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Shunt in critically ill Covid-19 ARDS patients: Prevalence and impact on outcome (cross-sectional study)

Introduction

Several autopsies studies reported that SARS-CoV-2- induces numerous vascular damages such thrombosis, apoptosis, edema, and anastomoses [1,2]. In hypoxemic Covid-acute respiratory distress syndrome (C-ARDS) patients, transcranial agitated saline microbubble doppler studies, demonstrated a trans-pulmonary bubble transit (TPBT) [3]. TPBT may occur in perfused non-aerated lung areas secondary to pulmonary vessels dilatation and anastomoses. A shunt through the patent foramen ovale (PFO) may occur in the case of low compliance ARDS with pulmonary arterial hypertension. We aimed to explore critical C-ARDS patients under mechanical ventilation (MV); using trans-thoracic echocardiography (TTE) coupled with bubble test (BT) (TTE+BT) in order to look for PFO or TPBT and determine its impact on outcome.

Patients and methods

Design and population

this single-center cross-sectional study enrolled consecutively patients from September 2020 to June 2021. Inclusion criteria were: **1-** Age ≥ 18 years old, **2-** patients with positive SARS-CoV-2 infection, **3-** severe ARDS based on the Berlin definition and **4-**under MV. Exclusion criterion was poor quality of ultrasound images or contrast test.

Protocol

The TTE+BT was performed within the first 24 h of MV by trained operators. Used ultrasonic device was of Aloka-ARIETTA V60 model from Hitachi Company. Referring to the technique used by Masi P and colleagues [4], the right-to-left shunt was sought on the four-chamber view by injecting 9.5 ml of gelatine solution aerated with 0.5 ml of room air via two syringes connected to a three-way stopcock. Up to three successful contrast studies were performed on each patient. The Shunt was quantified according to the number of passed bubbles as follows: minor (<10), moderate (10−30) and large (>30) [4-6].

Analysis

The data were analyzed using the SPSS Base 20 statistical software package. Continuous data were expressed as mean ± standard deviation (SD) or median [IQR 2575] and compared using the T student test or Mann-Whitney test as appropriate. Categorical variables, expressed as percentages, were compared using the chi-square test or Fisher exact test. Two-tailed *p* values inferior than 0.05 were considered significant.

Results

161 patients were admitted to the ICU for CVID pneumonia among them, 83 were intubated and in whom the TTE+BT was carried out. Eight patients were excluded for inconclusive TTE/BT (n=5) and for intolerance of the supine positioning (n=3). Finally, 75 patients with a complete TTE+BT study were considered in the study. A shunt was detected in 23 cases (prevalence=31%). It was identified as TPBT in 12 cases (16%) and quantified as important (>30 bubbles) in 3 cases. PFO was revealed in 11 cases (15%) and 6/11were important. As showed in the jointed Table 1, no major difference was observed for the baseline characteristics, para-clinical findings and therapeutic data. Patients in whom the shunt was detected have less hypertension (22% vs 56%, p= 0.01) and higher CRP (189 vs 142 mg/L, p = 0.024). All patients received, upon ICU admission, dexamethasone 6 mg daily for up to 10 days. Late steroids (2 weeks of unfavorable evolution), based on methylprednisolone 250 mg daily for 3 days followed by decreasing doses was prescribed in 7 patients without difference between groups. The presence of shunt did not extend MV duration or ICU-stay. Overall, the mortality was considerable regardless of the presence or not of the shunt.

Discussion

Our PFO prevalence (15%) was greater to that reported by Masi P and colleagues at 10% [4]; but lower than that reported in non Covid-ARDS patients (19.2%) [5]. TPBT prevalence (16%) was lower than that of Masi P, et al. (20%) [4] and even lower than that in non Covid-ARDS patients (26%) [6].

The mortality rate we reported is comparatively quite high. Some factors can be considered as contributors to higher mortality: **1-** the first and important reason is case mix in this cohort distinguished by its fragility of the underlying terrain (84% have at least one co morbidity), its illness severity (median SOFA = 6,5) and late timing of ICU admission (10 days on average). The case mix is, in fact, due to the local logistical strategy during this crisis that opted to devote our medical ICU entirely for very ill Covid patients, **2**- very limited availability of therapeutics and rescue therapies.

Weaknesses

We estimated that the single-center design, the TTE used for bubble contrast, the selective of only patients under MV and just within the 24H could limit the generalization of our results. It is important to point out that the external validity of our study represents a major issue. In order to overcome that, we have planned a project of a study on a larger scale with the objective to determine the prevalence of a right/left shunt and its prognostic impact in all ICU patients. The design differs by the type of population to be included (ICU patients with SARS-CoV-2 pneumonia requiring or not invasive ventilation) and the participation of four Tunisian intensive care units.

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Table 1
Study variables in all patients and compared according to the presence of shunt.*

