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ECHOCARDIOGRAPHIC FINDINGS IN PATIENTS UNDER MECHANICAL VENTILATION WITH COVID-19 ACUTE RESPIRATORY DISTRESS SYNDROME

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Abstract Coronavirus disease 2019 (COVID-19) produces a significant burden to severely ill patients affected by acute respiratory failure. The aim of this study was to describe echocardiographic findings in a series of mechanically ventilated patients with moderate and severe acute respiratory distress syndrome (ARDS) due to COVID-19. This was a single center, descriptive and cross-sectional study of prospectively collected data. Patients had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and moderate or severe ARDS. Initial echocardiogram was performed within 7 days of intensive care unit admission and every 15 days until mechanical ventilation ended, 28 days or death. Time spent by the physician for each study was measured. Multiple echographic measurements were acquired; 33 patients were analyzed. Total number of echocardiograms performed was 76. The median imaging time required to complete a standard study was 13 [10-15] minutes. Chronic structural abnormalities were present in 16 patients (48%), being LV hypertrophy the main finding in 11 patients (33%). The most frequent acute or dynamic finding was RV enlargement (43%) when considering all echocardiograms performed from admission to day 28 of follow-up. Other findings were: pulmonary hypertension (15%), new or dynamic left ventricle (LV) regional wall motion abnormalities (15%), new or dynamic LV global contractility deterioration (6%) and hypercontractility (12%).

Key words: echocardiography, acute respiratory distress syndrome right ventricle, COVID-19

Resumen ***Hallazgos ecocardiográficos en pacientes bajo ventilación mecánica con síndrome de dificultad respiratoria aguda por COVID-19.*** La enfermedad por coronavirus 2019 (COVID-19) produce una carga significativa para los pacientes gravemente enfermos afectados por insuficiencia respiratoria aguda. El objetivo de este estudio fue describir los hallazgos ecocardiográficos en una serie de pacientes ventilados mecánicamente con síndrome de dificultad respiratoria aguda (SDRA) moderado y grave debido a COVID-19. Se trata de un estudio unicéntrico, descriptivo y de corte transversal de datos recopilados en forma prospectiva. Los pacientes tenían una infección por el coronavirus SARS-Cov-2 y SDRA moderado o grave. El ecocardiograma inicial se realizó dentro de los 7 días del ingreso en la unidad de cuidados intensivos y luego cada 15 días hasta finalizar la ventilación mecánica, 28 días o fallecimiento. Se midió el tiempo empleado por el operador en cada estudio. Se adquirieron múltiples medidas ecográficas. Se analizaron 33 pacientes. El número total de ecocardiogramas realizados fue de 76. El tiempo necesario (mediana [RIQ]) para la obtención de las imágenes de un estudio estándar fue de 13 [10-15] minutos. Las anomalías estructurales crónicas estuvieron presentes en 16 pacientes (48%), siendo la hipertrofia ventricular izquierda la principal (11 pacientes, 33%). El hallazgo agudo o dinámico más frecuente fue el agrandamiento del ventrículo derecho (VD) (43%) al considerar todos los ecocardiogramas realizados desde el ingreso hasta el día 28 de seguimiento. Otros hallazgos fueron: hipertensión pulmonar (15%), anomalías del movimiento de la pared regional del VI nuevas o dinámicas (15%), deterioro de la contractilidad global del ventrículo izquierdo, nuevo o dinámico (6%), e hipercontractilidad (12%).

Palabras clave: ecocardiograma, síndrome de dificultad respiratoria aguda, ventrículo derecho, COVID-19

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KEY POINTS
Current knowledge

- Multimodal ultrasonography is a useful tool for the management of the critically ill patient at the bedside, although it is time consuming and not always possible in critical care. Limited information is available on echocardiographic findings in critically ill patients with mechanical ventilation and acute respiratory distress syndrome secondary to COVID-19.

