BRIEF RESEARCH COMMUNICATION

Comparison of Respiratory and Hemodynamic Parameters of COVID-19 and Non-COVID-19 ARDS Patients

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Abstract

Background: COVID-19 can cause a clinical spectrum from asymptomatic disease to life-threatening respiratory failure and acute respiratory distress syndrome (ARDS). There is an ongoing discussion whether the clinical presentation and ventilatory parameters are the same as typical ARDS or not. There is no clear understanding of how the hemodynamic parameters have been affected in COVID-19 ARDS patients. We aimed to compare hemodynamic and respiratory parameters of moderate and severe COVID-19 and non-COVID-19 ARDS patients. These patients were monitored with an advanced hemodynamic measurement system by the transpulmonary thermodilution method in prone and supine positions.

Patients and methods: Data of 17 patients diagnosed with COVID-19 and 16 patients diagnosed with other types of diseases with moderate and severe ARDS, mechanically ventilated, placed in a prone position, had advanced hemodynamic measurements with PiCCO, and stayed in the intensive care unit for more than a week were analyzed retrospectively. Patient characteristics and arterial blood gases analysis recorded at admission and respiratory and advanced hemodynamic parameters during the first week were compared in prone and supine positions.

Results: No difference was observed in the respiratory parameters including respiratory system compliance between COVID-19 and non-COVD-19 patients in prone and supine positions. In comparison of advanced hemodynamic parameters in the first week of intensive care, the extravascular lung water and pulmonary vascular permeability indexes measured in supine position of COVID-19 ARDS patients were found to be significantly higher than non-COVID-19 patients. Duration of prone position was significantly longer in patients diagnosed with COVID-19 ARDS.

Conclusions: The results of this study suggested that COVID-19 ARDS is a variant of typical ARDS with a different pathophysiology.

Keywords: ARDS patients, COVID-19, Hemodynamic parameters, Transpulmonary thermodilution method.

Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-23856

Introduction

The SARS-CoV-2 infection leads to a clinical spectrum from asymptomatic cases to severe respiratory failure and ARDS.[1-3] It is still discussed whether COVID-19 has any similarity with ARDS unrelated to COVID-19, even whether it is ARDS or not, along with the existence of various phenotypes.[4-6]

According to an international survey, transpulmonary thermodilution was used by 21% of respondents for detection of pulmonary edema in COVID-19 ARDS patients, but there is still little information on the hemodynamic parameters obtained by the transpulmonary thermodilution method in COVID-19 ARDS cases.[7] In this study, hemodynamic and respiratory parameters of moderate and severe COVID-19 ARDS patients and non-COVID-19 ARDS patients who underwent advanced hemodynamic monitoring via the transpulmonary thermodilution method in prone and supine positions were compared.

Materials and Methods

The study was approved by the University of Health Sciences Bakırkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee with the date of 08.06.2020 and decision number of 12. Information and consent forms were signed by the relatives of all the patients. The patients' data would be used retrospectively in scientific studies during their hospitalization in the intensive care unit.

Patients (Obtaining Patient Data)

Respiratory and advanced hemodynamic parameters of 1,015 patients who were registered with "ImdSoft-Metavision/QlinICU Clinical Decision Support Software (Israel)" hospitalized in the Intensive Care Clinic of Istanbul Bakırkoy Dr. Sadi Konuk Training and Research Hospital between 01.01.2019 and 01.06.2020, and patients' demographic data were obtained via Structured Query Language (SQL) inquiries. Among these patients, the data of 32 non-COVID and 108 confirmed

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How to cite this article: Asar S, Acicbe Ö, Sabaz MS, Tontu F, Canan E, Cukurova Z, *et al*. Comparison of Respiratory and Hemodynamic Parameters of COVID-19 and Non-COVID-19 ARDS Patients. Indian J Crit Care Med 2021;25(6):704–708.

