanical ventilation, the ventilator's settings were collected and the respiratory mechanics and lung recruitability were assessed once in supine position. Thus, airway and esophageal (when available) pressures were recorded during a 0.3-second end-inspiratory and a 1-to-2-second end-expiratory occlusion maneuvers, at the PEEP level previously set by the physician. The potential airway closure phenomenon was detected by measuring the airway opening pressure during a low flow (≤ 6 L/min) insufflation, as previously described (8). The potential for lung recruitment was assessed by the mean of the recruitment-to-inflation ratio (R/I ratio) computation, as previously detailed (8). By default, R/I ratio was assessed between 15 and 5 cm H_2O of positive end expiratory pressure (PEEP). However, in case of airway closure, the low PEEP was set above the airway opening pressure. Comparisons were made using nonparametric tests. A $p < 0.05$ was considered significant.

Results

Thirty consecutive non-COVID-19 and 30 consecutive COVID-19 ARDS patients were included in the report. Non-COVID-19 patients were enrolled between January 17, 2019 and March 3, 2020; COVID-19 patients between March 11, 2020 and April 03, 2020. Five COVID-19 and five non-COVID-19 patients experienced prone position before inclusion in the study. Etiologies for non-COVID-19 ARDS were the followings: pneumonia (n = 27, of which 10 were related to respiratory viruses), pulmonary vasculitis (n = 2) and non-cardiogenic shock (n = 1). A bacterial coinfection was documented in four COVID-19 patients at the time of inclusion. COVID-19 and non-COVID-19 patients did not differ significantly for age and

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ARDS severity, according to the PaO_2/FiO_2 ratio (Table 1). COVID-19 patients had a significantly higher body mass index.

Respiratory mechanics

Driving pressure as well as respiratory system compliance and resistance did not significantly differ between COVID-19 and non-COVID-19 patients (Table 1 and Figure 1A). These findings were similar in the subgroup of patients with esophageal pressure measurement (19/30 COVID-19 and 29/30 non-COVID-19 patients). Especially, chest wall compliances of COVID-19 and non-COVID-19 patients were similarly preserved (Table 1). In patients with a PaO_2/FiO_2 ratio below 150 mm Hg (20 COVID-19 and 17 non-COVID-19), the respiratory system compliance was also similar between two groups (43 mL/cm H_2O [34 – 48] *vs.* 45 mL/cm H_2O [31 – 56] respectively, $p = 0.68$). Airway opening pressure and R/I ratio were available in all but three patients. Airway closure phenomenon (airway opening pressure ≥5 cm H_2O) occurred more frequently in COVID-19 patients as compared to their counterparts [12/30 (40%) *vs.* 3/27 (11%), $p = 0.01$]. The twelve COVID-19 patients with airway closure phenomenon had a median airway opening pressure of 8 cm H_2O [5, 10] while the three non-COVID-19 patients with airway closure phenomenon had an airway opening pressure of 5, 5 and 9 cm H_2O, respectively. There was a weak but significant correlation between the body mass index and the airway opening pressure (Spearman's $\rho = 0.327$, $p = 0.017$).

Recruitability and COVID-19 phenotypes

Overall, the R/I ratio was significantly higher in COVID-19 than in non-COVID-19 patients (Table 1). However, the difference in high potential for recruitability (as defined by a R/I ratio ≥ 0.5) (8) between COVID-19 and non-COVID-19 patients did not reach statistical significance [9/30 (30%) *vs.* 4/27 (15%), $p = 0.17$].

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In COVID-19 patients, the R/I ratio was significantly correlated with the PaO_2/FiO_2 ratio (Spearman's ρ = - 0.44, p =0.001), but not with the respiratory system compliance (Spearman's ρ = 0.29, *p* = 0.12, Figure 1A). The times since the onset of the first COVID-19 symptom and since the onset of dyspnea were not correlated with the respiratory system compliance (spearman's ρ = - 0.005 and 0.162, *p* = 0.98 and 0.39, respectively) (Figure 1B) nor with the R/I ratio (spearman's ρ = - 0.320 and -0.221, *p* = 0.09 and 0.24, respectively). No other correlation was found between the duration of the disease and any of the respiratory mechanics parameters assessed.

Subgroups analysis

A subgroup analysis focusing on moderate ARDS in COVID-19 and non-COVID-19 patients found similar results.

