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Detection of Pulmonary Shunts by Transcranial Doppler in Hospitalized Non-mechanically Ventilated Coronavirus Disease-19 Patients

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BACKGROUND

In severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated disease coronavirus disease 2019 (COVID-19), hypoxemia mechanisms differ from those observed in acute respiratory distress syndrome. Hypoxemia and respiratory failure in COVID-19 are attributed to pulmonary angiopathy, increasing physiological pulmonary shunting[1-3]. Contrast-enhanced transcranial Doppler (TCD) with agitated saline of middle cerebral arteries (MCA) is a non-invasive method with a higher sensitivity for detecting right-to-left shunts than contrast-enhanced echocardiography[4]. TCD has been used to detect intrapulmonary shunts in COVID-19 patients undergoing invasive mechanical ventilation (IMV)[5]. We studied the relationship between intrapulmonary shunting, disease severity, and in-hospital outcome in COVID-19 patients not undergoing IMV (non-IMV).

METHODS

We conducted a prospective observational study at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán from September 7, 2020, to October 14, 2020, including consecutive hospitalized, non-IMV adult (≥18 years) patients presenting during the first 10 days from symptom onset, with a positive SARS-CoV-2 real-time polymerase chain reaction test from nasal swab samples, and a COVID-19 compatible chest computed tomography (CT) scan. We excluded patients transferred to other hospitals within

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the first 24 h after admission; those with a known history of pulmonary, liver, or structural heart disease; and patients undergoing hemodialysis or extracorporeal membrane oxygenation. The Institutional Research and Ethics Committees approved the conduction of the study (NER-3401-20-20). Signed informed consent was obtained from each patient.

We captured demographic characteristics, comorbidities, clinical information, chest CT scan, and laboratory findings in a database derived from electronic medical records. Lung involvement by chest CT-scan was semi-quantitatively classified as mild/moderate (20-50%) or severe (>50%) by experienced radiologists. We calculated the PaO_2/FiO_2 ratio using the FiO_2 provided by each oxygen delivery device (nasal cannula or simple face mask) when arterial blood gases (ABGs) were obtained.

In all patients, we performed a contrast-enhanced TCD of both MCA within the first 3 days after admission with a portable Digi-One™ ultrasound (Rimed Inc., NY, USA) using a 2 MHz transducer at an insonation level of 45-55 mm. Agitated saline was injected through a peripheral intravenous line in the upper extremity. The system software automatically counted the number of high-intensity signals (HITS), defined as unidirectional signals of a duration of <300 ms, with an amplitude of at least 3 dB greater than the background blood flow signal, within the Doppler spectrum and accompanied by a characteristic sound, during a 10-s Valsalva maneuver, which two researchers later manually validated. We performed a contrast-enhanced transthoracic echocardiogram in patients with a positive test to rule out right-to-left cardiac shunts.

We compared the characteristics and outcomes of patients with pulmonary shunts and those without shunts. Categorical variables are reported as frequencies and proportions. Continuous variables as the median with interquartile range (IQR) or as mean with SD. Analyses of differences between categorical variables were performed with the X^2 test and for continuous variables with the Student's t-test or Mann–Whitney U-test. Associations between the number of HITS, days of illness, $PaCO_2$ levels, and PaO_2/FiO_2 ratio were performed by simple linear regression. All values were two-tailed and considered significant when $p \leq 0.05$. Statistical analyses were performed with IBM SPSS Statistics, version 26 (IBM Corp., Armonk, NY, USA).

RESULTS

We studied 31 patients (87.5% men, and mean age: 44.4 ± 11.02 years). Eight patients had a positive HITS test; one patient was diagnosed with a patent foramen ovale, and 7 (22.5%) with pulmonary shunts. The median interval from symptom onset to admission was 7 days. There were no differences in demographics, comorbidities, ABG analysis, and chest CT findings between patients with and those without pulmonary shunts (Table 1). Patients with a positive HITS test had higher D-dimer and lower C-reactive protein levels. The median number of HITS was 5 (IQR: 3-11). There was no relationship between the number of HITS, $PaCO_2$ levels, PaO_2/FiO_2 ratio, or interval from symptom onset to admission (Fig. 1). At admission, all patients received intravenous dexamethasone (6 mg/day for 5-10 days) and thromboprophylaxis with either unfractionated heparin or enoxaparin before TCD was performed. None of the patients were receiving vasopressors or had a diagnosis of pulmonary bacterial coinfection when the TCD was performed. Five patients required IMV after TCD was performed (none with a positive HITS test). The number of days of in-hospital stay and outcome was similar between groups.

DISCUSSION

In this study, we detected intrapulmonary shunts in 22.5% of non-IMV patients with COVID-19. In contrast to the 83% of right-to-left shunts from an undetermined source described in COVID-19 patients undergoing IMV, in which the PaO_2/FiO_2 ratio correlated with the number of HITS[5], we did not observe this correlation. Disease severity by chest CT scan and PaO_2/FiO_2 ratio was similar between groups, but D-dimer levels were higher in patients with pulmonary shunts. These findings suggest that vascular pathology develops during the mild-to-moderate stages of COVID-19, probably due to microthrombosis and occlusion of alveolar capillaries[1,3]. Interestingly, none of the patients with a positive HITS test required IMV, and mortality rates were similar between groups,