Source of support: Nil

Conflict of interest: None

COVID-19 ARDS patients, sedated and mechanically ventilated (Maquet Servo-i, Sweden) using pressure control mode, stayed in intensive care unit for more than a week (7 days), and were diagnosed with moderate and severe ARDS according to the Berlin criteria, were analyzed. The definite COVID-19 diagnosis was confirmed by PCR (Bio-Speedy Covid-19 RT-Qpcr detection Kit-Bioeksen, Turkey) obtained from the nasal swab sample and chest computed tomography images. Advanced hemodynamic monitoring via the transpulmonary thermodilution method (PiCCO, Pulsion Medical Systems SE, Germany) was performed on 25 non-COVID ARDS patients and 40 COVID-19 ARDS patients. Continuous monitoring of central venous oxygen (CeVOX) saturation was performed to calculate oxygen delivery and oxygen consumption (ScVO2, DO2, and VO2) of 35 COVID-19 and 22 non-COVID-19 patients who received advanced hemodynamic monitoring via the transpulmonary thermodilution method. Twenty-four patients in both groups receiving vasopressors were not placed in prone position at admission or whose hemodynamic measurements were incomplete were not included in the analysis. Sixteen non-COVID-19 ARDS patients (four trauma, six postoperative, six pneumonia) and 17 COVID-19 ARDS patients who were intubated, sedated, and mechanically ventilated in pressure control mode, remained in the prone position for 12 to 24 hours after admission to the intensive care and had advanced hemodynamic measurements with the transpulmonary thermodilution method after each position change were included in the study.

Central venous pressure (CVP) was measured after placing the patients in prone and supine positions, and advanced hemodynamic measurements were carried out at the beginning and end of each position with the transpulmonary thermodilution method (PiCCO; Pulsion Medical Systems SE; Germany). CeVOX catheters were calibrated with arterial and venous blood gas measurements by entering the $ScvO_2$, SaO_2, and hemoglobin values at each position change. Oxygen delivery (DO_2) and oxygen consumption (VO_2) were computed by the PiCCO module. The per-minute peak inspiratory pressure (Ppeak), respiratory rate (RR), expiratory tidal volume (TVe), work of breathing ventilator (WOBv), inspiratory expiratory rate, and positive end expiratory pressure (PEEP) of the patients, retrieved from the data repository, were used in our analysis. Mechanical power was measured by applying Becher's pressure control simplified power equation to the per-minute respiratory parameters of the patients.[13] Each measurement corresponds to 1 minute (see electronic supplement). Similarly, the advanced hemodynamic parameters obtained with the transpulmonary thermodilution method and CeVOX catheters, such as systemic vascular resistance index (SVRI), cardiac output (CO), pulse contour cardiac index (PCCI), heart rate (HR), stroke volume variation (SVV), central venous oxygen saturation ($ScvO_2$), CVP, diastolic arterial pressure, *extravascular lung water index* (EVLWI), cardiac power index, cardiac function index (CFI), oxygen delivery (DO_2), oxygen consumption (VO_2), *pulmonary vascular permeability* index (PVPI), systolic arterial pressure, and mean arterial pressure average values per minute were obtained from the data repository. Additionally, patient characteristics, arterial blood gas analysis, and respiratory parameters during admittance from ICU were also obtained.

Statistical Methods

The GraphPad Prism (v 5.01) software was used for the statistical analysis in this study. The frequency distribution and percentages of qualitative variables such as gender were calculated and analyzed with chi-square and *Fisher's exact* tests. The homogeneity of the variables was evaluated via the Shapiro–Wilk normality test. Because the data were evaluated as non-homogeneous, the Mann-Whitney U test was used for binary variable comparisons. The Wilcoxon test was used to compare the dependent parameters measured consecutively within the group. The statistical analysis was carried out on median and interquartile range (IQR) values. The $p < 0.05$ values were considered statistically significant.

EVLWI values were mainly considered as primary outcome data in the comparison of 17 patients with severe COVID-19 pneumonia and 16 patients with moderate–severe non-COVID-19 ARDS. The mean and standard deviation (sd) values of *EVLWI* values for the patients in the groups were calculated as 14.51 ± 4.148 and 10.68 ± 3.832, respectively, and the group sample size was calculated as 1.13. The number of patients required in each group was calculated as 15 so that the power of the study could be above 90% with an error of $\alpha = 0.05$.

