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Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study

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Abstract

Purpose: To investigate whether COVID-19-ARDS differs from all-cause ARDS.

Methods: Thirty-two consecutive, mechanically ventilated COVID-19-ARDS patients were compared to two historical ARDS sub-populations 1:1 matched for PaO₂/FiO₂ or for compliance of the respiratory system. Gas exchange, hemodynamics and respiratory mechanics were recorded at 5 and 15 cmH₂O PEEP. CT scan variables were measured at 5 cmH₂O PEEP.

Results: Anthropometric characteristics were similar in COVID-19-ARDS, PaO₂/FiO₂-matched-ARDS and Compliance-matched-ARDS. The PaO₂/FiO₂-matched-ARDS and COVID-19-ARDS populations (both with PaO₂/FiO₂ 106 ± 59 mmHg) had different respiratory system compliances (Cr_s) (39 ± 11 vs 49.9 ± 15.4 ml/cmH₂O, *p* = 0.03). The Compliance-matched-ARDS and COVID-19-ARDS had similar Cr_s (50.1 ± 15.7 and 49.9 ± 15.4 ml/cmH₂O, respectively) but significantly lower PaO₂/FiO₂ for the same Cr_s (160 ± 62 vs 106.5 ± 59.6 mmHg, *p* < 0.001). The three populations had similar lung weights but COVID-19-ARDS had significantly higher lung gas volume (PaO₂/FiO₂-matched-ARDS 930 ± 644 ml, COVID-19-ARDS 1670 ± 791 ml and Compliance-matched-ARDS 1301 ± 627 ml, *p* < 0.05). The venous admixture was significantly related to the non-aerated tissue in PaO₂/FiO₂-matched-ARDS and Compliance-matched-ARDS (*p* < 0.001) but unrelated in COVID-19-ARDS (*p* = 0.75), suggesting that hypoxemia was not only due to the extent of non-aerated tissue. Increasing PEEP from 5 to 15 cmH₂O improved oxygenation in all groups. However, while lung mechanics and dead space improved in PaO₂/FiO₂-matched-ARDS, suggesting recruitment as primary mechanism, they remained unmodified or worsened in COVID-19-ARDS and Compliance-matched-ARDS, suggesting lower recruitment potential and/or blood flow redistribution.

Conclusions: COVID-19-ARDS is a subset of ARDS characterized overall by higher compliance and lung gas volume for a given PaO₂/FiO₂, at least when considered within the timeframe of our study.

Keywords: COVID-19, ARDS, Respiratory system mechanics, Mechanical ventilation, CT scan

Introduction

Acute respiratory distress syndrome (ARDS)—as currently defined—is a syndrome which broadly includes diverse conditions grouped on the basis of an oxygenation deficit of acute onset and bilateral radiographic infiltrates that cannot be attributed solely to a

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cardiovascular cause [1]. The severity of ARDS is classified by a single criterion only: oxygenation deficit, expressed as $\text{PaO}_2/\text{FiO}_2$ ratio. By this broad definition, hypoxemic patients with coronavirus disease 2019 (COVID-19) and bilateral chest X-ray infiltrates clearly satisfy the definition of ARDS. We have reported [2, 3] that severe hypoxemia with relatively well-preserved respiratory system compliance (Cr_s) measured under standard conditions is characteristic of COVID-19-ARDS, and it differs from ARDS of other causes (typical ARDS), while others did not recognize consistent differences [4–7]. However, the increased frequency of higher Cr_s in COVID-19-ARDS was noted by some of the same authors [4, 5], and a significantly higher Cr_s associated with severe hypoxemia was recently documented [8]. The heterogeneous nature of ARDS allows that—at the population level—there may be wide overlap between COVID-19-ARDS and typical ARDS, and these observations continue to drive a debate [6, 9]. It is worth remembering that during the Berlin conference, the experts' panel initially agreed on using an upper threshold of 40 ml/cmH₂O of respiratory system compliance (Cr_s) to qualify as severe ARDS. This variable was not implemented, however, as it did not add further prognostic value to bilateral infiltrates and $\text{PaO}_2/\text{FiO}_2$ ratio [10]. In other words, the $\text{PaO}_2/\text{FiO}_2$ ratio and the Cr_s deteriorated together in typical ARDS. This pairing may not occur in COVID-19-ARDS, where a discrepancy between the severities of hypoxemia and respiratory mechanics may be the key issue, rather than their individual absolute values per se.

Indeed, this discrepancy could be due to the underlying pathogenesis of COVID-19-ARDS, which is highly atypical and quite distinct from most other forms of typical ARDS that are routinely encountered [2, 11, 12]. In typical ARDS, the primary site 'hit' is the alveolar space, particularly in pulmonary ARDS. In contrast, in COVID-19-ARDS, the prevalent pathophysiological mechanism is initiated on the vascular side of the pulmonary unit. In addition, the endothelialitis, typical of COVID-19 patients, results in a powerful activation of the coagulation cascade, with micro and macro thrombosis occurring in pulmonary tissues and throughout the body [13–15]. Undoubtedly, microthromboses are recognized autopsy findings [16], and pulmonary artery filling defects (vascular occlusion or compression) have been described in typical ARDS for decades [17, 18]. A striking difference between typical ARDS and COVID-19-ARDS, however, is the remarkable frequency and extent to which pulmonary [15, 19] and extrapulmonary thrombosis [20] occur in the latter. While regional atelectasis, edema and fibrosis may coexist, disrupted vasoregulation strikingly alters the matching of perfusion to ventilation,

a pathophysiologic mechanism which may be the predominant contributor to hypoxemia in the early phase of this evolving disease [12, 21].

