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RESEARCH LETTER

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Cardiovascular phenotypes in ventilated patients with COVID-19 acute respiratory distress syndrome

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Approximately two-thirds of patients admitted to the intensive care unit (ICU) for coronavirus disease-19 (COVID-19) pneumonia present with the acute respiratory distress syndrome (ARDS) [1]. COVID-19-associated acute cardiac injury is frequently reported based on troponin and electrocardiographic changes [2], but its impact on cardiac function is yet unknown [3]. Accordingly, we sought to describe cardiovascular phenotypes identified using transesophageal echocardiography (TEE) in ventilated COVID-19 patients with ARDS and to compare them to those of patients with flu-induced ARDS.

All patients with confirmed COVID-19 who were mechanically ventilated for ARDS in our medical-surgical ICU underwent prospectively a TEE assessment during the first 3 days and whenever required by clinical events during ICU stay, as a standard of care. Similarly, all patients ventilated for flu-associated ARDS who underwent a TEE assessment over the last 2 years were retrospectively analyzed for comparison. Cardiovascular phenotypes were identified using previously

reported TEE criteria [4]. Same applied for acute cor pulmonale (ACP) [5]. TEE studies were read by two independent experts who had no access to the cause of ARDS and examination date. Results are expressed as medians and 25th–75th percentiles. Friedman ANOVA was used to compare quantitative parameters over time in COVID-19 patients, while Mann-Whitney *U* test and Fisher's exact test were used for comparison of continuous and categorical variables, respectively, with flu patients. No use of previous value or interpolation rule was used in the presence of missing data.

Eighteen consecutive COVID-19 patients and 23 flu patients (21 A-H1N1) were studied. COVID-19 patients were significantly older (70 [57–75] vs. 58 [49–64] years, $p = 0.006$), less severe (SAPSII 34 [30–38] vs. 43 [32–54], $p = 0.015$; SOFA 4 [2–4] vs. 6 [4–9], $p < 0.001$), required less vasopressor support (2/18 [11%] vs. 10/23 [43%], $p = 0.038$), and had longer time lag between first symptoms and ICU admission, tracheal intubation, and TEE examination when compared to flu patients (Table 1).

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Table 1 Characteristics, presentation and outcome of ventilated patients with COVID-19 and flu-related ARDS

