Heterogeneity of Ventilation/Perfusion Mismatch at Different Levels of PEEP and in Mechanical Phenotypes of COVID-19 ARDS

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BACKGROUND: COVID-19–related ARDS is characterized by severe hypoxemia with initially preserved lung compliance and impaired ventilation/perfusion ($\dot{V}/\dot{Q}$) matching. PEEP can increase end-expiratory lung volume, but its effect on $\dot{V}/\dot{Q}$ mismatch in COVID-19–related ARDS is not clear. METHODS: We enrolled intubated and mechanically ventilated subjects with COVID-19 ARDS and used the automatic lung parameter estimator (ALPE) to measure $\dot{V}/\dot{Q}$. Respiratory mechanics measurements, shunt, and $\dot{V}/\dot{Q}$ mismatch (low $\dot{V}/\dot{Q}$ and high $\dot{V}/\dot{Q}$) were collected at 3 PEEP levels (clinical PEEP = intermediate PEEP, low PEEP [clinical − 50%], and high PEEP [clinical + 50%]). A mixed-effect model was used to evaluate the impact of PEEP on $\dot{V}/\dot{Q}$. We also investigated if PEEP might have a different effect on $\dot{V}/\dot{Q}$ mismatch in 2 different respiratory mechanics phenotypes, that is, high elastance/low compliance (phenotype H) and low elastance/high compliance (phenotype L). RESULTS: Seventeen subjects with COVID-related ARDS age 66 [60–71] y with a P_{aO_2}/F_{IO_2} of 141 ± 74 mm Hg were studied at low PEEP = 5.6 ± 2.2 cm H_2O, intermediate PEEP = 10.6 ± 3.8 cm H_2O, and high PEEP = 15 ± 5 cm H_2O. Shunt, low $\dot{V}/\dot{Q}$, high $\dot{V}/\dot{Q}$, and alveolar dead space were not significantly influenced, on average, by PEEP. Respiratory system compliance decreased significantly when increasing PEEP without significant variation of P_{aO_2}/F_{IO_2} ($P = .26$). In the 2 phenotypes, PEEP had opposite effects on shunt, with a decrease in the phenotype L and an increase in phenotype H ($P = .048$). CONCLUSIONS: In subjects with COVID-related ARDS placed on invasive mechanical ventilation for > 48 h, PEEP had a heterogeneous effect on $\dot{V}/\dot{Q}$ mismatch and, on average, higher levels were not able to reduce shunt. The subject's compliance could influence the effect of PEEP on $\dot{V}/\dot{Q}$ mismatch since an increased shunt was observed in subjects with lower compliance, whereas the opposite occurred in those with higher compliance. *Key words: $\dot{V}/\dot{Q}$ mismatch; COVID-19; ARDS; PEEP; shunt; phenotypes.* [Respir Care 2023;68(2):188–198. © 2023 Daedalus Enterprises]

Introduction

COVID-19–related ARDS has peculiar characteristics, as compared to ARDS from other etiologies,[1] and its physiological sequelae have not been fully elucidated. In the early phase, some studies have suggested that COVID-19–related ARDS is characterized by a relatively preserved compliance[2] but severely compromised lung function, as reflected by impaired gas exchange. Many patients with COVID-19 improve oxygenation after prone positioning, but the response in terms of gas exchange is often not associated with an improvement in respiratory mechanics.[3]

It has been suggested that hypoxia in COVID-19–related ARDS is secondary to the redistribution of ventilation and perfusion and the onset of ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch. Recent evidence questions the role of impaired ventilation per se, making impaired $\dot{V}/\dot{Q}$ the prime suspect of hypoxia in COVID-19.[4] This has been hypothesized in several editorials and recently supported by computational models[5,6] and CT scan studies,[7] but a systematic bedside combined evaluation of shunt, low $\dot{V}/\dot{Q}$, and high $\dot{V}/\dot{Q}$ in invasively ventilated patients with COVID-19 is still missing, with $\dot{V}/\dot{Q}$ mismatch being difficult to assess at the bedside.

PEEP is one of the cornerstones of ARDS treatment. It has been shown to reduce shunt,[8] improve lung recruitment[9] and P_{aO_2}/F_{IO_2}.[10] However, increasing PEEP can enhance static stress and, therefore, the risk of overinflation or ventilator-induced lung injury.[11] The effect of PEEP in COVID-19–related ARDS is heterogeneous, with many patients poorly responsive to high PEEP levels[7] possibly related to the presence of heterogeneous and probably time-dependent compliance phenotypes.[12] Inappropriately high PEEP levels in patients with non-recruitable lung may worsen V̇/Q̇ mismatch by increasing wasted ventilation toward poorly perfused regions (high V̇/Q̇) and redistributing perfusion toward non-ventilated regions (increase of shunt and low V̇/Q̇).