To investigate whether and to what degree, COVID-19-ARDS differs from typical ARDS, we compared the physio-anatomical characteristics of COVID-19-ARDS patients with two historically matched cohorts of typical ARDS. Quantitative CT scan analysis, and measurements of respiratory system mechanics and gas exchange were performed under standardized and identical conditions, both in COVID-19-ARDS and typical ARDS, thus avoiding the biases of acquiring CT scans and physiological variables under highly heterogeneous "clinical" conditions.

Methods

Study population

Thirty-two COVID-19-ARDS patients, consecutively admitted to the ICU of ASST Santi Paolo e Carlo Hospital, Milan over the period between February 21st, 2020 and May 7th, 2020 were prospectively enrolled. This study was conducted in accordance with the pre-existing Ethics Committee approval that allows physiological and CT scan studies for all patients with severe respiratory failure admitted to our critical care unit (ethics committee numbers: 42937/2016 and 9890/2017). All had documented COVID-19 positive RT-PCR or nasal or pharyngeal swab and bilateral infiltrates documented by chest X-ray. This COVID-19-ARDS population was matched with cohorts from two separate non-COVID ARDS populations: one matched 1:1 for $\text{PaO}_2/\text{FiO}_2$ ($\text{PaO}_2/\text{FiO}_2$ -matched-ARDS) and a second one matched 1:1 for respiratory system compliance (Compliance-matched-ARDS). The values of $\text{PaO}_2/\text{FiO}_2$ ratio and Cr_s used for matching these cohorts were the ones measured in COVID-19-ARDS at 5 cmH₂O of PEEP during mechanical ventilation, immediately before the CT scan. The $\text{PaO}_2/\text{FiO}_2$ ratio and Cr_s of the two historical non-COVID ARDS cohorts were measured under exactly the same conditions.

The two matched, entirely independent population samples were extracted from our ARDS dataset which includes 232 patients studied between 2003 and 2018. These patients had previously been screened and included in clinical physiopathologic studies performed by our group over the same time span. Therefore, they met all criteria that define ARDS and underwent a common and standardized intervention (e.g., CT scan, PEEP trials, measurement of respiratory mechanics and gas exchange) and a standardized data collection protocol.

Measurements

In every studied patient (of both COVID-19-ARDS and the matched non-COVID ARDS populations), gas exchange, respiratory mechanics, hemodynamics and

CT scan variables were recorded under standardized conditions (Volume Controlled ventilation, tidal volume 7–8 ml/kg of Ideal Body Weight (IBW), muscle relaxation, 5 cmH₂O of Positive End-Expiratory Pressure, PEEP). Both COVID-19-ARDS and non-COVID ARDS population cohorts underwent CT scanning and PEEP testing within a median of 3 [IQR 1–4] days after the admission to ICU.

Gas exchange

We measured FiO₂, PO₂, PCO₂, hemoglobin saturation and derived variables (using arterial and central venous blood) and end-tidal PCO₂ (P_{ET}CO₂). Venous admixture was computed using central venous blood values as surrogates for the mixed venous ones [22].

Respiratory system mechanics

We measured plateau pressure, PEEP, driving pressure and respiratory system compliance at the standardized value of 5 cmH₂O.

CT-quantitative anatomical variables

In each patient, the whole lung CT was performed under static conditions during an end-expiratory hold at 5 cmH₂O of PEEP. Lung profiles of each CT scan slice were manually contoured, excluding hilar structures. Then, quantitative analysis was performed with dedicated software (Maluna [23]). We estimated lung weight, gas volume, amount of over-inflated tissue (voxel density – 1000 to – 900 Hounsfield Units, HU), well-aerated tissue (– 899 to – 500 HU), poorly aerated tissue (– 499 to – 100 HU) and non-aerated tissue (– 100 to +100 HU). Analyses were performed on each whole slice as well as on ten equally spaced segments along the sterno-vertebral axis.

PEEP response

All patients underwent a “PEEP-test” in which PEEP was raised from 5 to 15 cmH₂O while keeping constant respiratory rate, tidal volume and FiO₂. Gas exchange, hemodynamics and mechanical variables were re-measured at 15 cmH₂O of PEEP after a 15-min equilibration period (See Supplement for details.)

Statistical analysis

The one-to-one matching procedure was performed with the nearest-neighboring method using the optimal algorithm, without replacement, with the MatchIt package for R (R Foundation for Statistical Computing version 4.0.2) [24]. Data are presented as mean ± standard deviation. Student’s *t* test assessed the statistical significance of the difference between group means when data were distributed normally; otherwise, the Wilcoxon test

was used. Chi square test or Fisher’s exact test was used to construct the contingency tables. Linear regression tested the relationship between continuous variables. Two-way analysis of variance allowing interaction was used to evaluate the gas volume distribution along the segments of sterno-vertebral axis. These statistical analyses were performed with R (R Foundation for Statistical Computing version 4.0.2) and its package Tidyverse.