Table 1: Baseline characteristics and in-hospital outcomes of COVID-19 patients

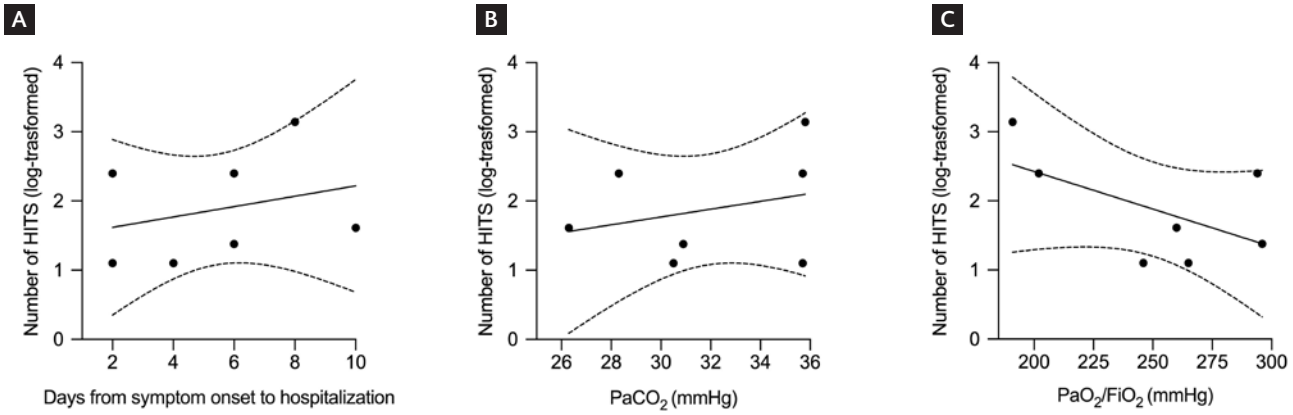
	All patients (n = 31)	Without pulmonary shunts (n = 24)	With pulmonary shunts (n = 7)	p-value
Age, mean (±SD), years	44.4 (11.02)	43.83 (10.37)	46.14 (13.83)	0.412
Sex, n (%), male	25 (80.6)	21 (87.5)	4 (57.1)	0.074
Comorbidities, n (%)				
Diabetes	6 (19.4)	5 (20.8)	1 (14.3)	0.7
Hypertension	7 (22.6)	5 (20.8)	2 (28.6)	0.667
Smoking	18 (58.1)	16 (66.7)	2 (28.6)	0.072
Chronic kidney disease	3 (9.7)	1 (4.2)	2 (28.6)	0.055
Obesity, BMI ≥30 kg/m^2	13 (41.9)	10 (41.7)	3 (42.9)	0.955
BMI, mean (±SD), kg/m^2	30.66 (7.91)	30.67 (7.38)	30.63 (10.19)	0.991
Days from symptom onset, median (IQR)	7 (5-8)	7 (6-8)	6 (2-8)	0.199
Inflammatory response biomarkers, median (IQR)				
D-dimer, ng/dL	639 (462-961)	594 (444-747)	1005 (800-1767)	0.017
Lactic dehydrogenase, U/L	305 (239-354)	310.5 (243.5-376.5)	261 (220-317)	0.317
Ferritin, ng/dL	522.6 (332.3-806.8)	570.7 (317-1335.6)	491.2 (332.3-621.8)	0.417
C-reactive protein, mg/dL	12.39 (5.87-20.01)	15.93 (8.32-21.65)	5.49 (3.26-11.63)	0.017
Neutrophil/lymphocyte ratio	6.7 (4.49-10.62)	6.45 (4.55-9.89)	9.93 (3.86-14.73)	0.563
ABGs, mean (±SD)				
pH	7.45 (0.047)	7.45 (0.05)	7.45 (0.06)	0.882
PaO_2, mmHg	73.25 (20.23)	72.06 (21.92)	77.34 (13.39)	0.552
$PaCO_2$, mmHg	30.96 (4.15)	30.69 (4.27)	31.89 (3.9)	0.513
HCO_3–, mmol/L	21.62 (2.95)	21.48 (3.09)	22.11 (2.54)	0.624
PaO_2/FiO_2,mmHg	216.74 (57.38)	208 (64)	251 (41)	0.099
Chest CT severity, n (%)				0.531
Mild/moderate, 20–50%	12 (38.7)	10 (41.7)	2 (28.6)	
Severe, >50%	19 (61.3)	14 (58.3)	5 (71.4)	
In-hospital outcomes, n (%)				
IMV	5 (16.1)	5 (20.8)	0	0.187
Days of in-hospital stay	7 (4-11)	7 (4-12)	7 (6-9)	0.661
Death	4 (12.9)	3 (12.5)	1 (14.3)	0.901

SD: standard deviation; BMI: body mass index; IQR: interquartile range; PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; HCO_3–: bicarbonate; FiO_2: fraction of inspired oxygen; CT: computed tomography; IMV: Invasive mechanical ventilation; ABGs: Arterial blood gases.

suggesting that the presence of intrapulmonary shunts in mild-to-moderate COVID-19 may not correlate with a worst outcome.

This study has limitations, including the small number of recruited patients and the description of chest CT findings by the total percentage of lung damage and not by the type of radiological finding (ground-glass/consolidation). Other limitations are that TCD was performed only on one occasion but not as a follow-up method, and that we did not include a non-COVID-19 control group.

Figure 1. Relationship between the number of HITS, days from symptoms onset to hospitalization, $PaCO_2$, and PaO_2/FiO_2 ratio. (**A**) Days from symptoms onset to hospitalization, $R^2 = 0.082$, p = 0.533. (**B**) $PaCO_2$, $R^2 = 0.079$, p = 0.54. (**C**) PaO_2/FiO_2 ratio, $R^2 = 0.328$, p = 0.179. Lines show regression line from a simple linear regression with 95% confidence intervals. HITS: high-intensity signals; $PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inspired oxygen.



In this study we demonstrate that intrapulmonary shunting may occur in mild to moderate COVID-19, and that pulmonary vascular pathology may not play a key role until the severe stages of the disease.

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