Results

In this study, demographic data, length of stay in intensive care and on ventilator, advanced hemodynamic parameters, and respiratory and blood gas parameters of patients with COVID-19 ($n = 17$) and non-COVID-19 ARDS ($n = 16$) were compared. The 71% (12) of the patients in the COVID-19 group and 81% (13) in the non-COVID-19 group were male. The effect of the gender distributions of the groups was analyzed using Fisher's exact test. Results showed that there was no gender difference ($p = 0.3$). Following ICU mortality was observed: 59% in the COVID-19 ARDS group and 50% in ARDS patients due to other causes. The survival rate of the groups was compared using chi-square test. We found no statistically significant difference between the groups ($p = 0.6$).

The age, height, weight, BMI, time of stay in the ICU, and duration of invasive mechanical ventilation, blood gas parameters at the admission to the intensive care unit and age and APACHE II and SOFA scores of the groups were compared by the Mann–Whitney *U* test. The results are presented in Table 1.

Respiratory parameters in the prone and supine positions during the first-week hospitalization of the COVID-19 patients who developed ARDS and severe non-COVID-19 ARDS patients in the ICU were compared by the Mann–Whitney *U* test. All the analysis results including the median and IQR values with *p*-values of the respiratory parameters for the prone and supine positions of the two groups are given in Table 2.

The analysis of the results indicated that not only all respiratory parameters but also respiratory parameters of the prone and supine positions of the groups were comparable (Table 2).

Advanced hemodynamic parameters of prone and supine positions of the two groups were compared with the Mann–Whitney U test. For the following parameters, there were no statistically significant differences calculated in both positions between two different patient groups: $ScvO_2$, DO_2, VO_2, SVR, PCCI, CO, CPI, CFi, SVV, CVP, ABP sys, ABP dias, and HR values. The EVLWI and PVPI values were similar in each patient group in the prone

Table 1: Comparison of patient characteristics and ABG results at ICU admission

	COVID-19 ARDS median (IQR)	*Non-COVID-19 ARDS median (QR)*	*p-value*
Age (year)	49 (57–67)	45 (54–69)	0.5
Height (m)	1.70 (1.60–1.75)	1.70 (1.62–1.79)	0.3
Predicted body weight (kg)	66 (52–70)	66 (59–74)	0.5
Body mass index (kg/m)	27.7 (26.2–29.7)	27.8 (23.6–29.7)	0.3
Length of stay in ICU (hr)	364 (231–486)	374 (196–575)	0.6
IMV duration (hr)	246 (193–419)	252 (161–504)	0.7
SOFA score	7 (10–12)	8 (10–13)	0.7
APACHE II score	21 (17–28)	21 (18–26)	0.9
pH, prone	7.27 (7.20–7.30)	7.31 (7.23–7.40)	0.2
BE (mEq/L)	−1.0 (−5.0 to 4.2)	−0.2 (−6.0 to 3.02)	0.8
PCO_2 (mm Hg)	59 (45–68)	48 (33–66)	0.3
PaO_2 (mm Hg)	66 (58–72)	58 (44–70)	0.1
FiO_2 (%)	51 (50–60)	44 (41–50)	0.009**
PaO_2/FiO_2	115 (97–132)	121 (100–146)	0.5
Lactate (mEq/L)	1.6 (1.2–2.3)	1.3 (1.6–2.0)	0.6

** indicates statistically significant with indicated p values.

Table 2: Comparison of respiratory parameters of COVID-19 and non COVID-19 ARDS patients at prone and supine positions

Respiratory parameters	*COVID-19ARDS (17) median (IQR)*	*Non-COVID-19 ARDS (16) median (IQR)*	*p value*
MP J/min—prone	17.7 (15.4–22.2)	17.3 (15.7–19.4)	0.6
MP J/min—supine	18.0 (14.5–21.1)	17 (13.4–19.6)	0.2
WOBv, J—prone	1.4 (1.2–1.6)	1.3 (1.1–1.5)	0.4
WOBv, J—supine	1.3 (1.2–1.5)	1.3 (1.0–1.5)	0.2
Ppeak, cmH_2O—prone	25.6 (24.0–29.2)	28.0 (24.9–29.1)	0.4
Ppeak, cmH_2O—supine	25.8 (23.7–28.0)	24.9 (23.2–27.9)	0.8
PEEP, cmH_2O—prone	9.2 (8.2–10.1)	9.0 (8.0–10)	0.5
PEEP, cmH_2O—supine	8.8 (7.9–10.0)	8.7 (8.1–9.9)	0.7
TVe, mL—prone	516.1 (505.5–557.6)	527.9 (453.9–546)	0.8
TVe, mL—supine	498.6 (465.1–538.5)	472.6 (494.9–554.8)	0.8
Cdyn, mL/cmH_2O—prone	34.6 (27.7–37.7)	36.9 (31.7–39.9)	0.2
Cdyn, mL/H_2O—supine	33.5 (25.3–38.9)	37.8 (29.9–39.2)	0.1
RR, 1/min—prone	14 (13–15)	12 (12–15)	0.05
RR, 1/min—supine	15 (13–16)	14 (12–15)	0.05
İ:E ratio—prone	0.6 (0.5–0.8)	0.5 (0.5–0.06)	0.08
İ:E ratio—supine	0.6 (0.5–0.7)	0.6 (0.5–0.8)	0.4