Results

Study population

COVID-19-ARDS (32 consecutive patients) and both non-COVID ARDS population cohorts (PaO₂/FiO₂-matched-ARDS and Compliance-matched-ARDS, 32 patients each) had similar baseline characteristics regarding age, sex, Ideal Body Weight and Body Mass Index. The Simplified Acute Physiology Score II (SAPSII), although lower in COVID-19-ARDS patients, was not statistically different from the comparison cohorts. However, it is likely that overall clinical severity in the PaO₂/FiO₂-matched-ARDS and Compliance-matched-ARDS groups was greater, as indicated by longer ICU length of stay (Table 1). PaO₂/FiO₂-matched-ARDS and Compliance-matched-ARDS had comparable distributions of prevalence regarding etiology of lung injury (*p*=0.86). The majority (68.7%) of both COVID-19-ARDS and PaO₂/FiO₂-matched-ARDS patients had PaO₂/FiO₂ ratios consistent with severe ARDS, based on the Berlin definition of ARDS severity. In contrast, severe ARDS represented only 18.7% of Compliance-matched-ARDS patients; (*p*<0.001) (Table 1). Outcome measures for the three populations are reported in Table 1.

Oxygenation and respiratory mechanics

When COVID-19-ARDS was compared to the PaO₂/FiO₂-matched-ARDS cohort, i.e., at similar oxygenation, its respiratory system compliance was significantly higher (49.9 ± 15.4 vs 39.9 ± 11.1 ml/cmH₂O; *p*=0.003, Fig. 1a) and plateau and driving pressures were significantly lower (Table 2). When COVID-19-ARDS was compared to the Compliance-matched-ARDS population, i.e., at similar respiratory system mechanics, the PaO₂/FiO₂ ratio was significantly lower in COVID-19-ARDS (106.5 ± 59 vs 160 ± 62 mmHg; *p*<0.001, Fig. 1b), as were the other oxygenation variables. In PaO₂/FiO₂-matched-ARDS patients, the PaO₂/FiO₂ ratio was linearly related with the respiratory system mechanics (*p*=0.036), whereas no significant correlation was found neither in Compliance-matched-ARDS (*p*=0.9), nor in COVID-19-ARDS (*p*=0.81, Figure E1).

Table 1 Baseline clinical characteristics of the three cohorts

	PF-ARDS (n = 32)	p value	CARDS (n = 32)	p value	Crs-ARDS (n = 32)
Age (years)	59 ± 17	0.96	58.9 ± 8.9	0.15	63.8 ± 16.2
Female (n – %)	8 (25)	0.2	4 (12)	0.21	9 (28.1)
Height (cm)	171 ± 10	0.14	175 ± 9	0.054	170 ± 9
Ideal Body Weight (kg)	66.5 ± 9.9	0.85	66.9 ± 7.2	0.47	65.3 ± 9.8
BMI (kg/m ²)	29 ± 8.2	0.57	28 ± 4.1	0.11	26 ± 6
PaO ₂ /FiO ₂ (mmHg)	106.3 ± 59.4	0.99	106.5 ± 59.6	< 0.001	160 ± 62
Crs (ml/cmH ₂ O)	39 ± 11.1	0.003	49.9 ± 15.4	0.97	50.1 ± 15.7
Causes of lung injury (n – %)					
Pneumonia	17 (53.1)		32 (100)		14 (43.8)
Aspiration	3 (9.4)		0 (0)		2 (6.3)
Sepsis	6 (18.7)		0 (0)		8 (25)
Trauma	3 (9.4)		0 (0)		3 (9.4)
Other	3 (9.4)		0 (0)		5 (15.6)
ARDS category (n – %)					
Mild	3 (9.4)	1	3 (9.4)	< 0.001	7 (21.9)
Moderate	7 (21.9)		7 (21.9)		19 (59.4)
Severe	22 (68.7)		22 (68.7)		6 (18.8)
SAPSI	43.5 ± 21.3	0.07	34.5 ± 12.1	0.07	41.1 ± 15.5
Days of mechanical ventilation before study	2.2 ± 2.2	< 0.001	0.8 ± 0.7	0.002	3.8 ± 4.5
ICU length of stay (days)	19.2 ± 12.2	0.07	13.7 ± 8.1	< 0.001	24.8 ± 13.4
ICU mortality (n – %)	17 (53.1)	0.21	12 (37.5)	1	12 (37.5)

Anthropometric and clinical characteristics of COVID-19-ARDS population (CARDS, middle column) and the two historical matched cohorts (PaO₂/FiO₂-matched-ARDS, left column and Compliance-matched-ARDS, right column)

BMI Body Mass Index, Crs respiratory system compliance, SAPSI Simplified Acute Physiology Score II, ICU Intensive Care Unit

CO₂ clearance and dead space

With regard to the ventilation parameters, COVID-19-ARDS and its two matched populations (PaO₂/FiO₂-matched-ARDS and Compliance-matched-ARDS) had comparable values for tidal volume, alveolar dead space ventilation and ventilatory ratio. Minute ventilation was significantly higher and PaCO₂ lower in COVID-19-ARDS, compared to PaO₂/FiO₂-matched-ARDS, due to a higher respiratory rate (Table 2).

CT scan variables

Despite similar total lung weights, patients with COVID-19-ARDS, compared to PaO₂/FiO₂-matched-ARDS, had significantly higher lung gas volume (1670 ± 791 vs 930 ± 644 mL; *p* < 0.001), a greater amount of normally aerated tissue (475 ± 185 vs 287 ± 154 g; *p* < 0.001) and less non-aerated tissue (591 ± 293 vs 960 ± 567 g; *p* = 0.002) (Table 2). The weights of the normally aerated and non-aerated lung tissues were similar in COVID-19-ARDS and in Compliance-matched-ARDS populations, but total lung gas volume was higher in COVID-19-ARDS compared to Compliance-matched-ARDS. Notably, the distribution

of gas volume was remarkably different for the three populations: patients with COVID-19-ARDS had the highest gas volumes in each lung segment, whereas the lowest gas volumes were measured in the corresponding segments of the PaO₂/FiO₂-matched ARDS population (Fig. 2).

