COVID-19 ARDS Is Characterized by Increased Dead Space Ventilation Compared With Non-COVID ARDS

Michele Bertelli, Federica Fusina, Chiara Prezioso, Erika Cavallo, Niccolò Nencini, Serena Crisci, Francesca Tansini, Letizia Mazzuca Mari, Laureta Hoxha, Fabiana Lombardi, and Giuseppe Natalini

BACKGROUND: ARDS in patients with coronavirus disease 2019 (COVID-19) is characterized by microcirculatory alterations in the pulmonary vascular bed, which could increase dead-space ventilation more than in non-COVID-19 ARDS. We aimed to establish if dead-space ventilation is different in patients with COVID-19 ARDS when compared with patients with non-COVID-19 ARDS. METHODS: A total of 187 subjects with COVID-19 ARDS and 178 subjects with non-COVID-19 ARDS who were undergoing invasive mechanical ventilation were included in the study. The association between the ARDS types and dead-space ventilation, compliance of the respiratory system, subjects' characteristics, organ failures, and mechanical ventilation was evaluated by using data collected in the first 24 h of mechanical ventilation. RESULTS: Corrected minute ventilation ($\dot{V}_E$), a dead-space ventilation surrogate, was higher in the subjects with COVID-19 ARDS versus in those with non-COVID-19 ARDS (median [interquartile range] 12.6 [10.2-15.8] L/min vs 9.4 [7.5-11.6] L/min; $P < .001$). Increased corrected $\dot{V}_E$ was independently associated with COVID-19 ARDS (odds ratio 1.24, 95% CI 1.07-1.47; $P = .007$). The best compliance of the respiratory system, obtained after testing different PEEPs, was similar between the subjects with COVID-19 ARDS and the subjects with non-COVID-19 ARDS (mean ± SD 38 ± 11 mL/cm H_2O vs 37 ± 11 mL/cm H_2O, respectively; $P = .61$). The subjects with COVID-19 ARDS received higher median (interquartile range) PEEP (12 [10-14] cm H_2O vs 8 [5-9] cm H_2O; $P < .001$) and lower median (interquartile range) tidal volume (5.8 [5.5-6.3] mL/kg vs 6.6 [6.1-7.3] mL/kg; $P < .001$) than the subjects with non-COVID-19 ARDS, being these differences maintained at multivariable analysis. In the multivariable analysis, the subjects with COVID-19 ARDS showed a lower risk of anamnestic arterial hypertension (odds ratio 0.18, 95% CI 0.07-0.45; $P < .001$) and lower neurologic sequential organ failure assessment score (odds ratio 0.16, 95% CI 0.09-0.27; $P < .001$) than the subjects with non-COVID-19 ARDS. CONCLUSIONS: Indirect measurements of dead space were higher in subjects with COVID-19 ARDS compared with subjects with non-COVID-19 ARDS. The best compliance of the respiratory system was similar in both ARDS forms provided that different PEEPs were applied. A wide range of compliance is present in every ARDS type; therefore, the setting of mechanical ventilation should be individualized patient by patient and not based on the etiology of ARDS. *Key words: Dead space; compliance; positive end expiratory pressure; acute respiratory distress syndrome; severe acute respiratory syndrome coronavirus-2.* [Respir Care 2021;66(9):1406–1415. © 2021 Daedalus Enterprises]

Introduction

ARDS was originally described as a syndromic pattern that was the final common pathway of different diseases. Their shared features were severe hypoxemia refractory to oxygen therapy and low compliance of the respiratory system.[1] Despite ARDS being a pivotal clinical presentation in patients with severe coronavirus disease 2019 (COVID-19), the appropriateness of defining criteria of ARDS for patients with COVID-19 pneumonia was debated due to the high value of respiratory system compliance reported by some investigators.[2,3] A high ratio of dead

space (V_D) to tidal volume (V_T) (V_D/V_T) is perhaps more relevant than compliance in characterizing ARDS, being V_D/V_T, the pathophysiologic measurement with the stronger association with outcome in subjects with ARDS.[4-6] Patients with COVID-19 present with typical abnormalities of the pulmonary circulation, such as small pulmonary vessel microangiopathy with thrombosis and hemorrhage compared with other forms of ARDS, including other viral lung infections.[7-11]

The microthrombotic lesions in pulmonary circulation could further worsen V_D ventilation in patients with COVID-19 ARDS when compared with patients with ARDS from other diseases. Recently, the association between V_D ventilation and mortality has also been confirmed in patients with COVID-19 ARDS[12]; nonetheless, the hypothesis that V_D ventilation is higher in patients with ARDS from COVID-19 than in patients with ARDS due to other diseases needs to be confirmed. The aim of our study was to establish if V_D ventilation was different in ARDS secondary to COVID-19 when compared with ARDS from other diseases. We also aimed to identify if any differences between COVID-19 ARDS and non-COVID-19 ARDS in terms of compliance of the respiratory system, subject characteristics, organ failures, and mechanical ventilation variables were present.

QUICK LOOK

Current knowledge

ARDS in patients with coronavirus disease 2019 (COVID-19) is characterized by microcirculatory alterations in the pulmonary vascular bed. These alterations could cause an increase in dead-space ventilation in patients with COVID-19 ARDS when compared with patients with non-COVID ARDS.

What this paper contributes to our knowledge

Higher dead-space ventilation was the distinguishing pathophysiologic characteristic of ARDS in the subjects with COVID-19 compared with non-COVID ARDS. The same wide range of compliance seems to be present in every ARDS type; therefore, the setting of mechanical ventilation should be individualized, and not based on the etiology of ARDS.