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The automatic lung parameter estimator (ALPE) is a noninvasive monitoring tool that provides bedside evaluation of V̇/Q̇ mismatch. The ALPE method consists of fitting a mathematical physiological model to steady-state bedside measurements of gas transport and ventilation yielding parameters of pulmonary shunt, low V̇/Q̇, and high V̇/Q̇. The ALPE model has been shown to agree well with the multiple inert-gas elimination technique (MIGET),[13,14] the standard for measuring V̇/Q̇ mismatch, which is technically challenging to perform at the bedside and has previously been used to characterize the effects of PEEP in non–COVID-19–related ARDS.[15]

In the current study we aimed at exploring the effect of 3 different PEEP levels (clinical, clinical + 50%, and clinical − 50%) on V̇/Q̇ mismatch in a cohort of subjects with moderate/severe COVID-19–related ARDS by directly assessing V̇/Q̇ using the ALPE. The primary outcome of the study was to evaluate the effect of PEEP on shunt, low V̇/Q̇, high V̇/Q̇, and alveolar dead space V_{Dalv} in COVID-19 ARDS. Our secondary outcome was to evaluate if different respiratory mechanics phenotypes can be associated to a different effect of PEEP on V̇/Q̇ mismatch.

QUICK LOOK

Current knowledge

COVID-19 ARDS is characterized by severe hypoxia with relatively preserved lung compliance. Patients with COVID-19 have high levels of ventilation/perfusion (V̇/Q̇) mismatch, also caused by impaired lung perfusion, but how PEEP impacts V̇/Q̇ mismatch in severe COVID-19 ARDS has not been studied yet.

What this paper contributes to our knowledge

Higher PEEP levels were not able to reduce shunt fraction in non-recruitable subjects. The subject's mechanical phenotype can influence the effect of PEEP on V̇/Q̇ mismatch in COVID-19–related ARDS. In patients with low compliance, higher PEEP levels may increase pulmonary shunt.

Methods

This is an analysis of data prospectively acquired between April 2021–January 2022. The study was approved by the ethical committee of the Emilia Romagna Centro (approval number 372/2021/Oss/AOUFe). Informed consent was obtained from the subject or by the next of kin according to the approval of the local ethics committee, and the analysis was conducted on anonymized individual data.

Inclusion and Exclusion Criteria

To be included in this study, subjects tested positive for SARS-CoV-2 infection (confirmed by real-time reverse transcription-polymerase chain reaction assays), were older than 18 y, received invasive mechanical ventilation, and fulfilled the criteria for ARDS according to the Berlin definition.[16] To ensure hemodynamic stability, patients requiring high dosages of vasopressors (defined as norepinephrine > 0.1 μg/kg/min) where excluded from enrollment.

Data Acquisition Protocol and Definitions

All subjects were intubated, sedated, and paralyzed as per clinical decision, mechanically ventilated in volume-

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Drs Karbing and Rees disclose relationships with Mermaid Care. The remaining authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.10242

controlled mode and in the supine semi-recumbent position. Subjects who were proned prior to the study were included if they were placed supine for at least 24 h prior to data collection.

V̇/Q̇ mismatch was assessed using the ALPE, integrated in the BEACON Caresystem (Mermaid Care A/S, Nørresundby, Denmark): The system includes a built-in pulse oximeter and a metabolic monitor with sidestream sampling of air flow, O_2, and CO_2 connected to the respiratory circuit via a sampling tube inserted between subjects and ventilator. Before the start of the study, subjects were ventilated as follows: tidal volume (V_T) 6–8 mL/kg/predicted body weight, breathing frequency to keep pH in the physiological range. The clinical PEEP was the one set by the treating physician prior to trial start, targeting the lowest respiratory system driving pressure (ΔP) in the latest clinical assessment of the subject.

V̇/Q̇ measurements were performed at 3 PEEP levels. The clinical value of PEEP was taken as reference (defined as "intermediate PEEP,"), whereas the 2 other levels of PEEP were calculated as follows: low PEEP = intermediate PEEP × 0.5 and high PEEP = intermediate PEEP × 1.5. The sequence of PEEP was intermediate, high, and low, and the measures were taken at least 20 min after changing the level of PEEP and only when the system reached a new stability, as automatically suggested by the BEACON Caresystem. The system does not perform a new ALPE measure until it reaches a new steady state.

Before respiratory mechanics measures and before each ALPE evaluation, an arterial blood gas sample was taken for analysis.

Respiratory Mechanics Data Collection

After obtaining an arterial blood sample, respiratory mechanics measurements were collected from the ventilator by performing an end-inspiratory and an end-expiratory pause (4 s each). Total PEEP, peak inspiratory pressure (PIP), and plateau pressure (P_{plat}) were assessed from the pressure signal. The ΔP of the respiratory system was calculated as P_{plat} − PEEP and as all pressure values are expressed in cm H_2O. The ventilatory ratio was calculated as previously described,[17] whereas V_T was integrated from the flow signal. Respiratory system compliance (C_{RS}) was calculated as $V_T/\Delta P$ and expressed as mL/cm H_2O. The phenotype names refer to elastance, which is opposite to C_{RS}, to maintain the nomenclature continuity with previously published papers on the same subject.[12]