Hemodynamics, venous admixture and non-aerated tissue

Hemodynamic values are presented in Table 2. In Fig. 3, we present venous admixture as a function of the fraction of non-aerated tissue. In each of the non-COVID ARDS cohorts, venous admixture increased with the fraction of non-aerated tissue (both *p* = 0.004). In contrast, in COVID-19-ARDS, the venous admixture remained approximately constant and independent from large variations in the observed fraction of non-aerated tissue (*p* = 0.75). The regression model also shows that in the COVID-19-ARDS population the constant term of the model equates to a venous admixture of 0.50 (95% CI 0.33–0.67), suggesting that significant venous admixture is theoretically present, even for an assumed zero fraction of non-aerated tissue. PaO₂/FiO₂ ratio and A-aPO₂ as a function of the fraction

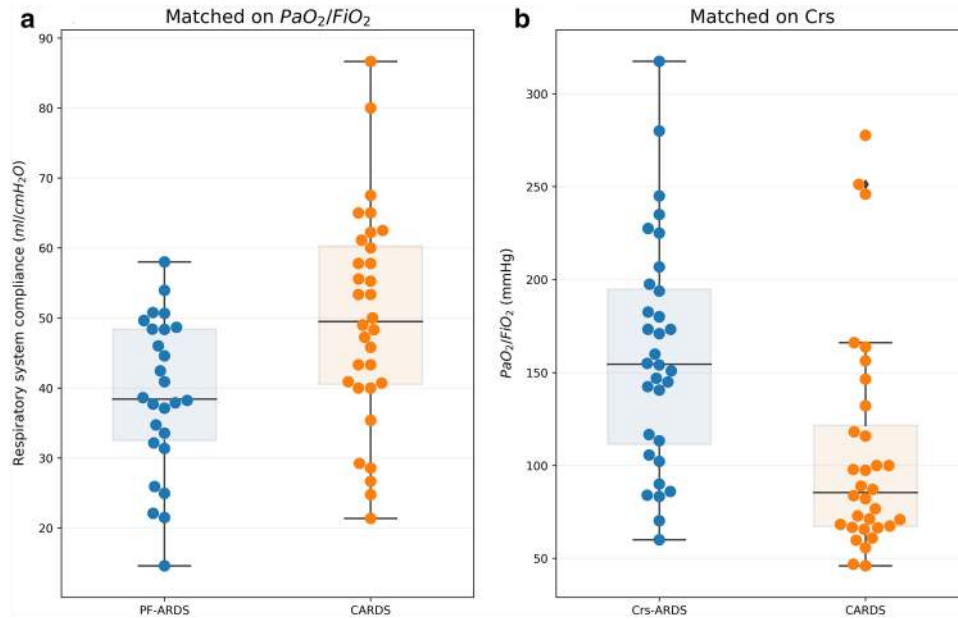


Fig. 1 **a** Respiratory system compliance in COVID-19-ARDS (orange) and in PaO₂/FiO₂-matched-ARDS populations (blue). The matched PaO₂/FiO₂ ratios were similar (COVID-19-ARDS = 106 ± 59 mmHg, PaO₂/FiO₂-matched-ARDS = 106 ± 60 mmHg). Note that, for the same PaO₂/FiO₂ ratio, the Crs in COVID-19-ARDS is significantly higher (~ 11 ml/cmH₂O) than in PaO₂/FiO₂-matched-ARDS (median values 49.5 and 38.4 ml/cmH₂O, respectively). **b** PaO₂/FiO₂ ratio in COVID-19-ARDS (orange) and in Compliance-matched-ARDS populations (blue). The matched respiratory system compliance values were similar (COVID-19-ARDS = 49.9 ± 15.4 ml/cmH₂O, Compliance-matched-ARDS = 50.1 ± 15.7 ml/cmH₂O). Note that, for the same Crs, the PaO₂/FiO₂ ratio in Compliance-matched-ARDS is significantly higher (~ 70 mmHg) than in COVID-19-ARDS (median values 155.0 and 85.4 mmHg, respectively)

of non-aerated tissue (Figures E2 and E3) showed the same behavior of venous admixture.

Response to PEEP test

The responses of the physiological variables to the PEEP test, i.e., increasing PEEP from 5 to 15 cmH₂O are summarized in Table 3. As shown, despite a similar increase in oxygenation in all three populations, the respiratory system mechanics and dead space all improved in the PaO₂/FiO₂-matched-ARDS cohort but did not change or deteriorated in patients with COVID-19-ARDS and those with Compliance-matched-ARDS.

Discussion

In this study, which compares COVID-19-ARDS patients with two different non-COVID-19 ARDS populations, we found the following: (1) COVID-19-ARDS patients, compared to PaO₂/FiO₂-matched ARDS (i.e., similar oxygenation), had consistently better respiratory system compliance and nearly double the end-expiratory gas volume as their counterparts in the comparison groups; (2) COVID-19-ARDS patients, compared to a separate population of non-COVID-19 ARDS patients matched on Crs (i.e., with similar respiratory system mechanics) had consistently worse oxygenation variables; (3)

COVID-19-ARDS, PaO₂/FiO₂-matched-ARDS, and Compliance-matched-ARDS experienced similar oxygenation improvement when raising PEEP from 5 to 15 cmH₂O. Importantly, however, while that oxygenation improvement in the PaO₂/FiO₂-matched-ARDS population was associated with significantly improved CO₂ clearance and respiratory mechanics, these variables did not change or deteriorated in both COVID-19-ARDS patients and Compliance-matched-ARDS patients.