Methods

This retrospective cohort study with prospectively collected data was performed at the Poliambulanza Foundation Hospital of Brescia in Lombardy, Italy. The referral ethics committee (Comitato Etico di Brescia) approved the study (NP4209). All consecutive adult patients (ie, ≥18 y old) admitted to the ICU from January 1, 2015, to May 31, 2020, with a diagnosis of ARDS (according to the Berlin definition criteria[13]) were screened by using the electronic clinical database. Patients were excluded from the analysis if (a) the criteria for ARDS diagnosis were not fulfilled or (b) they did not undergo invasive mechanical ventilation.

Two groups of subjects were created: (1) subjects with ARDS attributable to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection (COVID-19 ARDS); subjects were included in this group if respiratory symptoms started after February 18, 2020 (the day of the first reported case of SARS-CoV 2 infection in Italy) and they had a positive real-time polymerase chain reaction test result for SARS-CoV-2 on biologic samples; and (2) subjects with ARDS without SARS-CoV 2 infection (non-COVID-19 ARDS). Subjects were included in this second group if their ICU admission occurred before February 18 2020. A real-time polymerase chain reaction test for SARS-CoV-2 was not performed before this date. Patients with an ARDS diagnosis made after February 18, 2020, but with negative real-time polymerase chain reaction test results for SARS-CoV-2 were excluded from the analysis due to the uncertainty of the cause of the ARDS.

Demographic, clinical, and laboratory data, and outcomes were extracted from the electronic medical chart of the enrolled subjects. All measurements were taken from data collected during the first 24 h of invasive mechanical ventilation and the worst values (ie, the value farther from the normal range) after the setting of the best PEEP (see protocol of mechanical ventilation section) were used for the analyses. No measurements taken with the subjects in prone positioning were used for the analyses. All estimates of V_D ventilation had been taken while the subjects were in a steady-state condition.

Drs Bertelli, Fusina, Prezioso, Cavallo, Nencini, Crisci, Tansini, Mari, Hoxha, Lombardi, and Natalini are affiliated with the Department of Anesthesia and Intensive Care, Fondazione Poliambulanza Hospital, Brescia, Italy. Drs Prezioso, Cavallo, Nencini, Crisci, and Mari are affiliated with the Department of Anesthesiology and Intensive Care Medicine, Catholic University of The Sacred Heart, Rome, Italy. Dr Tansini is affiliated with the Department of Anesthesia and Intensive Care, University of Insubria, Varese, Lombardia, Italy.

The authors have disclosed no conflicts of interest.

Supplementary material related to this paper is available at http://www.rcjournal.com.

Correspondence: Federica Fusina MD, Department of Anesthesia, Intensive Care and Pain Medicine, via Bissolati, 57, Brescia, 25124, Italy. E-mail:f.fusina@gmail.com.

DOI: 10.4187/respcare.08786

Protocol of Mechanical Ventilation

Mechanical ventilation was applied according to our institutional ventilation protocol, which has been in use since 2012. A starting V_T of 6 mL/kg of ideal body weight[14] is set, and the PEEP associated with the lowest driving pressure (best PEEP) is chosen. This is the PEEP that guarantees the highest compliance. PEEP is progressively increased by 2 cm H_2O at a time, starting from a low value (0-4 cm H_2O). For each PEEP, airway inspiratory plateau pressure (Pplat) is measured with an end-inspiratory hold maneuver, and total PEEP is measured as the Pplat after an end-expiratory hold maneuver. Driving pressure (the pressure needed to inflate the V_T) is defined as Pplat – total PEEP. In the case of >1 PEEP associated with the same (lowest) driving pressure, the lowest PEEP is preferred if the oxygenation goal can be obtained with a $F_{IO_2} < 0.65$.

VT is progressively reduced (down to a minimum of 4 mL/kg) in the case of the impossibility to maintain a driving pressure of <15 cm H_2O or if an upward concavity of the airway pressure is observed during volume control, constant flow inflation (which suggests a stress index > 1[15]). Breathing frequency is set to obtain, when possible, a pH in the range of 7.30-7.40. However, a frequency >30 breaths/min is strongly discouraged. Hypercapnia and respiratory acidosis are tolerated to keep the driving pressure < 15 cm H_2O and the frequency < 30 breaths/min in the absence of hypotension refractory to vasopressor agents, low cardiac output with severe acute cor pulmonale, acute myocardial infarction, and/or intracranial pressure > 20 mm Hg. Also, F_{IO_2} is set with S_{pO_2} 90–95% and/or P_{aO_2} > 60–80 mm Hg as a target. During the period of low V_T protective ventilation neuromuscular blocking agents were used if patient-ventilator asynchronies were detected. The subjects usually were maintained in a semirecumbent position (20°-30°) and prone position was performed in the subjects with $P_{aO_2}/F_{IO_2} < 150$ mm Hg, alternating 16 h of pronation with 6 h in the supine/semirecumbent position (up to 30° trunk elevation). A heat-and-moisture exchanger (Dar Adult-Pediatric Electrostatic Filter Small, Covidien, Mansfield, Massachusetts) was used in all the subjects from the beginning of invasive mechanical ventilation to the beginning of weaning.