V̇/Q̇ Mismatch Data Collection

The automatic lung parameter estimation is a technique that allows estimation of bedside V̇/Q̇ mismatch in mechanically ventilated patients by evaluating the relationship between end-tidal O_2 (S_{aO_2}) and S_{pO_2} and the relationship between end-tidal CO_2 and P_{aCO_2}. The system identifies the fractions of ventilation and perfusion in a 3-compartment model of the lung, including 2 ventilated and perfused compartments and a further perfused-only compartment, describing pulmonary shunt. For calculations, cardiac output was estimated from cardiac index and body surface area, assuming a cardiac index of 3.7 L/min/m^2 as previously reported in an ICU population and used for ALPE calculations.[18]

The ALPE algorithm applies the principle that in the case of true pulmonary shunt S_{pO_2} will change little when changing F_{IO_2}. This contrasts with areas with low V̇/Q̇, where S_{aO_2} will change greatly with F_{IO_2}. Accordingly, through variation of F_{IO_2} in a minimum of 3 steps, the system mathematically estimates shunt and low V̇/Q̇ ratios. Further, the ALPE algorithm considers the end-tidal to arterial CO_2 gradient to account for the part of this gradient due to shunt and low V̇/Q̇ and the one due to high V̇/Q̇. Low V̇/Q̇ mismatch is expressed in mm Hg representing the difference in O_2 partial pressure between end-tidal gas and blood leaving lung capillaries prior to mixing with shunted blood. High V̇/Q̇ mismatch is likewise represented in mm Hg constituting the difference in CO_2 partial pressure between end-tidal gas and blood leaving lung capillaries. A high V̇/Q̇ index of > 0 mm Hg can be interpreted as insufficient removal of CO_2 due to high V̇/Q̇. The ALPE technique has been shown to agree with the MIGET[13] and has been applied in varied patient populations.[19-22] V_{Dalv} was calculated using the Enghoff modified Bohr method and, therefore, by assessing the ratio between P_{ETCO_2} and P_{aCO_2}, as in[23]

$$V_{Dalv}/V_t = \frac{P_{aCO_2} - P_{ETCO_2}}{P_{aCO_2}}$$

The difference in V̇/Q̇ components between high PEEP and low PEEP (V̇/Q̇ parameter at high PEEP − V̇/Q̇ parameter at low PEEP) was calculated and defined as ΔShunt, ΔLow V̇/Q̇, ΔHigh V̇/Q̇, and ΔV_{Dalv}. The same calculation was done for P_{aO_2}/F_{IO_2} ($\Delta P_{aO_2}/F_{IO_2}$) and compliance (ΔC_{RS}).

The F_{IO_2} selection during the ALPE was based on the suggestions done by the algorithm. To avoid the possibility of alveolar de-nitrogenation consequent to high inhaled F_{IO_2}, we used for the calculations an $F_{IO_2} \leq 0.8$ except when a higher F_{IO_2} was necessary for clinical management.

Finally, we defined 2 different compliance phenotypes[12] based on the median of C_{RS} at low PEEP.[24] Subjects were, therefore, classified as low compliance/high elastance (phenotype H) if C_{RS} was < median C_{RS} or as high compliance/low elastance (phenotype L) if C_{RS} was > median C_{RS}, as previously described by Chiumello et al.[25]

Statistical Analysis

Sample size could not be calculated a priori due to the absence of data regarding the main outcome of the study, that is, the distribution of V̇/Q̇ in subjects with COVID-19. We aimed at enrolling a number of subjects based on previous physiological studies in ARDS.[15,26] The normality of data distribution was tested using the Shapiro-Wilks normality test, and data report and test selection were appropriately based on its results. Continuous variables are expressed as median and interquartile range or mean ± SD, whereas categorical variables as counts (percentage). Comparison between independent groups was performed using the *t* test, Mann-Whitney U test, or chi-square test, depending on the data. Repeated measures were tested using the paired *t* test or Friedman test. A mixed-effect model analysis was performed to evaluate the effects of PEEP on shunt, V̇/Q̇ compartments, and lung mechanics. Shunt measures < 2% were considered not reliable and, therefore, analyzed as missing data. All *P* values refer to 2-tailed tests of significance, and $P < .05$ was deemed as statistically significant. Data were analyzed using SPSS 26 (IBM, Armonk, New York) and GraphPad Prism 8.4.3 (GraphPad software, San Diego, California).

Results

Subject Characteristics

We enrolled 17 critically ill subjects with COVID-19 admitted to the ICU for COVID-19–related ARDS. The main characteristics of the study population, including medical history and lung involvement evaluated by the admission chest radiograph, are shown in Table 1. Median age was 66 [60–71] y old; 13/17 (76%) were male, and they were enrolled after 5 [3–9] d of mechanical ventilation. At enrollment, the P_{aO_2}/F_{IO_2} was 141 ± 74 mm Hg, and the clinical level of PEEP was 10 ± 4 cm H_2O.