A comparison between COVID-19 patients and the 27 non-COVID-19 patients with pneumonia related ARDS retrieved similar findings as well. As compared to the ten non-COVID-19 patients with viral pneumonia, COVID-19 patients had a significantly higher BMI (27.9 kg/m^2 [24.2, 31.8] *vs.* 22.3 kg/m^2 [19.5, 26.4], *p* = 0.01) and a lower PaO_2/FiO_2 ratio (119 mm Hg [97, 163] *vs.* 146 mm Hg [131, 157], *p* = 0.04), but with comparable respiratory mechanics (data not shown).

Discussion

The main findings of our prospective observational study were as follows: the respiratory mechanics of COVID-19 related ARDS patients was heterogenous and as a global picture not much different from that of their non-COVID-19 counterparts; COVID-19 related ARDS patients had a higher R/I ratio suggesting a higher recruitabilty; we could not formally identify

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specific COVID-19 related ARDS phenotypes using a raw assessment of relationship between respiratory mechanics, recruitability, hypoxemia severity and time course of the disease.

While some authors have described COVID-19 related ARDS patients with intriguingly high compliance (3–5), others reported case series of patients with very low one (6). We found a higher R/I ratio in COVID-19 related ARDS, suggesting a higher recruitability. Gattinoni *et al.* proposed an integrative concept (5) hypothesizing a progressive transition from a phenotype characterized by low elastance, low lung weight, low recruitability and low ventilation-to-perfusion ratio to a second phenotype characterized by high elastance, high lung weight, high right-to-left shunt and high recruitability; the transition being mainly driven by the extent of the patient's ventilatory response and its ability to promote patient self-inflicted lung injury (P-SILI) (9). We could not retrieve such distinct phenotypes in our cohort, as no correlation was found between compliance, recruitability, or the time course of the disease. However, as we were not able to quantify the magnitude of the respiratory effort and the resulting negative pleural pressure swings prior to intubation, we could not assess the hypothesis of P-SILI as the leading mechanism of respiratory mechanics impairment during COVID-19 related ARDS. In addition, as our study was monocentric with a small sample size, our results may not be generalizable to all COVID-19 related ARDS patients. Nevertheless, the higher BMI in our COVID-19 patients as compared to their non-COVID-19 counterparts is consistent with previous report pointing out the high frequency of obesity in COVID-19 patients requiring mechanical ventilation (10). This may explain, at least partly, the higher proportion of airway closure phenomenon in our cohort.

In conclusion, given the various associations of respiratory mechanics, hypoxemia severity and lung recruitability in COVID-19 related ARDS patients, our results advocate for the systematic assessment of respiratory mechanics and recruitability at the bedside in order to personalize

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ventilator's settings in these patients. Larger cohort studies are warranted to scrutinize the phenotype(s) of COVID-19 related ARDS.

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Figure legend

Figure 1

A. Respiratory system compliance (C_{RS}) according to both the COVID-19 status and the recruitability. High recruitability denotes a recruitment-to-inflation ratio ≥ 0.5. Conversely, low recruitability denotes a recruitment-to-inflation ratio < 0.5. No significant difference was found between any subgroup. COVID- denotes non-COVID-19 patients; COVID+ denotes COVID-19 patients.

B. Respiratory system compliance (C_{RS}) plotted against the time since onset of COVID-19 symptoms. No correlation was found between the respiratory system compliance and duration of symptoms. Red squares represent patients with a recruitment-to-inflation ratio ≥ 0.5, blue circles represent patients with a recruitment-to-inflation ratio < 0.5.

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Table 1. Patients' characteristics, respiratory mechanics and recruitability