Measurements and Calculations

The Sequential Organ Failure Assessment (SOFA)[16] score during the first 24 h and the Simplified Acute Physiology Score (SAPS) II[17] were calculated. Compliance of the respiratory system was the ratio between V_T and driving pressure. The main estimate of V_D ventilation was performed with corrected $\dot{V}_E$.[13,18] Corrected $\dot{V}_E$ was calculated as $(\dot{V}_E \times P_{aCO_2})/40$ mm Hg, where 40 mm Hg is considered the physiologic value of P_{aCO_2}. V_D was also estimated with the ventilatory ratio and calculated V_D/V_T. The ventilatory ratio was calculated as (corrected $\dot{V}_E \times P_{aCO_2}$)/(ideal body weight × 100 mL/kg × 37.5 mm Hg), where 37.5 mm Hg is assumed to be the P_{aCO_2} during the ideal $\dot{V}_E$.[19] Calculated V_D/V_T was obtained from the Harris-Benedict formula for the resting energy expenditure and Weir estimate of the carbon dioxide production.[20]

The net V_T of instrumental V_D was calculated as the difference between V_T and instrumental V_D. Instrumental V_D was calculated as the sum of the internal volume of the heat-and-moisture exchanger (51 mL), of the catheter mount (Covidien Dar Catheter Mount with CO_2 Sampling Port; 22 mL) and of the endotracheal tube (ranging from 14 to 17 mL, depending on the size).[21] Corrected $\dot{V}_E$, V_D/V_T, and ventilatory ratio were also calculated by using net V_T of instrumental V_D instead of V_T.

Study Outcomes

The primary study end point was to assess if V_D ventilation (mainly assessed with corrected $\dot{V}_E$) was higher in the subjects with COVID-19 ARDS compared with those with non-COVID-19 ARDS when adjusted for other variables. The secondary outcome was to compare respiratory system compliance, subject characteristics, organ failures, and mechanical ventilation variables in the subjects with COVID-19 ARDS and those with non-COVID-19 ARDS.

Statistical Analysis

We planned to analyze the independent association between V_D ventilation (as estimated by corrected V_E) and the type of ARDS (COVID-19 ARDS or non-COVID-19 ARDS). We a priori decided to assess the following variables as possible covariates: compliance of the respiratory system, age, sex, body mass index, history of diabetes mellitus, history of arterial hypertension, and organ dysfunctions as assessed by the 6 fields of the SOFA score, PEEP, V_T/kg of ideal body weight, breathing frequency, airway Pplat, driving pressure. P_{aO_2}/F_{IO_2} and P_{aCO_2} were excluded from multivariable analysis because they were already included in respiratory SOFA score and corrected $\dot{V}_E$ calculation, respectively.

We estimated that 170 subjects with COVID-19 ARDS were needed to include all a priori planned explanatory variables in the logistic regression analysis, that is, 10 events for each predictor variable.[22] Variables were described with mean ± SD or median and interquartile range, as appropriate, whereas factor variables were described as count (%). A comparison of variables between the COVID-19 ARDS and the non-COVID-19 ARDS cohorts was performed with the *t* test for numeric normally distributed variables, Wilcoxon-Mann-Whitney test for ordinal and numerical not-normally distributed variables, and the Fisher exact test for nominal variables. The explanatory variables were

included in the multivariable model if they reached statistical significance at the bivariate analysis ($P < .05$). Residual multicollinearity in the regression models was assessed by using the variance inflation factor. Variables with a variance inflation factor > 5 were removed one by one from the model, beginning from the covariate with the highest variance inflation factor.

The association between V_D and COVID-19 ARDS was reassessed by substituting the corrected $\dot{V}_E$ with V_D/V_T and the ventilatory ratio. The analysis was also repeated, substituting respiratory SOFA with continuous P_{aO_2}/F_{IO_2}. A sensitivity analysis was conducted by using the V_T measurement with the exclusion of instrumental V_D. We compared V_D estimates (corrected $\dot{V}_E$, ventilatory ratio, estimated V_D/V_T) between COVID-19 ARDS and ARDS due to confirmed bacterial pneumonia (47 subjects), ARDS due to pneumonia without bacterial evidence on microbiologic examination (62 subjects), ARDS from trauma or abdominal disease (43 subjects), and ARDS from causes different from all of the above (26 subjects). The association between V_D estimates and the cause of ARDS (COVID-19, confirmed bacterial pneumonia, pneumonia without bacterial evidence on microbiologic examination, trauma or abdominal disease, other causes) was conducted with linear models by using COVID-19 ARDS as the reference level. $P < .05$ was considered significant. Statistical analyses were performed with R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

We included in the study 187 subjects with COVID-19 ARDS and 178 subjects with non-COVID-19 ARDS (the flow diagram is shown in Fig. 1). COVID-19 ARDS and non-COVID-19 ARDS differed for most of the analyzed variables, as shown in Table 1. Male sex was more frequent in the subjects with COVID-19 ARDS, who were also younger and had a higher body mass index than did the subjects with non-COVID-19 ARDS. A history of diabetes mellitus and arterial hypertension was less frequent in the subjects with COVID-19 ARDS than in those with non-COVID-19 ARDS. At ICU admission, respiratory failure was the only organ dysfunction that was more severe in the subjects with COVID-19 ARDS, whereas cardiovascular, neurologic, and coagulative SOFA scores were worse in the subjects with non-COVID-19 ARDS.

Despite the lower number of organ dysfunctions, mortality was higher in the subjects with COVID-19 ARDS when compared with the subjects with non-COVID-19 ARDS. All estimates of V_D (corrected $\dot{V}_E$, V_D/V_T, ventilatory ratio) were higher in the subjects with COVID-19 ARDS than in the subjects with non-COVID-19 ARDS (Table 2). The density distribution of corrected $\dot{V}_E$ in the subjects with COVID-19 ARDS and the subjects with non-COVID-19 ARDS is shown in Figure 2. Results did not vary when substituting respiratory SOFA with continuous P_{aO_2}/F_{IO_2} (see the supplementary materials at http://www.rcjournal.com).