Table 1. Demographic Characteristics of the Overall Enrolled Population

	Overall Population ($N = 17$)
Age, y	66 [60–71]
Male:female	13:4
Height, cm	169 ± 8
Weight, kg	80 [74–85]
BMI, kg/cm^2	28 [26–29]
SOFA	5 ± 3
Duration of mechanical ventilation, d	5 [3–9]
Prone positioning before the study	13 (76)
Prone positioning during ICU stay	17 (100)
Hypertension	14 (82)
Diabetes	10 (59)
COPD/asthma	0 (0)
Chronic immunosuppression	0 (0)
Number of quadrants affected on the chest radiograph	
1 quadrant	0 (0)
2 quadrants	3 (18)
3 quadrants	10 (59)
4 quadrants	4 (23)
Heart rate, beats/min*	83 ± 15
Mean arterial pressure, mm Hg*	86 ± 16
P_{aO_2}/F_{IO_2}, mm Hg*	141 ± 74
P_{aCO_2}, mm Hg*	67.6 ± 18.6
V_T, mL*	420 ± 49
Clinical PEEP, cm H_2O*	10 ± 4
F_{IO_2},*	0.8 ± 0.2
Lactate, mmol/L	1.6 ± 0.4
HCO_3^-, mmol/L	35.0 ± 6.6
pH	7.35 ± 0.90

Data are presented as *n* (%), mean ± SD, or median [interquartile range].
*Measured at enrollment.
BMI = body mass index
SOFA = Sequential Organ Failure Assessment score
V_T = tidal volume

Effect of PEEP on $\dot{V}_A/\dot{Q}$ Compartments, Gas Exchange, and Lung Elastance

The effect of PEEP on respiratory system mechanics and on V̇/Q̇ mismatch is shown in Table 2. Six measures of shunt (6/51) were excluded from the analysis because these values were < 2%. In the overall population, PEEP did not result in a significant variation in shunt ($P = .91$), low V̇/Q̇ ($P = .8$), high V̇/Q̇ ($P = .67$), and V_{Dalv} ($P = .08$), in V_{Dalv} (Fig. 1). No significant differences were found in P_{aO_2}/F_{IO_2} ($P = .26$) and ventilatory ratio ($P = .83$). Lung mechanics were impaired by the increased PEEP, since P_{plat} ($P < .001$) and PIP ($P < .001$) increased significantly, whereas C_{RS} decreased significantly ($P < .001$). Increased PEEP was not associated with a C_{RS} increase in any subject.

Comparison Between Different Compliance Phenotypes

At low PEEP, the median value of C_{RS} was 38 ml/cm H_2O; and based on this value, the population was divided into 2 groups corresponding to the 2 specific phenotypes (Table 3): low compliance/high elastance (phenotype H, 9/17 subjects) and high compliance/low elastance (phenotype L, 8/17 subjects). Subjects with phenotype L were slightly older, but no differences in the other baseline characteristics were significant (Table 3). Concerning the variation

Table 2. Main Results in the Overall Population

	Low PEEP	Intermediate PEEP	High PEEP	*P* PEEP
PIP, cm H_2O	29.0 ± 4.2	34.8 ± 3.6	42.6 ± 6.8	< .001
P_{plat}, cm H_2O	17.0 ± 3.2	22.8 ± 3.8	30.4 ± 6.6	< .001
C_{RS}, mL/cm H_2O	40 ± 12	36.6 ± 9.9	29.7 ± 9.8	< .001
Measured PEEP, cm H_2O	5.6 ± 2.2	10.6 ± 3.8	15 ± 5	< .001
P_{aO_2}, mm Hg	94.4 ± 51.2	100.2 ± 53.0	106.2 ± 39.4	.27
P_{aCO_2}, mm Hg	66.6 ± 17.2	67.4 ± 18.2	69.4 ± 20.2	.23
P_{aO_2}/F_{IO_2}, mm Hg	129.2 ± 73.8	135.0 ± 76.2	143.8 ± 58.6	.26
Ventilatory ratio	2.8 ± 1.0	2.8 ± 1.0	2.8 ± 0.8	.83
Shunt, %	34.8 ± 17.0	33.4 ± 14.2	32.8 ± 15.0	.91
Low V̇/Q̇, mm Hg	169.8 ± 157.8	183.8 ± 152.6	164.8 ± 112.0	.80
High V̇/Q̇, mm Hg	22.6 ± 10.2	22.8 ± 10.4	21.8 ± 9.0	.67
V_{Dalv}, %	31.8 ± 10.0	29.6 ± 11.6	29.6 ± 9.6	.08

Data are presented as mean ± SD or median [interquartile range]. One-way analysis of variance or mixed-effect analysis.
PIP = peak inspiratory pressure
P_{plat} = plateau pressure
C_{RS} = respiratory system compliance
V̇/Q̇ = ventilation/perfusion ratio
V_{Dalv} = alveolar dead space