| | COVID-19 (n = 18) | Flu (n = 23) | p value |
|--|-------------------|------------------|---------|
| Patients' characteristics | | | |
| Age, years | 70 (57–75) | 58 (49–64) | 0.006 |
| Male (%) | 12 (67) | 12 (52) | 0.524 |
| BMI, kg/m ² | 29 (26–32) | 29 (25–34) | 0.519 |
| Hypertension (%) | 11 (61) | 10 (43) | 0.350 |
| Diabetes mellitus (%) | 4 (22) | 3 (13) | 0.679 |
| Time from illness onset to ICU admission, days | 11 (7–13) | 5 (4–10) | 0.017 |
| Time from illness onset to intubation, days | 12 (8–15) | 6 (4–10) | 0.002 |
| Time from illness onset to echocardiography, days | 14 (9–17) | 13 (6–17) | 0.001 |
| SAPS II | 34 (30–38) | 43 (32–54) | 0.015 |
| SOFA score | 4 (2–4) | 6 (4–9) | < 0.001 |
| Clinical presentation and treatment | | | |
| ECG changes* (%) | 1 (5%) | 3 (13%) | 0.618 |
| Documented coinfection (%) | 3 (17) | 9 (39) | 0.171 |
| Septic shock (%) | 0 (%) | 10 (43) | – |
| Vasopressor support (%) | 2 (11) | 10 (43) | 0.038 |
| Prone position (%) | 10 (56) | 14 (61) | 1.000 |
| Neuromuscular blockers (%) | 17 (94%) | 12 (52%) | 0.005 |
| Biology on admission | | | |
| Troponin I (ng/L) | 73 (51–94) | 53 (37–66) | 0.020 |
| Lactate, mmol/L | 1.17 (0.89–1.57) | 1.51 (1.02–2.54) | 0.143 |
| Creatinine, μmol/L | 58 (42–87) | 88 (59–160) | 0.021 |
| Prothombine time, % | 87 (78–96) | 87 (71–101) | 0.979 |
| AST, U/L | 55 (27–71) | 107 (46–203) | 0.020 |
| ALT, U/L | 37 (27–65) | 45 (27–115) | 0.527 |
| CPK, U/L | 72 (34–103) | 419 (180–2456) | < 0.001 |
| White blood cell count, G/L | 7.98 (6.61–11.25) | 5.96 (4.02–8.05) | 0.003 |
| Lymphocyte count, G/L | 0.78 (0.55–1.05) | 0.75 (0.47–1.13) | 0.770 |
| Eosinophils count, G/L | 0.02 (0.02–0.09) | 0.01 (0.00–0.01) | 0.094 |
| Platelet count, G/L | 318 (218–425) | 172 (153–225) | < 0.001 |
| Hemoglobin, g/dl | 11.2 (10.2–12.3) | 13.1 (11.6–14.2) | 0.007 |
| Respiratory parameters | | | |
| PaO ₂ /FiO ₂ | 130 (81–217) | 70 (62–100) | < 0.001 |
| Arterial pH | 7.35 (7.29–7.45) | 7.32 (7.23–7.41) | 0.121 |
| PaCO ₂ , mmHg | 44 (33–51) | 47 (36–60) | 0.430 |
| RR, breaths/min | 24 (22–27) | 25 (24–28) | 0.139 |
| Tidal volume, mL/kg | 5.2 (4.5–6.2) | 5.3 (4.0–6.1) | 0.885 |
| PEEP, cmH ₂ O | 10 (8–12) | 10 (8–12) | 0.476 |
| Plateau pressure, cmH ₂ O | 23 (20–26) | 28 (20–28) | 0.144 |
| Driving pressure, cmH ₂ O | 12 (10–15) | 18 (17–18) | 0.001 |
| Respiratory-system compliance**, mL/cmH ₂ O | 38 (31–45) | 23 (22–27) | 0.001 |
| Hemodynamic parameters | | | |
| Heart rate, bpm | 90 (72–109) | 105 (69–118) | 0.494 |
| Mean arterial blood pressure, mmHg | 102 (85–110) | 78 (71–94) | < 0.001 |
| CVP, mmHg | 9 (7–10) | 11 (9–14) | 0.058 |
| Cardiovascular phenotypes | | | |

Table 1 Characteristics, presentation and outcome of ventilated patients with COVID-19 and flu-related ARDS (*Continued*)

| | COVID-19 (n = 18) | Flu (n = 23) | p value |
|---|-------------------|------------------|---------|
| ACP (%) | 3 (17) | 11 (48) | 0.051 |
| Severe ACP (%) | 1 (5) | 8 (35) | 0.054 |
| LV failure | 3*** (17) | 14 (61) | 0.009 |
| Hypovolemia | 2 (11) | 1 (4) | 0.573 |
| Hyperkinesia | 6 (33) | 7 (30) | 1.00 |
| Normal hemodynamic profile | 8 (44) | 5 (22) | 0.179 |
| Echocardiographic indices | | | |
| Cardiac index**** (L/min/m ²) | 3.1 (2.5–4.2) | 2.5 (2.0–3.0) | 0.034 |
| RVEDA/LVEDA | 0.55 (0.37–0.60) | 0.70 (0.54–0.80) | 0.021 |
| RVFAC, % | 46 (35–50) | 33 (24–39) | 0.002 |
| TAPSE, mm | 25 (23–29) | 18 (16–22) | < 0.001 |
| Tricuspid S', cm/s | 16.0 (15.0–20.5) | 12.2 (11.0–13.4) | 0.005 |
| TR peak velocity, m/s | 3.2 (2.9–3.6) | 2.9 (2.4–3.2) | 0.113 |
| IVC diameter, mm | 22 (19–26) | 22 (21–24) | 0.762 |
| LVEF (%) | 52 (44–61) | 44 (28–59) | 0.265 |
| LVOT VTI, cm | 22 (18–25) | 18 (13–24) | 0.106 |
| Mitral E/E' ratio | 7.3 (6.5–10.9) | 7.8 (6.1–10.6) | 0.730 |
| Outcome | | | |
| ICU mortality***** (%) | 1 (6) | 9 (39) | 0.025 |