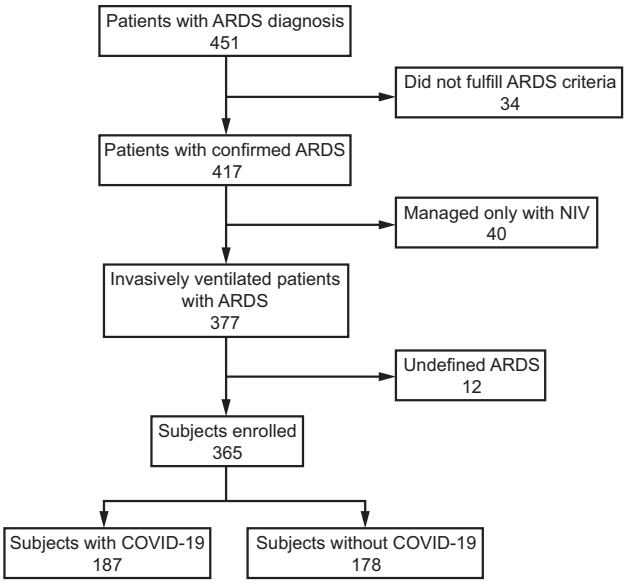

Fig. 1. Flow chart. NIV = noninvasive ventilation.

Mechanical ventilation was differently set in the subjects with COVID-19 ARDS and those with non-COVID-19 ARDS (Table 2): the subjects with COVID-19 ARDS had a lower V_T, higher breathing frequency, higher PEEP (Fig. 3) and higher F_{IO_2} than did the subjects with non-COVID-19 ARDS. With this different setting, compliance was similar in both groups (Fig. 4), as well as driving pressure and P_{aO_2}/F_{IO_2}. Applied PEEP did not correlate with either body mass index or with corrected $\dot{V}_E$ (Figs. 5 and 6). Multivariable analysis (Table 3) showed that increased corrected $\dot{V}_E$ was independently associated with COVID-19 ARDS. The association between V_D ventilation and COVID-19 was maintained when assessed by other indirect methods, such as the estimated V_D/V_T and the ventilatory ratio: odds ratio 1.06, 95% CI 1.01-1.12 ($P = .02$) and odds ratio 3.22, 95% CI 1.29-8.73 ($P = .02$) for V_D/V_T and ventilatory ratio, respectively. With the protocol of mechanical ventilation used in our subjects, lower VT and higher PEEP were independently associated with COVID-19 ARDS. When weighted for other variables, the subjects with COVID-19 ARDS had a lower risk of anamnestic arterial hypertension and neurologic dysfunction at ICU admission than did the subjects with non-COVID-19 ARDS.

Corrected $\dot{V}_E$, V_D/V_T, and the ventilatory ratio, when calculated by using net V_T of the instrumental V_D instead of V_T, were lower than the ones calculated with V_T and remained higher in the subjects with COVID-19 ARDS

Table 1. Subject Characteristics and Outcomes

	COVID-19 ARDS ($n = 187$)	Non–COVID-19 ARDS ($n = 178$)	P
Male, *n* (%)	146 (78)	115 (65)	.005
Age, median (IQR) y	67 (60–71)	71 (62–79)	.001
Body mass index, median (IQR) kg/m^2	28 (25–31)	25 (22–29)	<.001
Arterial hypertension, *n* (%)	41 (21.9)	107 (60.1)	<.001
Diabetes mellitus, *n* (%)	23 (12.3)	43 (24.2)	.004
SOFA scores, median (IQR)			
Respiratory	4.0 (3.0–4.0)	3.0 (3.0–4.0)	<.001
Coagulation	0 (0–0)	0. (0.–1.0)	<.001
Liver	0 (0–0)	0 (0–0.8)	.51
Cardiovascular	1.0 (1.0–4.0)	3.0 (1.0–4.0)	.007
Neurologic	0 (0–0)	2.0 (0–2.0)	<.001
Renal	0 (0–1.0)	0 (0–1.0)	.38
SAPS II, median (IQR)	37 (32–44)	48 (40–55)	<.001
ICU mortality, *n* (%)	94 (51.4)	64 (36.0)	.004
Hospital mortality, *n* (%)	96 (51.3)	70 (39.3)	.027

COVID-19 = coronavirus disease 2019
IQR = interquartile range
SOFA = Sequential Organ Failure Assessment
SAPS = Simplified Acute Physiology Score

Table 2. Mechanical Ventilation and Respiratory Physiology Characteristics

	COVID-19 ARDS ($n = 187$)	Non–COVID-19 ARDS ($n = 178$)	P
Corrected $\dot{V}_E$, median (IQR) L/min	12.6 (10.2–15.8)	9.4 (7.5–11.6)	<.001
V_D/V_T, median (IQR)	0.68 (0.59–0.74)	0.62 (0.52–0.70)	<.001
Ventilatory ratio, median (IQR)	2.02 (1.62–2.58)	1.62 (1.28–2.02)	<.001
V_T per kg of ideal body weight, median (IQR) mL/kg	5.8 (5.5–6.3)	6.6 (6.1–7.3)	<.001
Breathing frequency, mean ± SD breaths/min	23 ± 3	21 ± 5	<.001
PEEP, median (IQR) cm H_2O	12 (10-14)	8 (5-9)	<.001
Plateau pressure, mean ± SD cm H_2O	20 ± 4	23 ± 4	<.001
F_{IO_2}, mean ± SD	0.66 ± 0.17	0.61 ± 0.19	.003
Driving pressure, mean ± SD cm H_2O	11 ± 3	12 ± 3	.10
Compliance, mean ± SD mL/cm H_2O	38 ± 11	37 ± 11	.61
P_{aO_2}/F_{IO_2}, median (IQR)	131 (104-157)	134 (97-184)	.43
pH, mean ± SD	7.28 ± 0.11	7.34 ± 0.14	<.001
P_{aCO_2}, mean ± SD mm Hg	58 ± 15	46 ± 12	<.001