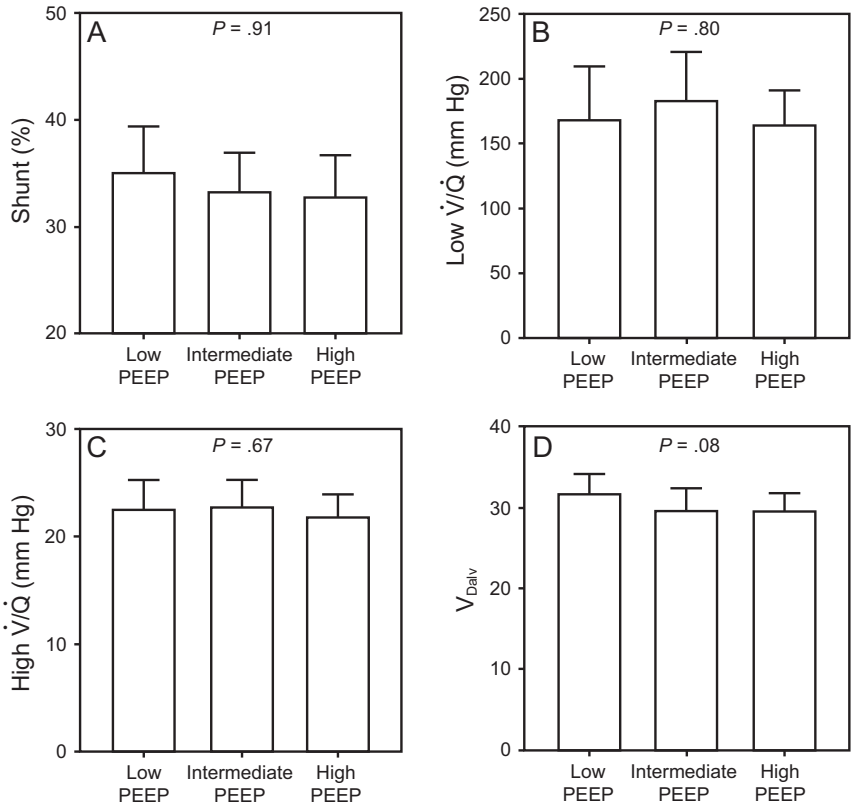

Fig. 1. Effect of PEEP on ventilation/perfusion mismatch in the overall population. Data are expressed as mean and standard error of the mean. *P* value for PEEP effect (mixed-effect analysis). V̇/Q̇ = ventilation/perfusion ratio; V_{Dalv} = alveolar dead space.

Table 3. Baseline Characteristics, Change of Respiratory Mechanics, and Gas Exchange Variables in the Phenotypes

	Phenotype H ($n = 9$)	Phenotype L ($n = 8$)	P
Age, y	59.8 ± 10.4	70.6 ± 5.6	.02
Height, cm	167 ± 8	171 ± 7	.28
Weight§, kg	80 [74–85]	81.5 [76.0–87.5]	.74
BMI§, kg/m^2	27.6 [25.7–28.1]	27.8 [26.5–29.4]	.61
SOFA	5.8 ± 2.2	4.8 ± 3.0	.38
Ventilator-free days	6.6 ± 8.4	1.6 ± 4.6	.15
Day of mechanical ventilation at study day§	7 [3–11]	5 [2–9]	.48
ICU LOS, d	25.2 ± 9.0	21.2 ± 7.6	.37
Male	6/9 (67)	7/8 (87)	.58
Survivors	4/9 (44)	1/8 (12.5)	.29
P_{aO_2}/F_{IO_2}, mm Hg*	140 ± 47	143 ± 100	.94
PEEP*, cm H_2O	9.8 ± 4.2	11.2 ± 3.4	.51
F_{IO_2}*	0.8 ± 0.2	0.8 ± 0.2	.85
V_T*, mL	409 ± 59	432 ± 33	.35

Data are presented as *n/n* (%), mean ± SD, or median [interquartile range].
*At enrollment Δ = difference between the measure at high PEEP and low PEEP (PEEP high − PEEP low).
§Mann-Whitney U test (otherwise *t* test for equality of means).
BMI = body mass index
SOFA = Sequential Organ Failure Assessment
LOS = length of stay
V_T = tidal volume

Table 4. Change of Respiratory Mechanics and Gas Exchange Variables in the Phenotypes

	Overall ($N = 17$)	Phenotype H ($n = 9$)	Phenotype L ($n = 8$)	P
ΔShunt	−2.1 ± 18.3	7.0 ± 18.2	−12.6 ± 12.6	.048
ΔLow V̇/Q̇	2.7 ± 186.0	−14 ± 168	16 ± 185	.74
ΔHigh V̇/Q̇	−1.4 ± 7.7	0.4 ± 8.0	−3.2 ± 5.8	.32
ΔV_{Dalv}	−3.4 ± 6.3	−2.6 ± 5.6	−3.4 ± 6.8	.83
ΔC_{RS}	−10.7 ± 8.8	−4.2 ± 3.2	−17.8 ± 8.7	.001
$\Delta P_{aO_2}/F_{IO_2}$	15.7 ± 41.6	13.0 ± 48.6	14.3 ± 38.0	.695

Data are presented as mean ± SD.
P value refers to the comparison between phenotypes; *t* test for equality of means.
Δ = difference between the measure at high PEEP and low PEEP (PEEP high − PEEP low).
V̇/Q̇ = ventilation/perfusion ratio
V_{Dalv} = alveolar dead space
C_{RS} = respiratory system compliance

in V̇/Q̇ mismatch between high PEEP and low PEEP, shunt decreased in the phenotype L (ΔShunt= −12.6 ± 12.6), whereas an average increase was seen in the phenotype H (ΔShunt = 7.0 ± 18.2). The ΔShunt was significantly different between the 2 groups ($P = .048$) (Table 4 and Fig. 3). Compliance was reduced at higher PEEP, and the variation was significantly different between the 2 groups, with a higher decrease in the phenotype L (−4.2 ± 3.2 vs −17.8 ± 8.7, $P = .001$) (Fig. 2, Table 4). No other significant differences were seen in V̇/Q̇ mismatch in response to PEEP (Table 5).