Patient populations

A single matching variable was used for each matching procedure. No other variables were included, due to the limited size of our ARDS dataset. The anthropometric characteristics of the three populations were not statistically different. Bilateral pneumonia was the only cause of lung injury in COVID-19-ARDS patients. By comparison, pneumonia accounted for 53.1% and 43.8% in PaO₂/FiO₂-matched-ARDS and Compliance-matched-ARDS cohorts, respectively, incidence frequencies similar to the LUNG-SAFE study (59.4%) of 3022 patients ($p=0.16$) [25]. The prevalence of sepsis was also similar among LUNG-SAFE, PaO₂/FiO₂-matched-ARDS and Compliance-matched-ARDS (16%, 18.7% and 25% in, respectively; $p=0.36$). Therefore, our sample of matched ARDS

Table 2 Gas exchange, respiratory mechanics, hemodynamics and CT variables of the three cohorts

	PF-ARDS (n = 32)	p value	CARDS (n = 32)	p value	Crs-ARDS (n = 32)
Oxygenation					
FiO ₂	0.74 ± 0.22	0.66	0.72 ± 0.18	< 0.001	0.51 ± 0.15
PaO ₂ (mmHg)	68.1 ± 17.4	0.75	66.7 ± 16.8	0.045	76.1 ± 19.6
PaO ₂ /FiO ₂ (mmHg)	106.3 ± 59.4	0.99	106.5 ± 59.6	< 0.001	160 ± 62
PAO ₂ (mmHg)	465 ± 148	0.73	453 ± 129	< 0.001	313 ± 107
AaPO ₂ (mmHg)	397 ± 156	0.77	386 ± 138	< 0.001	237 ± 113
SaO ₂ (%)	90.2 ± 5.3	0.78	90.6 ± 5.7	0.056	93.1 ± 4.1
CO₂ clearance					
Tidal volume (ml/kg IBW)	7.5 ± 1.6	0.52	7.7 ± 0.9	0.07	8.4 ± 1.9
Respiratory rate (bpm)	16.8 ± 3.9	0.014	18.7 ± 2	< 0.001	15.7 ± 3.6
Minute ventilation (l/min)	8.18 ± 2.21	0.002	9.82 ± 1.85	0.001	8.3 ± 1.76
PaCO ₂ (mmHg)	50.9 ± 13.6	0.027	44.7 ± 7.1	0.60	45.8 ± 9.9
P _{ET} CO ₂ (mmHg)	35.1 ± 8.6	0.44	33.6 ± 5.2	0.034	37.2 ± 7.5
Alveolar dead space	0.29 ± 0.18	0.17	0.23 ± 0.12	0.17	0.19 ± 0.14
Ventilatory ratio	1.72 ± 0.69	0.77	1.76 ± 0.45	0.11	1.57 ± 0.47
Respiratory Mechanics					
Plateau pressure (cmH ₂ O)	19.5 ± 4.1	0.035	17.2 ± 3.8	0.49	16.6 ± 3.7
Driving pressure (cmH ₂ O)	13.9 ± 4.2	0.014	11.3 ± 3.7	0.64	11.7 ± 3.7
Compliance _{rs} (ml/cmH ₂ O)	39 ± 11.1	0.003	49.9 ± 15.4	0.97	50.1 ± 15.7
Hemodynamics					
Heart rate (bpm)	92.1 ± 20.6	0.008	79 ± 18	0.018	89.3 ± 16.5
Mean arterial pressure (mmHg)	80.2 ± 9.4	0.09	85 ± 12	0.06	79.7 ± 10.4
ScvO ₂ (%)	75.4 ± 9.25	0.52	73.9 ± 6.5	0.30	76.5 ± 9.5
(a-v) O ₂ difference (ml/dl)	1.9 ± 1.14	0.004	2.78 ± 0.78	0.19	2.37 ± 1.24
Venous admixture	0.6 ± 0.24	0.049	0.48 ± 0.15	0.51	0.44 ± 0.26
Haemoglobin (mg/dl)	10.4 ± 1.5	< 0.001	12 ± 1.5	< 0.001	10.1 ± 1.1
CT scan					
Lung weight (g)	1729 ± 705	0.35	1596 ± 385	0.12	1409 ± 538
Lung gas volume (ml)	930 ± 644	< 0.001	1670 ± 791	0.043	1301 ± 627
Hyperinflated tissue (g)	2.85 ± 7.68	0.08	7.68 ± 13	0.47	4.80 ± 18
Normally aerated tissue (g)	287 ± 154	< 0.001	475 ± 185	0.14	412 ± 150
Poorly aerated tissue (g)	479 ± 250	0.48	522 ± 196	0.07	426 ± 418
Non-aerated tissue (g)	960 ± 567	0.002	591 ± 293	0.8	566 ± 475

Gas exchange, respiratory mechanics, hemodynamics and CT scan variables measured in COVID-19-ARDS (CARDs, middle column) and the two historical matched cohorts (PaO₂/FiO₂-matched-ARDS, left column and Compliance-matched-ARDS, right column)

PaO₂ arterial partial pressure of oxygen, PAO₂ alveolar partial pressure of oxygen, A-aPO₂ alveolar-arterial oxygen partial pressure difference, SaO₂ hemoglobin saturation of the arterial blood, PaCO₂ arterial partial pressure of carbon dioxide, PETCO₂ end-tidal partial pressure of carbon dioxide, ScvO₂ hemoglobin saturation of the central venous blood, (a-v) O₂ difference arterial-venous difference of oxygen content

patients appears representative of the ARDS populations enrolled in pre-COVID ARDS clinical trials. The distribution of mild, moderate and severe ARDS (as measured at 5 cmH₂O of PEEP [26]) in COVID-19-ARDS and in our PaO₂/FiO₂-matched-ARDS subgroup was identical (Table 2) [1]. In contrast, the overall severity of Compliance-matched-ARDS patients was lower, as the prevalence of severe ARDS category was only 18.8% vs 68.7% in COVID-19-ARDS. The general clinical severity, as indicated by SAPSII, tended to be lower in COVID-19-ARDS

patients, compared to the two non-Covid ARDS populations, perhaps accounting for their shorter length of stay in the ICU.