COVID-19 ARDS = subjects with ARDS secondary to severe acute respiratory syndrome coronavirus-2 infection
non–COVID-19 ARDS = subjects with ARDS not secondary to severe acute respiratory syndrome coronavirus-2 infection
$\dot{V}_E$ = minute ventilation
IQR = interquartile range
V_D/V_T = physiologic dead space fraction
V_D = dead space
V_T = tidal volume

than in the subjects with non-COVID-19 ARDS. The sensitivity analysis when using net V_T of the instrumental V_D confirmed the results of the primary analysis. The corrected $\dot{V}_E$ was higher in the subjects with COVID-19 ARDS than in the subjects with ARDS from all other causes (confirmed bacterial pneumonia, pneumonia without bacterial evidence on microbiologic examination, trauma or abdominal disease, causes different from all the above). This is also true for the ventilatory ratio and estimated V_D/V_T (see the supplementary materials at http://www.rcjournal.com).

Discussion

Our findings showed that higher V_D ventilation is the distinguishing pathophysiologic characteristic of COVID-

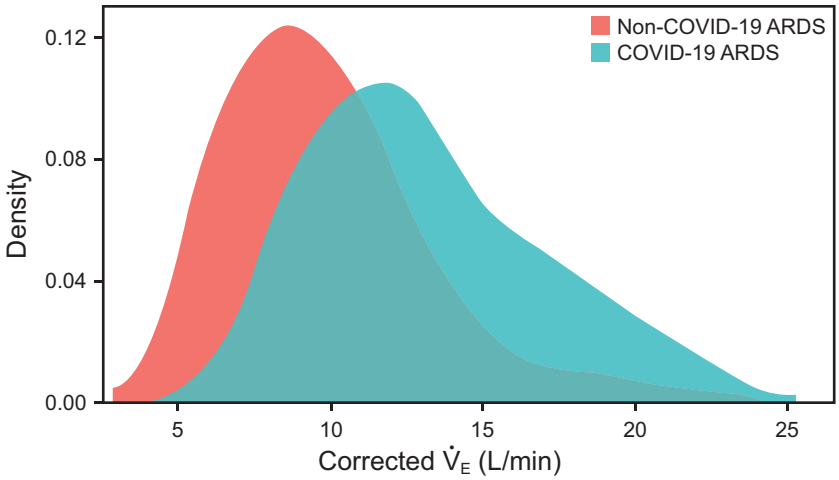

Fig. 2. Density distribution of corrected minute ventilation (V_E) in subjects with coronavirus disease 2019 (COVID-19) ARDS and non–COVID-19 ARDS.

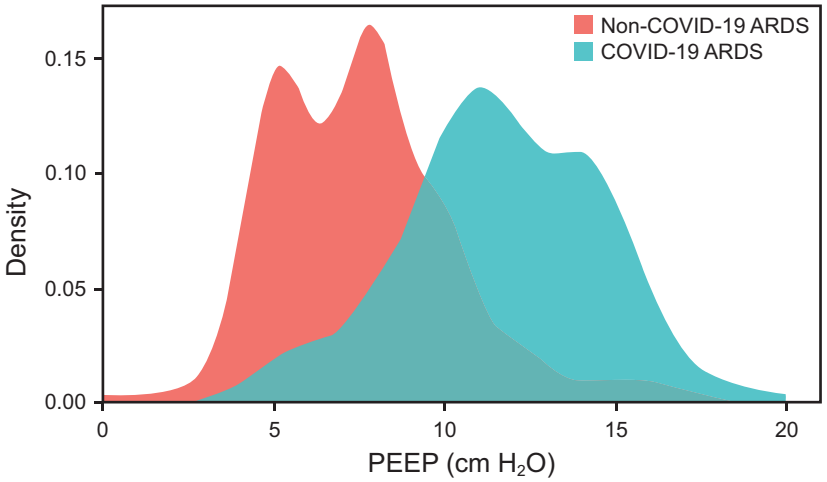

Fig. 3. Density distribution of PEEP in the subjects with coronavirus disease 2019 (COVID-19) ARDS and the subjects with non–COVID-19 ARDS.

19 ARDS compared with non-COVID-19 ARDS. This is true even when comparing V_D estimates between the subjects with COVID-19 ARDS and the subgroups of non-COVID-19 ARDS with different etiologies. However, the best compliance of the respiratory system was similar between the 2 kinds of ARDS assessed in the study. The increase of V_D ventilation in COVID-19 was consistent with the peculiar alterations in lung parenchyma found in this disease. Along with the presence of alveolar infiltrates, COVID-19 ARDS is characterized by a unique pattern of increased thrombosis in small pulmonary vessels.[8-11,23] This is the pathophysiologic basis for the increased V_D ventilation, as supported by the parallel increase of D-dimer concentration and the ventilatory ratio.[7]

The corrected $\dot{V}_E$, ventilatory ratio, and estimated V_D/V_T include P_{aCO_2} instead of alveolar carbon dioxide partial pressure P_{ACO_2}) (ie, on the Enghoff modification of the V_D equation proposed by Bohr) and, therefore, are sensitive to intrapulmonary shunt, diffusion impairment, and alveolar ventilation-perfusion ratio heterogeneity.[24] The ability to encompass in itself all the processes that impair lung function makes the corrected $\dot{V}_E$, ventilatory ratio, and V_D/V_T reliable tools for severity stratification and outcome prediction in patients with ARDS.[4-6] The corrected $\dot{V}_E$ has the main advantage of being simpler to calculate at the bedside than the ventilatory ratio and V_D/V_T. We are confident that our results on V_D ventilation can be generalizable to other patients with ARDS because the ventilatory ratio shown in our article is similar to what was previously observed. In particular, the observed average ventilatory ratio in subjects