Contribution to current knowledge

- In this series, the main echocardiographic findings were right ventricular dilatation, pulmonary hypertension and new or dynamic regional left ventricular contractility disorders.

Coronavirus Disease 2019 (COVID-19) produces a significant burden to severely ill patients affected by acute respiratory failure. Beside lung injury, it has been described in this setting endothelial damage, thromboembolic disease and cardiac dysfunction. However, systematic evaluations of these other potential problems are lacking.

Bedside ultrasound is a valuable tool for critical care patient's management[1-4]. During last year, multi-organ point-of-care ultrasound including lung ultrasound and focused cardiac ultrasound as a clinical adjunct has played a significant role in triage, diagnosis and medical management of COVID-19 patients[5]. Echocardiography and vascular Doppler are useful for non-invasive hemodynamic status interpretation and monitoring[6-8]. They provide different Doppler and bidimensional measures for hemodynamic parameters and key aspects for the interpretation of hemodynamic instability and respiratory failure[9-10]. These systematic assessments in critical care subjects might improve patient care and prognosis[11].

The aim of this study was to describe echocardiographic findings in a series of mechanically ventilated patients with moderate and severe ARDS (acute respiratory distress syndrome) due to COVID-19.

Materials and methods

This was a single center, descriptive and cross-sectional study of prospectively collected data.

All patients admitted between June 1 and December 31 2020, to the ICU (intensive care unit) of our center were screened for eligibility. We included patients with laboratory-confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection defined by a positive result of real-time reverse transcriptase–polymerase chain reaction assay of nasal or pharyngeal swabs, and moderate or severe ARDS as defined by the Berlin criteria[12].

Exclusion criteria were age <18 years and patients with withhold life sustaining measures.

Clinical management (including mechanical ventilation settings and pharmacological therapies) followed our center treatment guidelines.

An electronic case report form (REDCap electronic data capture tools[13]) hosted at *Instituto Universitario* CEMIC was used for data collection. Information regarding demographic, anthropometric and clinical data (comorbidities[14], severity scores[15, 16], vital signs, type of respiratory support, respiratory parameters, laboratory tests including blood gas analysis) were collected on the day of admission to the ICU.

Following inclusion, an initial echocardiogram was performed within 7 days of ICU admission and every 15 days afterwards until mechanical ventilation ended, 28 days or death. Additional echocardiograms were performed on an "as needed" basis, according to the attending ICU physician. All echocardiographic assessments were performed by a single physician with extensive experience. Each evaluation was recorded for a second validation by another expert. Time spent by the physician for each study was measured. The following echographic measurements were acquired: left ventricle (LV) ejection fraction (Simpson's method or eyeball assessment by two independent trained physicians) (LVEF); LV hypercontractility was defined by a LVEF greater than 80% with low LV end systolic volume or diameter;LV regional wall abnormalities (assessed by two independent trained physicians); Mitral Doppler: E peak velocity and E/A ratio; Tissue Doppler: septal e' peak velocity and E/e' ratio; LV outflow tract velocity time integral (VTI); Right ventricle outflow tract acceleration time (pulmonary hypertension was considered when acceleration time was lower than 85 ms); Estimated systolic pulmonary pressure (PsP) by tricuspid regurgitation peak velocity and central venous pressure (measured by central catheter when available, or estimated by inferior vena cava visualization). Pulmonary hypertension was considered when the estimated PsP was greater than 40 mmHg; Right ventricle (RV) diameter (measured from subcostal 4 chamber view and apical 4 chamber view; mild RV enlargement was defined as diameter greater than 75% of LV diameter and moderate/severe RV enlargement when it was greater or equal to 100%); Tricuspid annular plane systolic excursion (TAPSE; RV systolic dysfunction was defined when TAPSE was lower 17 mm)

A diagnostic interpretation or conclusion was also provided by the performing physician, when chronic or acute significant changes were found in the study.

