Effects of High PEEP on Intrapulmonary Shunt Ratio in Patients With SARS-CoV-2–Induced ARDS

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Introduction

Early in the COVID-19 pandemic, the scientific community questioned whether this infection led to typical ARDS or not. Gattinoni et al[1] proposed a subdivision of COVID-19 ARDS into 2 phenotypes: L for low elastance, ventilation-perfusion ratio, lung weight, and recruitability; and H for high elastance, right-to-left shunt, lung weight, and recruitability. However, numerous studies failed to confirm these findings, leading authors to contest this classification.[2] Nevertheless, the correct identification of the respiratory phenotype of COVID-19 ARDS seems of critical importance. Indeed, the use of high PEEP is expected to be beneficial in phenotype H, whereas a deleterious effect is expected in phenotype L. We conducted a study to describe early respiratory and hemodynamic modifications in response to high PEEP in subjects with COVID-19, using a pulmonary artery catheter for intrapulmonary shunt ($\dot{Q}_S/\dot{Q}_T$) determination and the recruitment-to-inflation (R/I) ratio to assess the lung recruitment potential. The primary objective of the study was to assess the effect of high PEEP on $\dot{Q}_S/\dot{Q}_T$ in comparison with low PEEP. Secondary objectives were to evaluate whether high R/I correlated with a drop in $\dot{Q}_S/\dot{Q}_T$ with low versus high PEEP and to describe advanced physiologic variables at each PEEP.

Methods

We prospectively included 15 subjects diagnosed with SARS-CoV-2–induced ARDS hospitalized between April 20, 2020–November 2, 2020. SARS-CoV-2 infection was confirmed by real-time reverse transcriptase-polymerase chain reaction assay of nasal swabs or lower respiratory tract samples. Subjects or their surrogates received oral and written information at ICU admission or prior to invasive mechanical ventilation. Written informed consent was waived. French institutional authority for personal data protection (National Commission for Information Technology and Freedom, registration number DEC20-102) and ethics committee (ID-CRB 2020-A00957-32, ref 2020/32) approved the study.

Inclusion criteria were (1) subjects intubated for < 72 h at time of enrollment with moderate-to-severe ARDS (P_{aO_2}/F_{IO_2} < 200 mm Hg)[3] and (2) pulmonary artery catheter insertion as part of the standard ICU care. Exclusion criteria were pregnant women, patients age < 18, patients not benefiting from social security, with contraindication to pulmonary artery catheter, spontaneous breathing, documented respiratory co-infection, extracorporeal membrane oxygenation, intracardiac shunt, or a cardiac disorder leading to erroneous left ventricular end-diastolic pressures measured by pulmonary artery occlusion. Transthoracic echocardiography was routinely performed to look for the presence of right-left intracardiac shunt, including patent foramen ovale.

All subjects received deep intravenous sedation and neuromuscular blockers as part of standard care and were

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Key words: COVID-19; SARS-CoV-2; ARDS; pulmonary artery catheter; intrapulmonary shunt ratio; recruitment-to-inflation ratio.

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This trial was registered on ClinicalTrials.gov, number NCT-04347928.

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Table 1. Physiologic Variables at Two Levels of PEEP

	High PEEP 15 cm H_2O	Low PEEP 5 cm H_2O	*P*
Hemodynamic			
Systemic			
Heart rate, beats/min	67 (64–80)	75 (69–90)	.002
CI, $L/min/m^2$	2.9 (2.3–3.5)	3.6 (2.8–4.3)	.001
iSV, mL/m^2	37 (33–50)	42 (37–48)	.03
SAP, mm Hg	114 (104–146)	125 (119–139)	.12
MAP, mm Hg	76 (67–92)	79 (67–92)	.19
DAP, mm Hg	58 (51–64)	59 (48–69)	.67
CVP, mm Hg	9 (6–15)	9 (4–13)	.02
PAOP, mm Hg	11 (8–17)	10 (7–14)	.008
iSVR, dynes/seconds/cm^{-5}/m^2	2,592 (1,800–2,938)	2,098 (1,725–2,663)	.056
Pulmonary			
PASP, mm Hg	37 (33–42)	41 (33–44)	.58
PAMP, mm Hg	25 (22–33)	26 (20–31)	.13
PADP, mm Hg	20 (16–26)	16 (13–23)	.03
iPVR, dynes/seconds/cm^{-5}/m^2	440 (409–634)	416 (338–644)	.035
Respiratory			
Intrapulmonary shunt, %	0.27 (17.1–34.0)	0.36 (26.9–53.1)	$<$ .001
P_{aO_2}/F_{IO_2}, mm Hg	197 (107–303)	66 (58–113)	$<$ .001
P_{aCO_2}, mm Hg	46.6 (45.8–54.1)	47.5 (44.3–56.7)	.52
P_{plat}, cm H_2O	27 (26–29)	15 (15–17)	$<$ .001
Driving pressure, cm H_2O	11 (10–13)	10 (9–11)	.01
C_{RS}, mL/cm H_2O	36.4 (30.8–43.0)	40.0 (36.7–52.5)	.006
Mechanical power, J/min	32.3 (28.4–34.7)	19.1 (16.4–24.7)	$<$.001
Physiologic dead space, %	31 (21–35)	28 (21–35)	.3
Metabolic			
DO_2, mL/min	1,033 (746–1316)	987 (827–1,257)	.49
$\dot{V}_{O_2}$, mL/min	272 (248–344)	303 (257–344)	.23
S_{vO_2}, %	68 (64–79)	67 (53–70)	.002
Lactate, mmol/L	1.3 (1.0–1.4)	1.2 (1.0–1.4)*	.02