	COVID-19	Non-COVID-19	*p* value
Patients, n	30	30	
Age, years	58 [49, 67]	66 [52, 73]	0.15
Male, n (%)	26 (87)	22 (73)	0.19
Height, cm	175 [167, 178]	170 [165, 175]	0.25
BMI, kg/m^2	28 [24, 31]	22 [20, 27]	**< 0.01**
Noninvasive ventilatory support prior to intubation, n (%) *	16 (53)	10 (33)	0.19
Duration of noninvasive ventilatory support, days	1 [0, 1.75]	1 [0, 2.25]	0.77
FiO_2 level, %,	70 [52, 80]	60 [40, 80]	0.55
PaO_2/FiO_2, mm Hg	119 [97, 163]	136 [120, 167]	0.075
ARDS severity, n (%)			0.22
Moderate	19 (63.3)	24 (80)	
Mild	3 (10.7)	4 (13.3)	
Severe	8 (26.7)	2 (7.1)	
Tidal volume, mL/kg of PBW	6.0 [5.9, 6.7]	6.3 [5.9, 6.4]	0.18
Respiratory rate, cycles/min	28 [28, 30]	26 [25, 30]	**0.03**
PEEP, cm H_2O	10 [8, 12]	8 [8, 10]	0.33
auto-PEEP, cm H_2O	1 [1, 2]	1 [1, 2]	0.2
Airway opening pressure ≥ 5 cm H_2O[†], n (%)	12 (40)	3 (11)	**0.01**
R/I ratio[†]	0.40 [0.23, 0.50]	0.20 [0.05, 0.30]	**0.01**
High recruitability, n (%)	9 (30)	4 (15)	**0.17**
Pplat, cm H_2O	21 [20, 24]	20 [17, 24]	0.22
Driving pressure, cm H_2O	10 [8, 12]	9 [8, 11]	0.64
Rrs, cm H_2O/L/s	16 [14, 19]	16 [13, 18]	0.61
Crs, ml/cm H_2O	44 [35, 51]	42 [30, 55]	0.84
Patients with esophageal pressure, n	19	29	
BMI, kg/m^2	30 [26, 32]	22 [20, 28]	**< 0.01**
PaO_2/FiO_2, mm Hg	111 [96, 128]	135 [120, 159]	**0.02**
$P_{Lend\text{-}insp}$, cm H_2O	14 [14, 18]	14 [9, 17]	0.26
$P_{Lend\text{-}exp}$, cm H_2O	2 [0, 4]	0 [0, 1]	0.06
Ccw, ml/cm H_2O	144 [116, 360]	113 [92, 150]	0.06

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Clung, ml/cm H_2O	59 [44, 72]	57 [47, 90]	0.81
E_L/Ers	0.69 [0.63, 0.89]	0.64 [0.52, 0.80]	0.11

Continuous variables are expressed as median [interquartile range].

Definition of abbreviations: BMI: Body mass index; ARDS: acute respiratory distress syndrome; PBW: predicted body weight; PEEP: positive end expiratory pressure; auto-PEEP was computed as total PEEP minus applied PEEP; R/I ratio: recruitment-to-inflation ratio (8); Pplat: plateau pressure; Rrs: respiratory system resistance; Crs: respiratory system compliance; $P_{Lend\text{-}insp}$: transpulmonary pressure at end inspiration, computed as follows: $P_{Lend\text{-}insp}$ = Pplat x (E_L/Ers) where E_L is the lung elastance and Ers the respiratory system elastance (11); $P_{Lend\text{-}exp}$: transpulmonary pressure at end expiration, computed as follows: $P_{Lend\text{-}exp}$ = PEEPt – $P_{ESend\text{-}exp}$ where PEEPt is the total PEEP and $P_{ESend\text{-}exp}$ is the end expiratory esophageal pressure value; Ccw: chest wall compliance; Clung: lung compliance.

High recruitability denotes patients with R/I ratio ≥ 0.5.

[*] Noninvasive ventilatory supports were continuous positive airway pressure (n = 13), noninvasive ventilation (n = 1) and high flow nasal cannula (n = 2) for COVID-19 patients; and high flow nasal cannula (n = 10) for non-COVID-19 patients.

[†] Not available in three non-COVID-19 patients.