* indicates statistically found to be significant with indicated p values.

position while the same parameters were statistically different in the supine position (Table 3).

Discussion

The median values of respiratory parameters for patient groups were comparable in the first week. Ferrando et al. reported that no difference was found between 741 COVID-19 ARDS and non-COVID-19 ARDS cohorts in terms of tidal volume, PEEP, Plato pressure, compliance, and driving pressure.[8] In the studies of Graselli et al., median compliance values were found 28% higher in 301 COVID-19 ARDS patients in Italy.[9] Grieco et al. found compliance slightly higher in 30 COVID-19 ARDS patients.[10] Even though Gattinoni et al. reported the existence of two different phenotypes with low and high compliances among COVID-19 patients, there are still discussions on this issue.[11,12]

Between both groups, a significant difference was found between EVLWI and PVPI values measured in the supine position in the first week of intensive care. However, no difference was observed between oxygen delivery and consumption, which are other advanced hemodynamic parameters. Higher EVLWI and PVPI values in COVID-19 ARDS patients were thought to be associated with the severity of the disease. It is known that EVLWI and PVPI values are associated with ARDS severity.[13] Published studies have

Table 3: Comparison of advanced hemodynamic parameters of COVID-19 and non-COVID-19 ARDS patients at prone and supine positions

Advanced hemodynamic parameters of the groups	*COVID-19 ARDS (17) median (IQR)*	*Non-COVID-19 ARDS (16) median (IQR)*	*p-value*
Duration of prone position (hr)	72 (32–106)	41 (18–50)	0.006**
EVLWİ (mL/kg) prone	14.4 (11.1–16.9)	11.9 (9.1–15.4)	0.1
EVLWİ (mL/kg) supine	14.5 (10.8–16.9)	9.9 (8–11.8)	0.008**
PVPİ prone	2.9 (1.9–3.4)	2.4 (1.9–2.8)	0.3
PVPİ supine	3.1 (2.1–3.7)	2.1 (1.7–2.3)	0.01*
$ScvO_2$ (%) prone	82 (77.5–85.8)	79.9 (72.3–82.4)	0.1
$ScvO_2$ (%) supine	78 (73.1–85.3)	78.8 (76.3–80.8)	0.7
DO_2 (mL/min) prone	971 (775.9–1,455)	801.7 (652.4–1,027)	0.1
DO_2 (mL/min) supine	895 (613.3–1,034)	834.5 (572.9–894.7)	0.2
VO_2 (mL/min) prone	134.8 (76.5–175.2)	165.2 (97.6–181.8)	0.3
VO_2 (mL/min) supine	170.4 (93.67–213.4)	165.0 (103.9–187.1)	0.7
SVRİ (dyn sec cm^{-5} m^2) prone	1,647 (1,512–2,379)	1,850 (1,411–2,467)	0.8
SVRİ (dyn sec cm^{-5} m^2) supine	1,966 (1,672–2,327)	1,852 (1,634–2,395)	0.8
PCCİ (L/min/m^2) prone	3.3 (2.8–4.2)	3.5 (2.5–4.4)	0.8
PCCİ (L/min/m^2) supine	2.9 (2.5–3.7)	3.2 (2.4–3.9)	0.8
CO (L/min) prone	6.2 (5.1–8.1)	6.4 (5.2–7.6)	0.6
CO (L/min) supine	5.9 (5.1–7.5)	5.7 (4.5–7.2)	0.6
CPİ (W/m^2) prone	1.3 (0.9–1.5)	1.2 (0.9–1.6)	0.9
CPİ (W/m^2) supine	0.9 (0.8–1.4)	0.9 (0.7–1.4)	0.8
CFİ (L/min) prone	5.3 (4.2–5.6)	4.7 (4.3–6.9)	0.6
CFİ (L/min) supine	4.5 (4.2–6.0)	4.5 (4.3–6.0)	0.8
SVV (%) prone	8.7 (7.2–12.1)	7.5 (3.6–12.2)	0.3
SVV (%) supine	9.8 (6.7–10.8)	9.1 (4.4–14.5)	0.8
CVP (mm Hg) prone	8.3 (6–10.0)	7.6 (5.7 to13.6)	0.6
CVP (mm Hg) supine	7.1 (6.1–10.0)	7 (4.9–8.2)	0.2
ABP sys (mm Hg) prone	134 (119–144)	121 (113–150)	0.6
ABP sys (mm Hg) supine	124 (111–135)	128 (116–133)	0.6
ABP dias (mm Hg) prone	64 (57–72)	66 (59–72)	0.7
ABP dias (mm Hg) supine	58 (51–68)	58 (56–66)	0.7
HR prone (1/min)	97 (90–118)	86 (80–106)	0.5
HR supine (1/min)	91 (75–103)	84 (79–103)	0.5