Discussion

In this study we found that, in critically ill subjects with COVID-19–related ARDS, PEEP determined an overall heterogeneous effect on V̇/Q̇ mismatch. At higher PEEP we detected no significant modification of V̇/Q̇ but a significant decrease of C_{RS} and, therefore, less protective mechanical ventilation. Interestingly, when comparing subjects with different respiratory mechanics, the effect of PEEP on shunt was significantly different and opposite, with a shunt reduction in subjects with a higher C_{RS} (phenotype L) and a shunt increase in those with a lower C_{RS} (phenotype H).

The pathophysiology of acute respiratory failure in COVID-19–related ARDS has been suggested to be different, as compared to non–COVID-19–related ARDS. Previous studies using electrical impedance tomography underlined the atypical effect of PEEP in COVID-19–related ARDS, especially on the potential for lung recruitment and on the presence of high dead-space fraction.[27] The derangement of the vessels' ability to react to hypoxia (hypoxic vasoconstriction)[1,28,29] and the presence of signs of hypercoagulability and microthrombosis[30,31] have drawn the attention more to the vascular side of gas exchange. Moreover, the high compliance of the respiratory system that usually characterizes patients with COVID-19 in the early phase despite severe hypoxemia is a further hint of limited involvement of alveolar spaces, as compared to vascular abnormalities. Our study explored these hypotheses by directly assessing V̇/Q̇

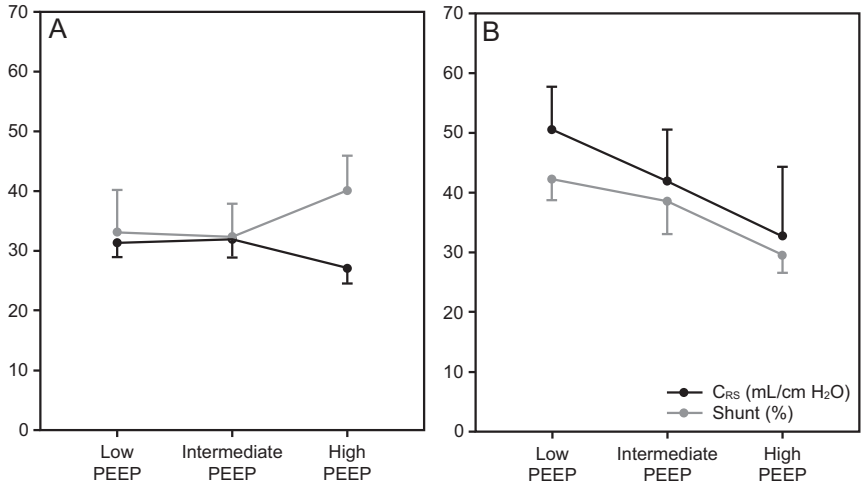

Fig. 2. Shunt and respiratory system compliance in the 2 mechanical phenotypes: phenotype L (A) and phenotype H (B). Data are shown as mean ± standard error of the mean. C_{RS} = respiratory system compliance.

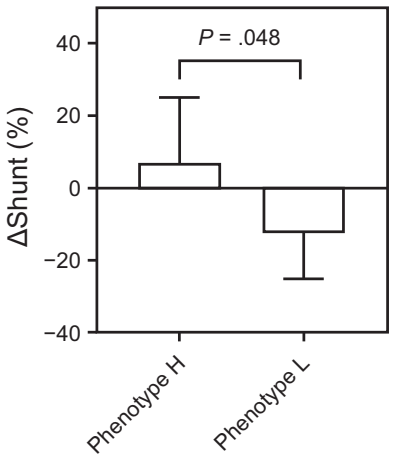

Fig. 3. Difference in Shunt (ΔShunt) between high PEEP and low PEEP (ΔShunt = Shunt high PEEP − shunt low PEEP) in the 2 phenotypes. Mean ± SD.

mismatch in invasively ventilated subjects with COVID-19 ARDS.

PEEP can generate 2 effects: alveolar recruitment in patients who are responders, who by increasing lung volume at the end of expiration will increase P_{aO_2} and lung compliance; and decrease P_{aCO_2}. In this group of patients, ventilation of perfused areas will improve, whereas shunt and dead space will decrease. However, patients with decreased lung compliance do not respond to higher PEEP levels, which generate alveolar overdistention and worsening of gas exchange due to hypoventilation secondary to an increase in dead space.