Abbreviations: *BMI* body mass index, *SAPSII* Simplified Acute Physiology Score, *SOFA* Sepsis Organ Failure Assessment, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CPK* creatinine phosphokinase, *RR* respiratory rate, *PEEP* positive end-expiratory pressure, *CVP* central venous pressure, *ACP* acute cor pulmonale, *LV* left ventricle, *RVEDA* right ventricular end-diastolic area, *LVEDA* left ventricular end-diastolic area, *RVFAC* right ventricular fractional area change, *TAPSE* tricuspid annular plane systolic excursion, *TR* tricuspid regurgitation, *IVC* inferior vena cava, *LVEF* left ventricular ejection fraction, *LVOT* left ventricular outflow tract, *VTI* velocity-time integral, *ICU* intensive care unit

*One patient had anterior negative T-wave in the COVID-19 group; 2 patients had inferior negative T-wave, and 1 patient had anterior negative T-wave in the flu group [2]

**Calculated as the tidal volume divided by the driving pressure (difference between the inspiratory plateau pressure and positive end-expiratory pressure)

***One patient was diagnosed with a Tako-tsubo syndrome during transesophageal echocardiography examination performed shortly after tracheal intubation, after 6 days of high-flow nasal cannula; full recovery of left ventricular systolic function was documented under mechanical ventilation 10 days later

****Measured using the Doppler method applied at the left ventricular outflow tract

*****As per April 24, with still 6 patients hospitalized in the intensive care unit, 5 of them being invasively ventilated

The prevalence of left ventricular (LV) failure (3/18 [17%] vs. 14/23 [61%], $p = 0.009$), ACP (3/18 [17%] vs. 11/23 [48%], $p = 0.051$), and severe ACP (1/18 [5.5%] vs. 8/23 [35%], $p = 0.054$) was significantly lower in COVID-19 patients. Hypovolemic and hyperkinetic phenotypes were similarly observed in both groups (Table 1). Despite similar tidal volume and PEEP level, COVID-19 patients had significantly higher P/F ratio and respiratory-system compliance, and lower driving pressure than flu patients (Table 1). Pulmonary embolism was identified in none of COVID-19 patients but in one flu patient with ACP. COVID-19 patients with ACP tended to exhibit lower respiratory-system compliance (34, 32, and 30 mL/cmH₂O) when compared to others (40 [31–45] mL/cmH₂O). Hemodynamic profile of COVID-19 patients remained stable during the first 3 days of ICU stay (Table 2).

The higher prevalence of LV failure and lower cardiac index in patients with flu-related ARDS is presumably related to septic cardiomyopathy since they sustained associated septic shock more frequently than COVID-19 patients. Depressed indices of RV systolic function and elevated central venous pressure reflecting systemic venous congestion reflect the higher prevalence of RV failure in flu ARDS patients (Table 1). This presumably results from the lower P/F, higher driving pressure, and lower respiratory-system compliance observed in this group. COVID-19 patients with ACP tended to have lower respiratory-system compliance than their counterparts, presumably due to distinct ARDS phenotypes [6]. This pilot study is limited by its small sample size and the retrospective comparison with historical flu-related ARDS patients.