	Overall results	Comparative results		
	All population ($n = 75$)	Absence of shunt ($n = 52$)	Presence of shunt ($n = 23$)	p
Clinical characteristics				
Age (years), med [IQR]	64 [54–71]	64.5 [56–71]	61 [53–70]	0.63
Sex-ratio (M/F)	51/24	36/16	15-Aug	0.79
BMI (kg/m^2), med [IQR]	26.2 [24.2–31]	27.5 [24–31]	25.9 [24.4–27.6]	0.16
No co morbidity, n (%)	12 (16)	8 (15,4)	4 (17,4)	0,26
Diabetes mellitus, n (%)	28 (38)	23 (44)	5 (22)	0.07
Hypertension, n (%)	34 (45)	29 (56)	5 (22)	**0.01**
Time from onset to:				
- ICU admission (days), med [IQR]	10 [8–14]	9,5 [7–13]	10 [7–12,5]	0,88
-Ventilation (days), med [IQR]	12 [9–15]	12 [10–15]	10 [7.5–14.5]	0.09
SOFA score, med [IQR]	6.5 [4–9]	6 [3.5–8.5]	7 [4–9.5]	0.18
Biology findings				
P/F, med [IQR]	78 [69–102]	81 [68–106]	77 [70–98]	0.97
PCO_2 (mm Hg), med [IQR]	50 [42–61]	50.5 [41–59.7]	48 [44–61]	0.62
CRP (mg/l), med [IQR]	156 [99–235]	142 [84–201]	189 [138–271]	**0.024**
Lymphocytes (el/ml), med [IQR]	630 [400–820]	650 [405–827]	580 [390–730]	0.52
D dimer (μg/l), med [IQR]	1934 [737–6035]	1971 [1064–7086]	1493 [679–4107]	0.24
HS Troponines, med [IQR]	16 [6.5–69]	16.5 [7–72]	13 [6–69]	0.56
CT findings (45 achieved and all without injection)				
CT lesions ≥ 50%, n (%)	26/45 (58)	14/27 (52)	12/18 (67)	0.37
Ventilator settings, med [IQR]				
Tidal volume (ml), med [IQR]	400 [400–425]	400 [400–436]	400 [380–425]	0.31
RR (c/mn), med [IQR]	26 [24–28]	26 [26–28]	26 [24–28]	0.86
PEEP (cm H_2O), med [IQR]	8 [8–10]	8 [8–10]	8 [8–10]	0.65
Driving pressure (cm H_2O), med [IQR]	19 [16–20]	19 [16–20]	19 [16–20]	0.96
Resp Compl (ml/ cmH_2O), med [IQR]	23 [19–28]	23 [19.2–28]	22 [18–28]	0.61
Therapeutic data				
Steroids, n (%):	75 (100)	52 (100)	23 (100)	–
- Early (dexamethasone 6 mg intravenous daily for up to 10 days)	75 (100)	52 (100)	23 (100)	–
- Late (2 weeks of unfavorable evolution (methylprednisolone 250 mg daily for 3 days followed by decreasing doses)	7 (9,5)	5 (9,6)	2 (8,7)	0,66
Vasopressors, n (%)	48 (64)	36 (69)	12 (52)	0.21
Neuromuscular blockers, n (%)	73 (97)	51 (98)	22 (96)	0.52
Prone position, n (%)	70 (93)	47 (91)	23 (100)	0.31
ECMO, n (%)	3 (4)	2 (4)	1 (4,5)	–
TTE/BT features				
LVEF (%), med [IQR]	57 [48–63]	56 [48.5–62]	60 [48–63]	0.93
E/A, med [IQR]	0.9 [0.76–1.11]	0.9 [0.78–1.13]	0.9 [0.69–1.03]	0.31
E/E', med [IQR]	6.9 [5.7–8.7]	7 [6–9]	6.05 [5.7–8.4]	0.42
VTI (cm), med [IQR]	22.4 [19–25.5]	22.7 [19–25.3]	22.2 [19.5–25.6]	0.66
CO (l/mn), med [IQR]	5.65 [4.21–7.67]	5.6 [4.03–8.18]	5.6 [4.6–6.8]	0.83
SPAP (mm Hg), med [IQR]	38 [32–45]	37 [31.5–44]	39 [35–45]	0.24
TAPSE (mm), med [IQR]	17 [15–19]	17 [15–20]	16 [13–18.7]	0.25
ACP, n (%)	18 (24)	10 (20)	8 (35)	0.24
Outcomes				
MV duration (days**),** med [IQR]	8 [5–12]	7 [4–12]	8 [6–10]	0.84
ICU-LOS (days**),** med [IQR]	10 [7–14.5]	10 [6–16]	10 [7.5–13]	0.69
Mortality, n (%)	58 (78%)	40 (77%)	18 (78%)	0.22

ACP: Acute Cor pulmonale, BMI: body mass index, BT: bubble test, CO: cardiac output, E/A: Ratio between early (E) and late (A) diastolic peak velocity, E/E': early diastolic velocity peak (E) divided by the maximum mitral ring velocity at the start of diastole (E'), ECMO: Extracorporeal membrane oxygenation, ICU: intensive care unit, LOS: length of stay, LVEF: left ventricle ejection fraction, MV: mechanical ventilation P/F: ratio of partial pressure of oxygen in arterial blood and fraction of inspired oxygen, PaCO2: partial pressure of carbon dioxide in arterial blood, PEEP: positive end-expiratory pressure, PFO: patent foramen ovale, RR: respiratory rate, SPAP: systolic pulmonary artery pressure, SOFA: sequential organ failure assessment score, TAPSE: Tricuspid annular plane systolic excursion, TPBT: transpulmonary bubble transit, TTE: tansthoracic echography, VTI: Velocity Time Integral.

* To note that Ventilation data, P/F and pCO_2 were taken at the time of TTE; Laboratory data were taken at admission.

Conclusion

A right/left shunt was detected in almost a third of patients ventilated for C-ARDS with similar proportions between TPBT and PFO and no worsening effect was showed on P/F ratio, MV duration, ICU stay or mortality.

Ethics approval and consent to participate

The study was approved by the local ethics committee of the hospital. The legal representatives of the included patients were informed by the study protocol and gave their consent. The investigation was

conforming to the ethical norms of Helsinki declaration and its subsequent revisions.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Credit authorship contribution statement

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