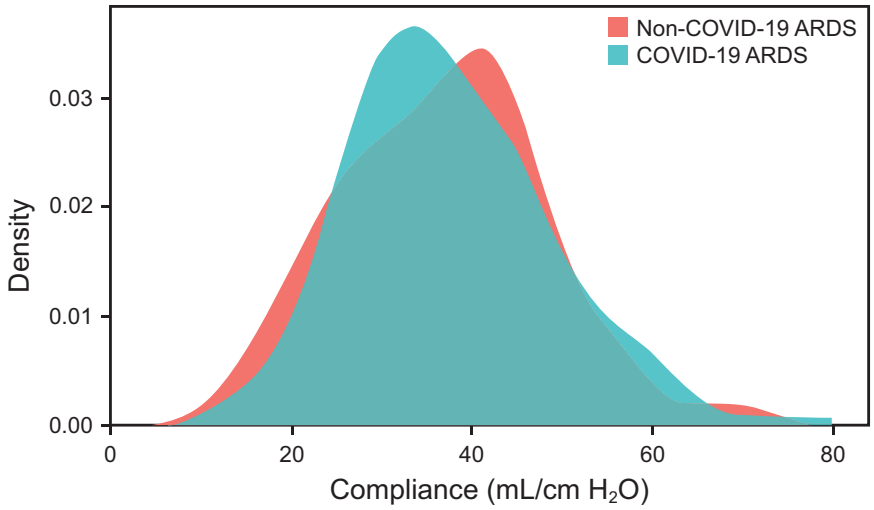

Fig. 4. Density distribution of compliance of respiratory system in the subjects with coronavirus disease 2019 (COVID-19) ARDS and non–COVID-19 ARDS.

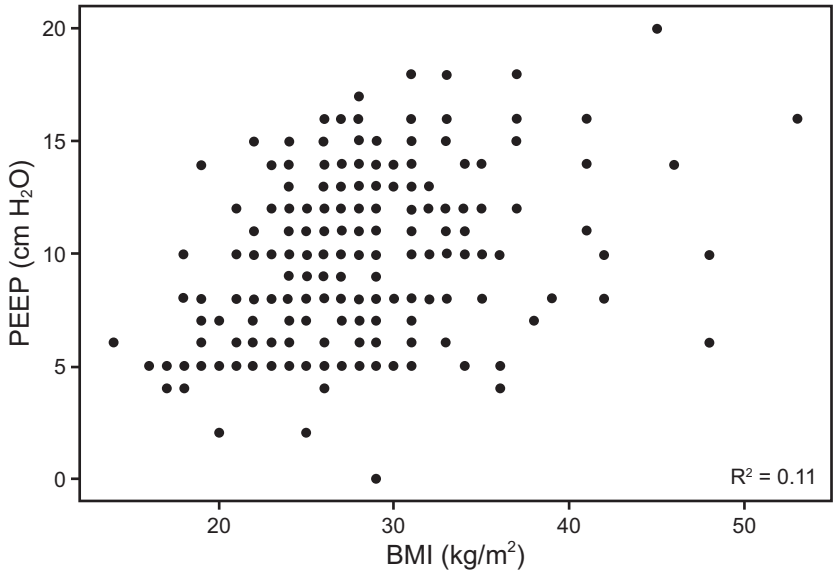

Fig. 5. Relationship between PEEP and body mass index (BMI).

with non-COVID-19 ARDS was in the range of 1.47-1.9[19,25] and, in subjects with COVID-19 hypercapnic, it ranged from 2.08 to 2.1.[9,23]

The V_D ventilation is strongly affected by the instrumental V_D, mainly during protective ventilation.[21] Instrumental V_D was similar between our subjects with non-COVID-19 ARDS and those with COVID-19 ARDS because the same heat-and-moisture exchanger model has been in use in our ICU for the past 20 years, and our mechanical ventilation protocol recommends its use from the beginning of invasive mechanical ventilation to the start of weaning. Therefore, the association between V_D ventilation estimates and non-COVID-19 ARDS/COVID-19 ARDS condition should not be affected by instrumental V_D. The corrected $\dot{V}_E$, V_D/V_T, and ventilatory ratio calculated with net V_T of the instrumental V_D were ~20% lower than the ones obtained when using V_T. The calculations with net V_T of the instrumental V_D could be useful to better evaluate our data and to compare them with data obtained in other settings, where different instrumental V_D might be present.

The average compliance in patients with non-COVID-19 ARDS has been estimated to be 38 mL/cm H_2O,[26] but a wide distribution has been reported.[13] Previous studies in subjects with COVID-19 reported a wide range of values of compliance, ranging from 29 to 49 mL/cm H_2O.[7,27-29] The mean ± SD compliance of the respiratory system reported

in our subjects with COVID-19 ARDS and in those with non-COVID-19 ARDS was similar: 38 ± 11 mL/H_2O versus 37 ± 12 mL/H_2O, respectively (Table 2 and Fig. 4) and did not differ from what was previously reported.[7,27-29] Different phenotypes of ARDS with low and high compliance have been advocated[29] but analysis of our data confirmed that they characterize all ARDS types and do not represent a specific feature of COVID-19.