* and ** indicate statistically found to be significant with indicated p values.

reported that severe ARDS rates are higher in COVID-19 ARDS patients than non-COVID-19 ARDS patients.[8,9] Although we did not find publications where EVLWI and PVPI measurements were performed in COVID-19 patients, there are studies comparing the total lung weights that indicate water increase in the lung. In the comparison between 301 COVID patients and non-COVID ARDS patients by Graselli et al., no difference was detected between the two cohorts in terms of total lung weight.[9] Gattinoni et al. reported in their article that there were phenotypes with higher total lung weight and edema in COVID-19 ARDS patients.[11] Our study revealed that our COVID-19 patient population was more consistent with the manifestation defined as phenotype H with high pulmonary edema and high elastance. Although each group of patients seems to have some difference in the prone position, statistical analysis showed that such observed difference was not statistically significant.

The supine position EVLWI and PVPI values of non-COVID-19 ARDS patients were found to be lower compared to the prone position values. However, when the prone and supine values of this patient group were compared, they were not found to be statistically significant. Still, this statistically insignificant decrease was considered as a recovery inclination. It is a known fact that non-COVID-19 ARDS patients benefit from protective mechanical ventilation treatment and prone position. The minimal decrease in EVLWI and PVPI values in this group has been thought to result from the postprone effect. It is known that the prone position improves the ventilation/perfusion balance by opening the pulmonary-dependent lung areas and leading to better gas exchange by causing homogeneity in the lung tissue.[14] Prone position is eventually known to reduce EVLW and pulmonary vascular permeability indices and contribute to permanent recovery in non-COVID ARDS patients.[15]

Similarly, COVID-19 ARDS patients were expected to benefit from the mechanical ventilation and position maneuvers within the first 7 days. However, no decrease was seen in EVLWI and PVPI values in COVID-19 patients in this study. This phenomenon indicates a difference in the pathophysiology between COVID-19 ARDS and the non-COVID-19 patients with ARDS due to other causes. For this reason, COVID-19 ARDS patients had to be placed

in the prone position for a longer time than non-COVID-19 ARDS patients (Table 3). The prone position was thought to temporarily improve the ventilation/perfusion balance by recruiting pulmonary-dependent lung areas in COVID-19 ARDS patients. However, this temporary effect did not cause a tendency to decrease in EVLWI and PVPI values as in patients with ARDS due to other causes. The mortality rate, duration of stay in the intensive care unit, and duration of invasive mechanical ventilation were very similar between the two patient groups (Table 1).

In conclusion, this study demonstrated that lung-protective mechanical ventilation and prone positioning had limited effect on EVLWI and PVPI values, which are permanent indicators of lung recovery, in the early period of the disease course (first week) of COVID-19 ARDS group of patients compared to non-COVID ARDS group of patients. We suggest that COVID-19 ARDS patients should be placed in the prone position for a longer time and more often. The COVID-19 ARDS manifestation is thought to be a variant of typical ARDS.

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