In our study we found that, overall, shunt fraction was not affected in subjects with COVID-19–related ARDS by varying PEEP between average levels of 5–15 cm H_2O. This finding is in line with recent computed tomography (CT) scan studies where PEEP-induced recruitment of subjects with COVID-19 was found to be marginal and not clinically significant.[7] Moreover, we found that higher PEEP levels were associated with a worsening of lung mechanical properties, underlining the inability of higher PEEP to increase the ventilated lung, at least without some important hyperinflation. Our data confirm previous studies showing that hyperinflation can be found in subjects with COVID-19 on invasive mechanical ventilation and at volumes and PEEP levels usually considered safe for non–COVID-19 ARDS.[32,33]

Based on respiratory mechanics and on the evidence coming from CT scan showing low amounts of non-ventilated lung,[1] patients with COVID-19 have been previously classified into 2 different phenotypes: the phenotype H (ie, low compliance/high elastance) and the phenotype L (ie, high compliance/low elastance). Generally, these 2 phenotypes are thought to be consequent (phenotype L > phenotype H), and the phenotype H is considered to be more similar to non–COVID-19 ARDS, but this classification is still controversial, and a cutoff value to define these 2 categories is still unknown.[34,35]

Nevertheless, we were able to assess a different and unexpected behavior of subjects with different mechanical properties in response to PEEP. In subjects with a higher compliance (phenotype L), high PEEP levels resulted in a significant reduction of shunt of > 10% but, at the same time, a significant reduction of C_{RS} and no significant effect on oxygenation. In contrast, in the phenotype H, higher levels of PEEP increased shunt with limited effect on C_{RS}. No other significant differences among phenotypes could be seen in V̇/Q̇ mismatch.

Table 5. Mechanical Measures and Gas Exchange at Different PEEP levels in the 2 Phenotypes

	Phenotype H ($n = 9$)	Phenotype L ($n = 8$)	P
P_{aO_2}/F_{IO_2}, mm Hg			
Low PEEP	123.2 ± 58.4	136.8 ± 94.4	.72
Intermediate PEEP	128.4 ± 52.6	142.6 ± 100.0	.59
High PEEP	136.2 ± 63.4	152.4 ± 55.8	.59
PIP, cm H_2O			
Low PEEP	29.8 ± 4.2	27.8 ± 4.2	.36
Intermediate PEEP	35.4 ± 3.8	33.8 ± 3.2	.38
High PEEP	42.2 ± 6.4*	43.2 ± 7.8	.79
P_{plat}, cm H_2O			
Low PEEP	18.4 ± 3.4	15.2 ± 2.0	.044
Intermediate PEEP	23.4 ± 4.0	22.0 ± 3.6	.45
High PEEP	30.0 ± 6.2*	30.8 ± 7.4*	.79
PEEP, cm H_2O			
Low PEEP	4.8 ± 2.4	6.6 ± 1.4	.14
Intermediate PEEP	9.8 ± 4.2	11.2 ± 3.6	.48
High PEEP	14.0 ± 5.4*	16.2 ± 4.8*	.37
Ventilatory ratio			
Low PEEP	2.8 ± 0.8	2.6 ± 1.0	.82
Intermediate PEEP	2.8 ± 1.0	2.6 ± 1.0	.68
High PEEP	2.8 ± 0.8	2.8 ± 0.8*	.94
C_{RS}, mL/cm H_2O			
Low PEEP	31.4 ± 6.9	50.5 ± 7.2	< .001
Intermediate PEEP	31.9 ± 8.7	41.9 ± 8.6	.032
High PEEP	27.1 ± 7.4	32.7 ± 11.7*	.25
Shunt, %			
Low PEEP	29.4 ± 20.0	42.0 ± 8.6	.18
Intermediate PEEP	30.0 ± 15.4	37.6 ± 12.4	.30
High PEEP	40.2 ± 15.6	26.4 ± 12	.08
Low $\dot{V}_A/\dot{Q}$, mm Hg			
Low PEEP	186.6 ± 181.8	148.4 ± 131.4	.65
Intermediate PEEP	203.4 ± 176.8	161.6 ± 128.6	.59
High PEEP	172.4 ± 117.8	156.2 ± 112.6	.78
High V̇/Q̇, %			
Low PEEP	20.6 ± 10.2	25.2 ± 10.4	.41
Intermediate PEEP	22.6 ± 12.0	23.0 ± 9.4	.93
High PEEP	21.2 ± 11.2	22.6 ± 6.4	.74
V_{Dalv}			
Low PEEP	28.8 ± 10.4	35.8 ± 8.4	.18
Intermediate PEEP	26.6 ± 11.2	33.2 ± 11.6	.26
High PEEP	26.2 ± 7.8	33.4 ± 10.4	.13

Data are presented as median [interquartile range] or mean ± SD; *t* test for equality of means or Wilcoxon-Mann-Whitney test.
* $P < .05$ for paired *t* test compared to the low PEEP step.
PIP = peak inspiratory pressure
P_{plat} = plateau pressure
C_{RS} = respiratory system compliance
$\dot{V}_A/\dot{Q}$ = ventilation/perfusion ratio
V_{Dalv} = alveolar dead space

The difference in both cases was not related to a significant change in the P_{aO_2}/F_{IO_2}, supporting the hypothesis that shunt is not the only mechanism responsible for hypoxia.[5,7] If hypoxemia is not related to recruitable shunt (ie, atelectasis due to alveolar/airway collapse) but to blood flow redistribution, higher PEEP is not useful and may be dangerous.[36] Indeed, in subjects with lower compliance (phenotype H), the "paradoxical" effect of PEEP on increasing shunt may be explained by the presence of non-recruitable lung: The increase of PEEP was not able to recruit closed regions but still could overdistend already aerated lung, contribute to capillary collapse[37] and to the redistribution of perfusion toward shunted regions.[38] This mechanism was also supported by the lack of improvement in lung mechanics with any of the subjects in which PEEP was increased.