It should be considered that, in clinical studies, compliance is usually calculated when applying PEEP, it, nonetheless, is well known that, in patients with ARDS, this value is often higher than compliance without PEEP.[30-32] Compliance related to the aerated lung is the so-called starting compliance, which is measured without PEEP.[32] Therefore, if compliance is measured with PEEP, then compliance should not be considered as a marker of severity of the pulmonary disease but as an effect of PEEP on the mechanical properties of the respiratory system. This is particularly true when PEEP is applied to minimize driving pressure and hence to optimize compliance.[33] Therefore, analysis of our data supported the idea that optimized compliance is similar in COVID-19 ARDS and non-COVID-19 ARDS, and, from this point of view, PEEP and not compliance could be considered as an index of the reduction of functional residual capacity and aerated volume.

Table 3. Multivariable Analysis: Variables Independently Associated With COVID-19 ARDS

Variable	Adjusted OR (95% CI)	*P*
Corrected $\dot{V}_E$, L/min	1.24 (1.07–1.47)	.007
Age, y	0.98 (0.95–1.02)	.32
Body mass index, kg/m^2	1.10 (1.00–1.22)	.064
Respiratory SOFA	1.43 (0.78–2.72)	.26
Coagulation SOFA	0.73 (0.41–1.26)	.27
Cardiovascular SOFA	0.86 (0.65–1.13)	.28
Neurologic SOFA	0.16 (0.09–0.27)	<.001
Sex, male	0.67 (0.23–1.90)	.45
Arterial hypertension	0.18 (0.07–0.45)	<.001
Diabetes mellitus	1.24 (0.41–3.85)	.71
V_T per kg of IBM, mL/kg	0.48 (0.27–0.81)	.009
Breathing frequency, breaths/min	0.99 (0.85–1.15)	.88
PEEP, cm H_2O	1.48 (1.27–1.77)	< .001

COVID-19 = coronavirus disease 2019
$\dot{V}_E$ = minute ventilation
SOFA = Sequential Organ Failure Assessment
V_T = tidal volume
IBM = ideal body weight

PEEP set to reduce driving pressure was not correlated to body mass index (Fig. 5), which suggested that the role of PEEP was not simply to counteract the effects of obesity on respiratory mechanics and gas exchange function. Moreover, the lack of a relationship between PEEP and corrected $\dot{V}_E$ supports the idea that our approach to PEEP titration should not be associated with an increase in V_D if high PEEP values are required (Fig. 6). Our findings showed that some variables frequently associated with COVID-19 ARDS, and sometimes presented as characteristic of this disease (eg, male sex, arterial hypertension, and diabetes mellitus[34-38]) have the same or a lower risk to be detected in COVID-19 ARDS compared with non-COVID-19 ARDS.

The present study had 3 main limitations. First, the results of the analysis deserve further confirmation because of the retrospective design of the study, despite the data being prospectively collected. Second, this was a single-center study, so the results are related to the context in

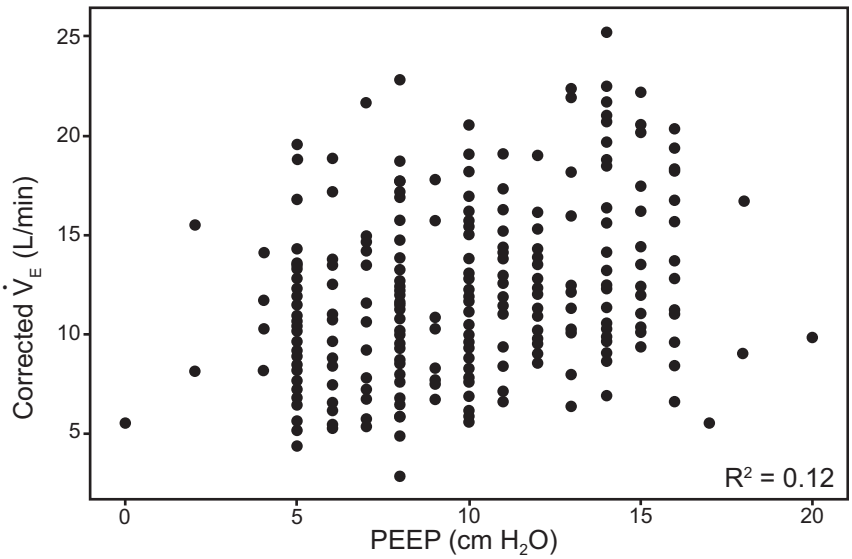

Fig. 6. Relationship between corrected minute ventilation ($\dot{V}_E$) and PEEP.

which data were collected. Our analysis could have low relevance for ICUs with different ventilatory strategies. Third, the matching of matching subjects with COVID-19 ARDS and subjects with non-COVID-19 ARDS could be troublesome. We chose to match the 2 cohorts by the need for invasive mechanical ventilation. This approach left a substantial heterogeneity between the groups, and the independent association with the main outcome (V_D ventilation) was assessed with a multivariable analysis to account for known confounders. It has been shown that multivariable analysis gives results that are similar to propensity score stratification.[39,40]

For these reasons, we are confident that our analysis can reliably support the main study finding that V_D ventilation was higher in the subjects with COVID-19 ARDS than in the subjects with non-COVID-19 ARDS, which also has a strong pathophysiologic basis on the ventilation-perfusion ratio derangement due to microvascular pulmonary thrombosis peculiar to COVID-19. In addition, our results are not applicable to patients with ARDS who did not need invasive mechanical ventilation, who were excluded from the analysis. However, it can also be possible that some patients with mild ARDS were excluded from the analysis because they are often not diagnosed as having ARDS in the medical record.[18] This bias toward only the most severe forms of ARDS is supported by the 39% mortality observed in our non-COVID-19 ARDS population.