This first study assessing hemodynamically ventilated COVID-19 patients with TEE shows a lower

Table 2 Evolution of hemodynamic profile during daily transesophageal echocardiography assessments of COVID-19 patients ventilated for ARDS

| | Day 1 (n = 18) | Day 2 (n = 10) | Day 3 (n = 12) | p value |
|---|------------------|------------------|------------------|---------|
| Respiratory parameters | | | | |
| PaO ₂ /FiO ₂ | 130 (81–217) | 128 (100–210) | 137 (98–187) | 0.066 |
| PaCO ₂ , mmHg | 44 (33–51) | 50 (32–56) | 47 (37–57) | 0.964 |
| RR, breaths/min | 24 (22–27) | 27 (20–28) | 24 (24–30) | 0.651 |
| PEEP, cmH ₂ O | 10 (8–12) | 10 (8–13) | 10 (10–12) | 0.444 |
| Plateau pressure, cmH ₂ O | 23 (20–26) | 22 (18–27) | 24 (21–27) | 0.127 |
| Driving pressure, cmH ₂ O | 12 (10–15) | 11 (9–12) | 13 (11–17) | 0.368 |
| Tidal volume, mL/kg | 5.2 (4.5–6.2) | 5.3 (4.6–6.6) | 5.5 (4.3–6.7) | 0.210 |
| Respiratory-system compliance*, mL/cmH ₂ O | 38 (31–45) | 33 (33–53) | 37 (28–45) | 0.692 |
| Hemodynamic parameters | | | | |
| Heart rate, bpm | 90 (72–109) | 93 (78–107) | 98 (89–104) | 0.368 |
| CVP, mmHg | 9 (7–10) | 7 (6–10) | 9 (5–13) | 0.678 |
| Mean blood pressure, mmHg | 102 (85–110) | 105 (87–110) | 95 (84–109) | 0.102 |
| Lactate, mmol/L | 1.17 (0.89–1.57) | 1.85 (1.24–3.01) | 1.62 (1.49–1.95) | 0.264 |
| Echocardiography indices | | | | |
| Cardiac index (L/min/m ²)** | 3.1 (2.5–4.2) | 2.8 (2.6–3.9) | 4.1 (3.2–4.8) | 0.115 |
| RVEDA/LVEDA | 0.55 (0.37–0.60) | 0.53 (0.35–0.66) | 0.55 (0.48–0.58) | 0.549 |
| RVFAC, % | 46 (35–50) | 40 (33–46) | 40 (32–58) | 0.821 |
| TAPSE, mm | 25 (23–29) | 24 (20–28) | 25 (23–28) | 0.368 |
| Tricuspid S', cm/s | 16.0 (15.0–20.5) | 16.1 (14.0–18.1) | 16.8 (14.9–19.9) | 0.867 |
| TR peak velocity, m/s | 3.2 (2.9–3.6) | 3.0 (2.7–3.7) | 3.6 (2.4–3.9) | 0.060 |
| IVC diameter, mm | 22 (19–26) | 24 (14–30) | 22 (17–24) | 1.000 |
| LVEF, % | 52 (44–61) | 46 (41–64) | 55 (49–60) | 0.549 |

Abbreviations: *RR* respiratory rate, *PEEP* positive end-expiratory pressure, *CVP* central venous pressure, *RVEDA* right ventricular end-diastolic area, *LVEDA* left ventricular end-diastolic area, *RVFAC* right ventricular fractional area change, *TAPSE* tricuspid annular plane systolic excursion, *TR* tricuspid regurgitation, *IVC* inferior vena cava, *LVEF* left ventricular ejection fraction

*Calculated as the tidal volume divided by the driving pressure (difference between the inspiratory plateau pressure and positive end-expiratory pressure)

**Measured using the Doppler method applied at the left ventricular outflow tract

prevalence of LV and RV failure than in flu-related ARDS patients. Whether herein reported cardiovascular phenotypes are influenced by the type of COVID-19 ARDS remains to be determined [6]. These preliminary data warrant confirmation in large-scale multicenter cohorts.

Abbreviations

ACP: Acute cor pulmonale; ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; ICU: Intensive care unit; LV: Left ventricle; RV: Right ventricle; SAPS II: Simplified acute physiology score II; SOFA: Sepsis-related organ failure assessment

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Authors' contributions

BE, MG, ALF, and PV included patients, analyzed the data, and drafted the manuscript. NM and TL collected and analyzed the data and reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Consent for publication

N/A

Competing interests

None

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