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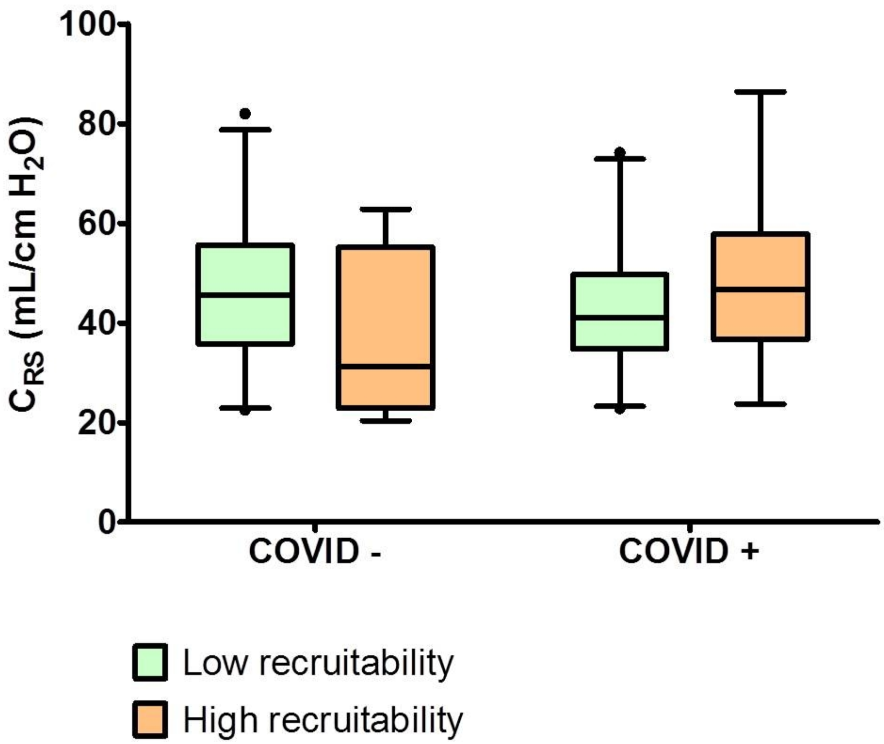

A. Respiratory system compliance (CRS) according to both the COVID-19 status and the recruitability. High recruitability denotes a recruitment-to-inflation ratio ≥ 0.5. Conversely, low recruitability denotes a recruitment-to-inflation ratio < 0.5. No significant difference was found between any subgroup. COVID- denotes non-COVID-19 patients; COVID+ denotes COVID-19 patients.

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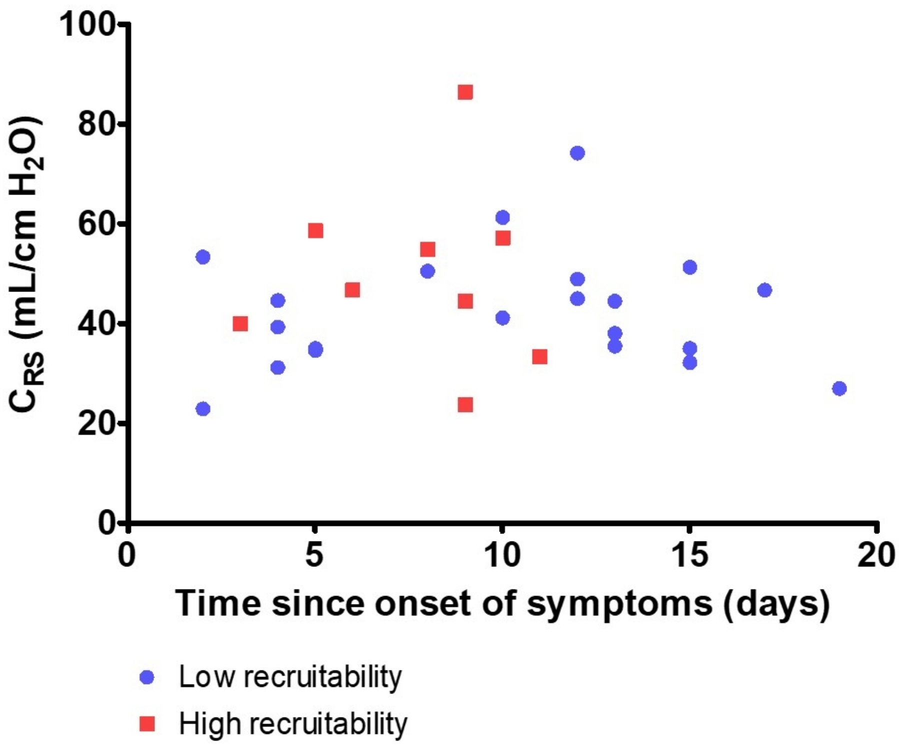

B. Respiratory system compliance (CRS) plotted against the time since onset of COVID-19 symptoms. No correlation was found between the respiratory system compliance and duration of symptoms. Red squares represent patients with a recruitment-to-inflation ratio ≥ 0.5, blue circles represent patients with a recruitment-to-inflation ratio < 0.5.

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