Oxygenation, lung mechanics and the mechanism of hypoxemia

Differently from typical ARDS, where the decrease of PaO₂/FiO₂ ratio is associated with a decrease in Crs, in our COVID-19-ARDS population PaO₂/FiO₂ ratio and Crs were unrelated. This has also been found in a recent

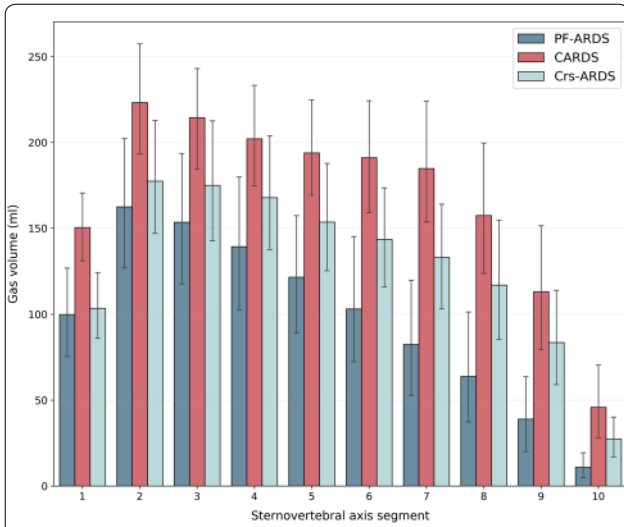


Fig. 2 Lung gas volume measured in the 10 equally spaced lung segments along the sterno-vertebral axis (level 1 = closest to the sternum, level 10 = closest to the vertebra). The gas volume of both the PaO₂/FiO₂-matched-ARDS (dark blue) and Compliance-matched-ARDS (light blue) was significantly different from COVID-19-ARDS (*p* < 0.001 and *p* = 0.043, respectively). Note that the gas volume was higher in COVID-19-ARDS, even compared to the Compliance-matched-ARDS. The extent of the differences is particularly evident in the most dependent lung regions, where the gas volume at each level was even more than double in COVID-19-ARDS than in PaO₂/FiO₂-matched-ARDS

larger study comparing typical ARDS with COVID-19-ARDS [8]. This contrasts with the decision taken in Berlin to exclude Crs from the ARDS definition as unnecessary, as it added no prognostic value to the PaO₂/FiO₂ ratio alone [10]. It is then possible that the mechanisms leading to hypoxemia are somehow different between COVID-19-ARDS and typical ARDS. Hypoxemia due to venous admixture [27] originates from two potential mechanisms: true right to left shunt (i.e., perfusion of non-aerated tissue) and/or low ventilation-perfusion (V_A/Q) ratio (perfusion of poorly ventilated lung regions). In typical ARDS, the primary component of venous admixture is right-to-left shunt. Accordingly, the greater the fraction of non-aerated tissue, the greater the venous admixture [28, 29]. In COVID-19-ARDS the venous admixture was unrelated to the non-aerated tissue fraction; indeed, it was very high even when the fraction of non-aerated tissue was very low (Fig. 3). This observation strongly suggests that the major component of the venous admixture in COVID-19-ARDS is ventilation-perfusion mismatch, rather than true right-to-left shunt. The important role of V_A/Q mismatch in COVID-19-ARDS is consistent with (but not entirely explained by) the reported high incidence of micro and macro thrombosis in this disease [11, 14, 30, 31] and with the importance of markers of immune-thrombosis (e.g., D-dimers) in the outcome of COVID-19-ARDS [8].