Conclusions

Indirect measurements of VD were higher in the subjects with COVID-19 ARDS compared with the subjects with non-COVID-19 ARDS. The best compliance of the respiratory system was similar in both ARDS forms provided that different PEEPs were applied. The same wide range of compliance seems to be present in every ARDS type; therefore, the setting of mechanical ventilation should be individualized, patient by patient, and not based on the etiology of ARDS.

ACKNOWLEDGMENTS

The authors thank the clinical staff who treated the patients at Poliambulanza Foundation Hospital. We thank Dr Marco Marri for helping with data collection.

REFERENCES

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet 1967;2(7511):319-323.
2. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care 2020;24(1):154.
3. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med 2020;201(10):1299-1300.
4. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet J-F, Eisner MD, Matthay MA. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med 2002;346 (17):1281-1286.
5. Cepkova M, Kapur V, Ren X, Quinn T, Zhuo H, Foster E, et al. Pulmonary dead space fraction and pulmonary artery systolic pressure as early predictors of clinical outcome in acute lung injury. Chest 2007;132(3):836-842.
6. Kallet RH, Zhuo H, Liu KD, Calfee CS, Matthay MA; the National Heart Lung and Blood Institute ARDS Network Investigators. The association between physiologic dead-space fraction and mortality in subjects with ARDS enrolled in a prospective multi-center clinical trial. Respir Care 2014;59(11):1611-1618.
7. Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med 2020;8(12):1201-1208.
8. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383(2):120-128.
9. Schenck EJ, Hoffman K, Goyal P, Choi J, Torres L, Rajwani K, et al. Respiratory mechanics and gas exchange in COVID-19-associated respiratory failure. Ann Am Thorac Soc 2020;17(9):1158-1161.
10. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol 2020;7(6): e438-e440.
11. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol 2020;2(7):e437-e445.
12. Fusina F, Albani F, Bertelli M, Cavallo E, Crisci S, Caserta R, et al. Corrected minute ventilation is associated with mortality in ARDS caused by COVID-19. Respir Care 2021;66(4):619-625. [Epub ahead of print] doi: 10.4187/respcare.08314.
13. ARDS Definition Task Force; Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307(23):2526-2533.
14. Acute Respiratory Distress Syndrome Network; Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342(18):1301-1308.
15. Terragni PP, Filippini C, Slutsky AS, Birocco A, Tenaglia T, Grasso S, et al. Accuracy of plateau pressure and stress index to identify injurious ventilation in patients with acute respiratory distress syndrome. Anesthesiology 2013;119(4):880-889.
16. Vincent JL, Moreno RP, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22 (7):707-710.
17. Le Gall J, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270(24):2957-2963.
18. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al; LUNG SAFE Investigators, ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315 (8):788-800.
19. Sinha P, Calfee CS, Beitler JR, Soni N, Ho K, Matthay MA, Kallet RH. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. Am J Respir Crit Care Med 2019;199(3):333-341.

20. Beitler JR, Thompson BT, Matthay MA, Talmor D, Liu KD, Zhuo H, et al. Estimating dead-space fraction for secondary analyses of acute respiratory distress syndrome clinical trials. Crit Care Med 2015;43 (5):1026-1035.
21. Lellouche F, Delorme M, Brochard L. Impact of respiratory rate and dead space in the current era of lung protective mechanical ventilation. Chest 2020;158(1):45-47.
22. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49(12):1373-1379.
23. Liu X, Liu X, Xu Y, Xu Z, Huang Y, Chen S, et al. Ventilatory ratio in hypercapnic mechanically ventilated patients with COVID-19-associated acute respiratory distress syndrome. Am J Respir Crit Care Med 2020;201(10):1297-1299.
24. Robertson HT. Dead space: the physiology of wasted ventilation. Eur Respir J 2015;45(6):1704-1716.
25. Sinha P, Singh S, Hardman JG, Bersten AD, Soni N; Australia and New Zealand Intensive Care Society Clinical Trials Group. Evaluation of the physiological properties of ventilatory ratio in a computational cardiopulmonary model and its clinical application in an acute respiratory distress syndrome population. Br J Anaesth 2014;112(1):96-101.
26. Henderson WR, Chen L, Amato MBP, Brochard LJ. Fifty years of research in ARDS. Respiratory mechanics in acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;196(7):822-833.
27. Ziehr DR, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. Am J Respir Crit Care Med 2020;201 (12):1560-1564.
28. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the Seattle region — case series. N Engl J Med 2020;382(21):2012-2022.
29. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, Camporota L. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020;46(6):1099-1102.
30. Suter PM, Fairley B, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 1975;292(6):284-289.
31. Suter PM, Fairley HB, Isenberg MD. Effect of tidal volume and positive end-expiratory pressure on compliance during mechanical ventilation. Chest 1978;73(2):158-162.
32. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total respiratory system in acute respiratory failure: computed tomographic scan study. Am Rev Respir Dis 1987;136(3):730-736.
33. Amato MBP, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372(8):747-755.
34. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab 2020;318(5):E736-4E741.
35. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia – a systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr 2020;14(4):395-403.
36. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020;109(5):531-538.
37. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al; COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020;323(16):1574-1581.
38. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180(7):934-943.
39. Stürmer T, Joshi M, Glynn RJ, Avorn J, Rothman KJ, Schneeweiss S. A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates compared with conventional multivariable methods. J Clin Epidemiol 2006;59(5):437-447.
40. Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehran R, et al. Comparison of propensity score methods and covariate adjustment: evaluation in 4 cardiovascular studies. J Am Coll Cardiol 2017;69(3):345-357.