Data are presented as median (interquartile range).
*1 missing value.
CI = cardiac index
iSV = indexed stroke volume
SAP = systolic arterial pressure
MAP = mean arterial pressure
DAP = diastolic arterial pressure
CVP = central venous pressure
PAOP = pulmonary artery occluded pressure
iSVR = indexed systemic vascular resistance
PASP = pulmonary artery systolic pressure
PAMP = pulmonary artery mean pressure
PADP = pulmonary artery diastolic pressure
iPVR = indexed pulmonary vascular resistance
P_{plat} = plateau pressure
C_{RS} = respiratory system compliance
DO_2= oxygen delivery
$\dot{V}_{O_2}$ = oxygen consumption
S_{vO_2} = mixed venous blood oxygen saturation

ventilated in volume controlled ventilation mode; tidal volume (V_T) set at 6 mL/kg of ideal body weight; breathing frequency up to 35 breaths/min, adjusted to maintain arterial pH $>$ 7.30; and F_{IO_2} at 1.0 to allow $\dot{Q}_S/\dot{Q}_T$ calculation. A 6.0 French pulmonary artery catheter was inserted into the right internal jugular vein to a pulmonary artery. End-tidal CO_2 (P_{ETCO_2}) was measured with a capnometer. R/I and detection of airway closure were assessed as previously described.[4,5] All measurements were carried out with the head of the bed elevated 30°, volume-controlled mode with V_T 6 mL/kg (predicted body weight), and constant inspiratory flow 60 L/min. After 30 min at PEEP level of 15 cm H_2O, the frequency was lowered to 10 breaths/min, and the expired V_T displayed by the ventilator was noted. PEEP

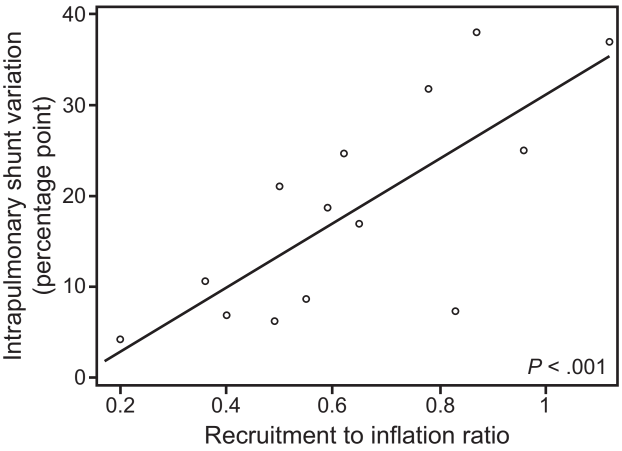

Fig. 1. Linear correlation between recruitment-to-inflation ratio and intrapulmonary shunt difference. Pearson correlation test ($r = -0.79$, $P < .001$).

was then reduced to 5 cm H_2O, and the expired V_T displayed by the ventilator immediately after the maneuver was recorded. The previous breathing frequency was resumed, and PEEP was maintained at 5 cm H_2O for 30 min. Low-flow inflation (5 L/min) from PEEP 5 cm H_2O ($V_T = 9$ mL/kg) was then performed to detect possible airway closure. Airway closure was detected by inspection of the pressure-time curve, and airway opening pressure was determined using cursors on the ventilator display.

A threshold of 0.5 was used to differentiate poorly recruitable from highly recruitable subjects, as described by Chen et al.[4] All physiological measurements and blood sample collections were performed at each level PEEP after 30 min. These data allowed for calculation of $\dot{Q}_S/\dot{Q}_T$, physiological dead space, mechanical power, systemic and pulmonary vascular resistance, oxygen consumption, oxygen delivery, and respiratory system compliance.

Categorical variables are expressed as *n* (%). Continuous variables are expressed as median (interquartile range). Measures at high and low PEEP levels were compared using Wilcoxon signed-rank test. Relationship between R/I and $\dot{Q}_S/\dot{Q}_T$ was assessed using Pearson correlation coefficient. Statistical testing was conducted at 2-tailed α-level 0.05. Data were analyzed using the SAS software version 9.4 (SAS Institute, Cary, North Carolina).