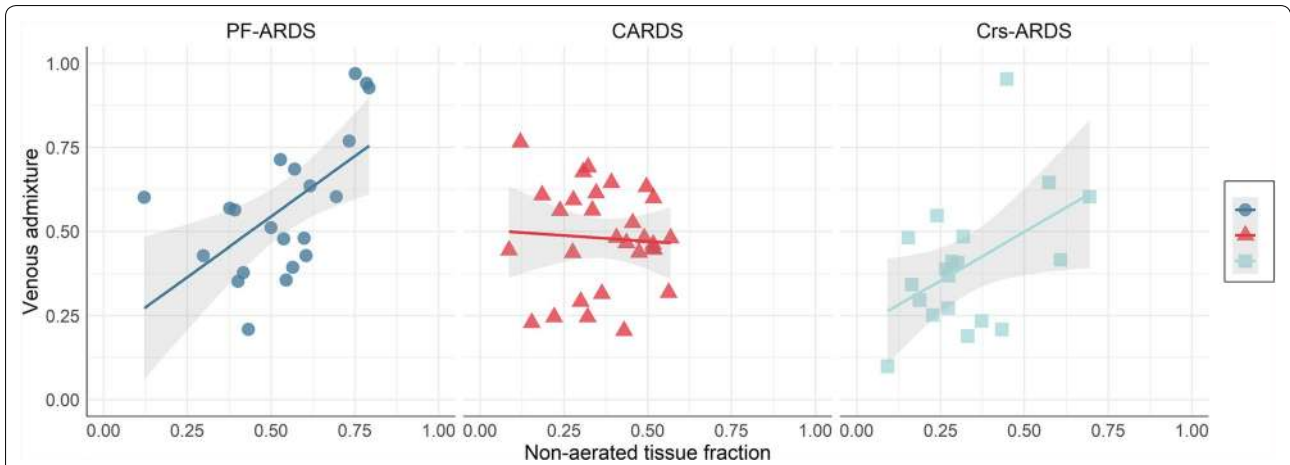


Fig. 3 Venous admixture as a function of the fraction of non-aerated tissue, in PaO₂/FiO₂-matched-ARDS (PF-ARDS, left panel), COVID-19-ARDS (CARDS, middle panel) and Compliance-matched-ARDS (Crs-ARDS, right panel). As shown, in PaO₂/FiO₂-matched-ARDS and Compliance-matched-ARDS, the venous admixture increases proportionally with similar slopes (0.83 and 0.89, respectively) with the increase fraction of non-aerated tissue, implying a coupling between the shunt fraction and the fraction of non-aerated tissue. In contrast, in COVID-19-ARDS, the two variables were uncoupled. The relationships followed the regression equations: PaO₂/FiO₂-matched-ARDS, venous admixture = 0.83 × fraction of non-aerated tissue + 0.14, *p* = 0.003, *R*² = 0.32 (22 observations). CARDS, venous admixture = - 0.07 × fraction of non-aerated tissue + 0.5, *p* = 0.75, *R*² = - 0.03 (29 observations). Crs-ARDS, venous admixture = 0.89 × fraction of non-aerated tissue + 0.13, *p* = 0.004, *R*² = 0.35 (19 observations). Missing data were due to the lack of central venous blood samples

Table 3 Gas exchange, respiratory mechanics and hemodynamic response to the PEEP increase (5–15 cmH₂O)

	PF-ARDS (n = 32)	p value	CARDS (n = 32)	p value	Crs-ARDS (n = 32)
Oxygenation					
Δ PaO ₂ (mmHg)	+ 35.2 ± 46.3	0.27	+ 24.9 ± 24.3	0.77	+ 23 ± 27.1
Δ PaO ₂ /FiO ₂ (mmHg)	+ 46.1 ± 51.2	0.25	+ 33.3 ± 35.8	0.27	+ 47.3 ± 60.6
Δ SaO ₂ (%)	+ 5 ± 4.6	0.84	+ 5.2 ± 5.6	0.10	+ 3.3 ± 3.3
CO₂ clearance					
Δ PaCO ₂ (mmHg)	− 0.78 ± 3.3	0.027	+ 1.29 ± 3.94	0.33	+ 0.33 ± 3.8
Δ EtCO ₂ (mmHg)	+ 1.5 ± 2.6	0.62	+ 1.9 ± 2.4	0.60	+ 1.44 ± 3.5
Δ Alveolar dead space	− 0.05 ± 0.08	0.10	− 0.016 ± 0.066	0.91	− 0.019 ± 0.086
Δ ventilatory ratio	− 0.02 ± 0.1	0.02	+ 0.07 ± 0.21	0.09	0 ± 0.14
Respiratory mechanics					
Δ plateau pressure (cmH ₂ O)	7.9 ± 3.2	0.002	+ 10.6 ± 2.9	0.29	+ 9.9 ± 2.6
Δ driving pressure (cmH ₂ O)	− 1 ± 3.3	0.016	+ 1 ± 2.6	0.25	+ 0.23 ± 2.7
Δ Crs (ml/cmH ₂ O)	+ 2.5 ± 8.4	0.02	− 4.1 ± 12.5	0.21	+ 0.28 ± 15.3
Hemodynamics					
Δ Heart rate (bpm)	− 10 ± 25	0.07	− 1 ± 7	0.45	− 2 ± 6
Δ Mean arterial pressure (bpm)	− 3.7 ± 8.1	0.12	− 0.1 ± 9.8	0.89	+ 0.3 ± 9.3
Δ SvO ₂ (%)	+ 2.9 ± 4.9	0.32	+ 4.4 ± 6.2	0.051	− 0.2 ± 8.7
Δ (a–v) O ₂ difference (ml/dl)	+ 0.38 ± 0.42	0.51	+ 0.49 ± 0.82	0.93	+ 0.52 ± 0.88
Δ venous admixture	− 0.12 ± 0.11	0.54	− 0.13 ± 0.11	0.88	− 0.14 ± 0.18

Changes of gas exchange, respiratory mechanics and hemodynamics increasing positive-end expiratory pressure from 5 to 15 cmH₂O measured in COVID-19-ARDS (CARDS, middle column) and the two historical matched cohorts (PaO₂/FiO₂-matched-ARDS, left column and Compliance-matched-ARDS, right column). The change of a variable (Δ) is calculated as the value at 15 cmH₂O—value at 5 cmH₂O

PaO₂ arterial partial pressure of oxygen, PAO₂ alveolar partial pressure of oxygen, A-aO₂ alveolar-arterial oxygen partial pressure difference, SaO₂ hemoglobin saturation of the arterial blood, PaCO₂ arterial partial pressure of carbon dioxide, PETCO₂ end-tidal partial pressure of carbon dioxide, ScvO₂ hemoglobin saturation of the central venous blood, (a–v) O₂ difference arterial–venous difference of oxygen content