In our study, application of varying PEEP levels, within typical bedside ranges, did not significantly improve average V̇/Q̇ mismatch. This supports the use of alternative treatments, like prone positioning,[3,39] inhaled nitric oxide, and almitrine,[28,40] that can modify V̇/Q̇ mismatch and potentially reduce both high V̇/Q̇ and low V̇/Q̇[41] in patients not responding to higher PEEP.

We found that also V_{Dalv} and ventilatory ratio were high, as previously found,[42] but not modified by PEEP. This can be mainly related to the presence of subclinical microthromboses that were previously described in COVID-19 lung autopsies.[43]

Time can influence the mechanical characteristics of the lung, deteriorating compliance and possibly leading to lung fibrosis.[44] Our findings must be, therefore, put into context: We enrolled subjects within a median of 5 d of intubation, and our data may, therefore, depict a limited phase of the disease and not its entire course. For example, Protti et al[45] found using CT scan that recruitability was high in a series of 40 subjects with COVID-19 using CT by evaluating subjects within the first 3 d of mechanical ventilation. The authors observed that the P_{aO_2}/F_{IO_2} increased when increasing PEEP. We did not directly assess recruitability, but from our data on compliance and P_{aO_2}/F_{IO_2}, we can affirm that the time of study may represent a determinant information for the interpretation of these data and must be considered when putting our paper into context of the previous literature.

To our knowledge, this is the first study that evaluates the V̇/Q̇ in subjects with COVID-19 using this bedside approach. Furthermore, we tested different PEEP levels (low, intermediate, and high). Despite this, our study has some limitations. First, a limited number of subjects were enrolled in the study. The study of V̇/Q̇ mismatch despite being quite simple and noninvasive requires dedicated time and personnel that was not always available in the hospital during the COVID pandemic. Nevertheless, the study sample is comparable with other physiological studies on ARDS and V̇/Q̇ mismatch.[15] Second, the order of the PEEP steps was not randomized. Moreover, metabolic monitors as used for the ALPE calculations can have measurement errors at $F_{IO_2} > 0.5$; but the impact of modifying F_{IO_2} on

measured oxygen consumption ($\dot{V}_{O_2}$) is reduced by the machine waiting for oxygen steady state and, therefore, removing all dynamic changes in $\dot{V}_{O_2}$ due to changes in F_{IO_2}.

Another limitation is related to the limited range of PEEP levels explored. Our choice was based on several factors, including the risk of pneumothorax, barotrauma, and hemodynamic compromise in subjects with moderate to severe ARDS,[46] the necessity to collect a blood sample to perform each ALPE calculation, the necessity to wait for lung stability before evaluating the subjects, and a strategy of PEEP titration previously successfully used by our group.[47] For all these reasons, we think that the approach used by selecting the 3 levels of PEEP is reasonable to balance the accuracy of the data and the risk for the subjects. Moreover, since a recruitment maneuver was not part of our practice also for its possible detrimental effects and since a long time may be needed for lung recruitment after increasing PEEP, we did not randomize the PEEP orders. This can expose our findings to a certain amount of carry-over effect that cannot be excluded but was limited by the PEEP order selection.

Finally, due to the absence of invasive hemodynamic monitoring, the cardiac index was estimated using the internal algorithm of the ALPE machine, which is in line with recent findings on cardiac index in subjects with COVID-19.[48] All subjects were hemodynamically stable, with no history of cardiac disease, not undergoing high dose of vasopressors, and not affected by acute cardiac dysfunction, as pointed out by the clinical point-of-care ultrasound performed at the entrance for each patients with COVID-19 of our ICU. Moreover, during the trial, the analysis of hemodynamic parameters, such as mean systolic artery pressure, heart rate, and the rate of infusion of vasopressor/inotrope, did not change significantly. Nevertheless, as the gas exchange parameters are calculated from the relationship between end-tidal and arterial levels of oxygen and carbon dioxide, physiological changes in pulmonary shunt due to changes in cardiac output[49] would still be encompassed by the shunt estimated using the ALPE method.

Our results suggest that high PEEP did not increase C_{RS}, and V̇/Q̇ mismatch was not improved by changing end-expiratory lung volume. Under these circumstances, unnecessarily high PEEP levels are detrimental to V̇/Q̇ improvement and C_{RS}, particularly in the subjects with the lowest compliance (phenotype H). Tailoring PEEP, considering the different compliance phenotypes, and providing alternatives to PEEP in patients with no response to PEEP with respect to respiratory mechanics could represent an invaluable approach to guide appropriate organ oxygenation while maintaining lung-protective ventilation in COVID-19.

Conclusions

In subjects with COVID-19–related ARDS that underwent invasive mechanical ventilation for $>$ 48 h, PEEP had a heterogeneous effect on V̇/Q̇ mismatch and, on average, higher levels were not able to reduce shunt. The subject's compliance could influence the effect of PEEP on V̇/Q̇ mismatch, since an increase in shunt was observed in subjects with lower compliance, whereas a decrease in shunt in those with a higher compliance.

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