Results

Demographic data and physiological variables recorded at each PEEP level are presented in Table 1. At high PEEP, compared to low PEEP, $\dot{Q}_S/\dot{Q}_T$ was lower (27.4% [17.1–34.0] vs 36.1% [26.9–53.1], $P < .001$), whereas P_{aO_2}/F_{IO_2} was higher (197 [107–303] mm Hg vs 66 [58–113] mm Hg, $P < .001$). Cardiac index was lower at high PEEP compared to low PEEP (2.9 [2.3–3.5] L/min vs 3.6 [2.8–4.3] L/min, $P = .001$), without consequences on metabolic parameters. High PEEP was associated, compared to low PEEP, with lower system compliance (36.4 [30.8–43.0] mL/cm H_2O vs 40.0 [36.7–52.5] mL/cm H_2O, $P = .006$), higher driving pressure (11 [10–13] cm H_2O vs 10 [9–11] cm H_2O, $P = .01$), and higher mechanical power (32.3 [28.4–34.7] J/min vs 19.1 [16.4–24.7] J/min, $P < .001$). Three subjects had airway opening pressure > 5 cm H_2O. None of them had airway opening pressure > 10 cm H_2O. Median R/I was 0.6 (0.4–0.8), and 10 subjects had R/I ≥ 0.5. R/I and $\dot{Q}_S/\dot{Q}_T$ difference was statistically correlated ($r = -0.79$, $P < .001$) (Fig. 1).

Discussion

High PEEP reduced $\dot{Q}_S/\dot{Q}_T$ (−25%), with small hemodynamic modifications but at the cost of a rise in mechanical power. We found a proportion of 67% highly recruitable subjects (R/I ≥ 0.5) within 72 h of mechanical ventilation for COVID-19 ARDS, consistent with previously published data.[6] Our study contributes to the growing body of evidence suggesting that COVID-19 ARDS presents similar characteristics with typical ARDS regarding recruitability, even early in the disease. Furthermore, an analysis of the LUNG SAFE study[7] found a prevalence of 12% phenotype L in non–COVID ARDS, suggesting that this phenotype is not unique to COVID-19 ARDS. We also found a strong correlation between R/I and $\dot{Q}_S/\dot{Q}_T$ variation. Unlike Beloncle et al,[6] we did not use a surrogate of mixed venous blood saturation (S_{vO_2}) for $\dot{Q}_S/\dot{Q}_T$ calculation. Indeed, studies have shown that central venous blood saturation and S_{vO_2} correlation is highly variable, potentially producing large errors in derived parameters.[8]

It seems important to note the strong heterogeneity in our results regarding the effects of high PEEP. Indeed, in the low recruitability group (R/I < 0.5), the use of high PEEP, compared to low PEEP, seemed associated with reduction in compliance (35 [25–35] mL/cm H_2O vs 44 [40–53] mL/cm H_2O) and with moderate decrease in $\dot{Q}_S/\dot{Q}_T$ (22.7 [13.3–29.3] mL/cm H_2O vs 26.9 [23.2–34.5] mL/cm H_2O) (data not shown). In contrast, in the highly recruitable group (R/I ≥ 0.5), high PEEP, compared with low PEEP, did not appear to induce any change in compliance (40 [33–43] mL/cm H_2O vs 40 [36–48] mL/cm H_2O) but was associated with marked fall in $\dot{Q}_S/\dot{Q}_T$ (28.1 [20.1–34.2] mL/cm H_2O vs 50.7 [38.2–63.2] mL/cm H_2O) (data not shown). These results underline the inconsistent benefit expected from high PEEP levels. Accordingly, the choice of PEEP should be individualized.

Our study has several limitations. First, the small number of subjects limits its power in detecting small differences and does not allow generalization to a large population of COVID-19 ARDS. Moreover, the limited sample size does not allow us to perform subgroup analyses, which could describe the heterogeneity of COVID-19 ARDS profiles, especially in terms of recruitability, compliance, and potential impact of subject morphology. Second, the characterization at 2 PEEP levels does not allow determination of optimal PEEP. Third, measurements were not repeated to assess changes over time in recruitability. Fourth, additional hemodynamic evaluation through transthoracic echocardiography was not performed. Consequently, we were not able to assess the respective involvements of right heart failure or reduced cardiac preload to explain the reduction in cardiac index observed at high PEEP.

In conclusion, most subjects presenting with COVID-19 ARDS had R/I $\geq$ 0.5. High level of PEEP improved oxygenation and reduced $\dot{Q}_S/\dot{Q}_T$, with a strong statistical correlation between R/I and $\dot{Q}_S/\dot{Q}_T$ variation.

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