Respiratory system compliance and lung gas volume

The relative importance of V_A/Q mismatching as opposed to right-to-left shunt in COVID-19-ARDS is consistent with its relatively higher lung gas volume, which correlates with the respiratory system compliance (see Figure E4). Moreover, the gas volume was remarkably higher in COVID-19-ARDS compared to PaO₂/FiO₂-matched-ARDS for each lung section along the gravitational axis, including the most dependent ones, which are almost gasless in typical ARDS (Fig. 2). Again, this difference, likely due to the vasocentric nature of COVID-19-ARDS (as compared to ‘gas space-centered’ nature of typical ARDS), is not entirely surprising. Unexpectedly, however, we found that Compliance-matched-ARDS patients had lower gas volume than did COVID-19-ARDS patients, despite having similar values of respiratory system mechanics. The interpretation of these findings is currently only speculative. However, it is tempting to hypothesize that the increased gas volume in COVID-19-ARDS is caused by newly formed emphysema-like functional regions that may develop as a consequence of the ischemic changes and diffuse micro thromboses described in autopsy findings [11, 14].

Response to PEEP

The improved oxygenation in our PaO₂/FiO₂-matched-ARDS patient cohort in response to the PEEP test was likely due recruitment. Indeed, these patients were more recruitable, as indicated by higher baseline non-aerated tissue mass in conjunction with a significant decrease of plateau pressure and an improvement of Crs when PEEP was raised. In contrast, Compliance-matched-ARDS and COVID-19-ARDS patients, with lower baseline non-aerated tissue mass, showed unaltered or worsened respiratory system mechanics and PaCO₂ in response to the PEEP test (Table 3). These findings suggest—in line with previous observations—[32, 33] that the primary mechanism of oxygenation improvement was a decrease/redistribution of blood flow away from airless zones rather than recruitment.

Atypical features of COVID-19-ARDS

Our data suggest that COVID-19-ARDS is an atypical subset of ARDS. We may then wonder why, for a given severity of hypoxemia, the Crs values of our COVID-19-ARDS patients appear higher than those reported by other authors [6, 34]. As the virus is the same worldwide, its manifestations everywhere should be more or less consistent. The differences observed among various

reports may depend on two main factors: the timing of the observations and the conditions of measurement. Indeed, COVID-19-ARDS evolves rather rapidly with time, as reflected by a CT scan appearance that shifts progressively from bilateral ground glass opacities to overt consolidations/collapse [35]. Crs changes accordingly [36]. It is not surprising that, with passing time, Crs may decrease to impressively low values. The conditions of measurement are also important. Most studies, such as the largest one yet published on COVID-19 pathophysiology [8], report Crs values measured under the prevailing “clinical conditions”. In all cohorts of our COVID-19-ARDS, PaO₂/FiO₂-matched-ARDS and Compliance-matched-ARDS populations, all measurements were performed at a standard PEEP of 5 cmH₂O. It is obvious that Crs measured at 10–15 cmH₂O of PEEP may lead to different values than those we report here.

Clinical implications

Our COVID-19-ARDS patients were studied 9.6 ± 4 days after the onset of symptoms and were compared with “early” historical ARDS patients (within 1 week from admission). Within this initial timeframe, the sharp physio-anatomic distinctions between non-COVID-ARDS and COVID-19-ARDS suggest the need to modify our standard practice of ARDS management for COVID-19 patients. Specifically, the dramatically greater gas volume and better compliance of COVID-19 lungs, when present, discourage interventions intended to further inflate the lungs. Indeed, for a similar marginal improvement of oxygenation in response to a PEEP increment, signs of overdistension became manifest in our COVID-19 patients. In contrast, respiratory mechanics improved and PaCO₂ decreased in the PaO₂/FiO₂-matched-ARDS cohort. Attempts to aggressively recruit the lung to improve O₂ exchange by applying higher than customary levels of mean airway pressure seem ill-advised during this early disease phase. We must stress, however, that COVID-19 pneumonia rapidly evolves with time. Consequently, the safest ventilatory strategy could well be different at different stages which range from initial modest ground-glass opacities with preserved Crs to an intermediate stage (as described in the present study), to a final stage characterized by extensive opacities, prevalent fibrosis, and very low Crs.

Limitations

These data are unique in documenting physiologic measurements and quantitative images under identical conditions in closely matched COVID-19-ARDS and non-COVID-ARDS patients. However, our study has several limitations: first, the limited size of our historical ARDS dataset. Second, patients were enrolled in a single

center, within a limited time frame of their illnesses. Earlier or later stages may present sharply different behaviors. In addition, we did not perform a second CT scan at 15 cmH₂O. Finally, a comprehensive set of hemodynamic data were not acquired, preventing full characterization of the mechanisms underlying the gas exchange variations we observed.

Conclusion

COVID-19-ARDS and non-COVID ARDS patients differ significantly in their radiological and physiological features, both in terms of the relationship between oxygenation and lung mechanics and their responses to PEEP. The different stages of the disease call for a rethinking of the traditional lung protective ventilation targets which take into account the peculiarities of this novel ARDS variant.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-020-06281-2>) contains supplementary material, which is available to authorized users.

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Author contributions

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Compliance with ethical standards

Conflicts of interest

The authors have no interests to disclose.

Ethics approval

Ethics Committee approval that allows physiological and CT study for all patients with severe respiratory failure admitted to our critical care unit (ethical committee numbers: 42937/2016 and 9890/2017).

Consent to participate

None.

Consent for publication

All authors have approved the manuscript.

Availability of data and material

Dataset available upon reasonable request.

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