Transthoracic echocardiography is not always possible in critical care patients due to difficulty in achieving acceptable images from classic transthoracic views (left parasternal, apical and subxiphoid). In addition to this, when feasible, it may require a long time to perform. We defined three categories for possible study outcomes, dividing them into adequate, suboptimal and inadequate. All inadequate studies were not considered for analysis and only suboptimal and adequate studies were used for final analysis. A study was defined as adequate when 2 or more of the classic views offered acceptable images and more than 70% of the 10 prespecified measures could be correctly achieved. The study was suboptimal when only one of the classic views offered acceptable images or less than 70% of prespecified measures could be achieved. Finally, it was considered inadequate when none of the classic views offered acceptable images or less than 40% of pre-specified measures could be achieved.

Results

Forty-five patients fulfilled the inclusion criteria. After exclusions (4 patients who were never intubated, 2 patients

with withhold of life sustaining measures and 6 patients with inadequate echocardiographic acoustic windows), 33 patients were analyzed. From these 33 patients, 7 (21%) had only the initial study available for analysis, and the rest underwent echocardiographic follow up until day 28 (Fig. 1).

Continuous variables are presented as median and interquartile range [IQR]. Categorical variables are expressed as frequencies (percentages).

The total number of echocardiograms performed was 76, of which 48 (64%) had an adequate acoustic window while in the remaining 28 (36%) the acoustic window was suboptimal. The median imaging time required to complete a standard study in this setting was 13 [10-15] minutes. It should be noted that this time measurement does not include the time required for personal protective equipment donning and doffing as well as the time taken to clean the equipment.

Table 1 summarizes the patients' demographic and clinical characteristics at ICU admission and their clinical outcomes. 57% were male and median age was 63.5 [59.5-79.5] y/o. 54.5% had chronic arterial hypertension and median body mass index was 31 [25-36] kg/m^2. Median SOFA and APACHE II scores at ICU admission were 3 [3-6] and 11 [9-12], respectively. ARDS severity was moderate in 69% and severe in 31% of the cases. Mortality at day 28 of follow-up was 48% (16 patients).

Chronic structural abnormalities were present in 16 of the 33 patients included for analysis (48.5%). The main finding was mild LV myocardial hypertrophy in 11 patients. Other findings were left atrial enlargement (mild in 5 patients and moderate or severe in 2 patients), aortic valve regurgitation (3 patients), mitral valve regurgitation (5 patients) and 1 patient with mild aortic valve stenosis.

Table 2 summarizes main findings of the echocardiogram performed at admission.

At the initial echocardiographic assessment, RV dilation was present in 13 patients (39%): 12 of them had mild RV enlargement, while the remaining had moderate/severe RV enlargement. When all 76 echocardiograms were included, RV dilation was present in 33 studies (43%): 4 of them had moderate/severe RV dilation and the remaining mild. Other findings were: pulmonary hypertension (5 patients - 15%); new or dynamic LV regional wall motion abnormalities (5 patients - 15%), including 3 patients with inverted Takotsubo like image; new or dynamic LV global contractility deterioration (2 patients - 6%); hypercontractility present in 4 patients (12%) (usually associated with tachycardia); finally, 1 patient with atrial enlargement that had no thrombotic complications in the first echocardiogram developed a new large left atrial clot that generated LV inflow tract obstruction with consequent irreversible shock during his follow up.

All 7 patients with regional or global wall motion abnormalities had complete recovery within 28-day follow-up.

One of the patients with a Takotsubo like pattern in the initial echocardiogram, had 2 more Takotsubo events associated with septic complications during the follow-up. This patient underwent a final echocardiographic assessment at 60 days and showed a total recovery.

From the 7 studies with a LV outflow tract VTI less than 17 cm, 3 had systolic dysfunction with Takotsubo pattern, 1 had systolic dysfunction with an acute regional septal and anterior contractility disorder, 2 had hypovolemic

Fig. 1. Flow chart in patients under mechanical ventilation with COVID-19 acute coronary distress syndrome

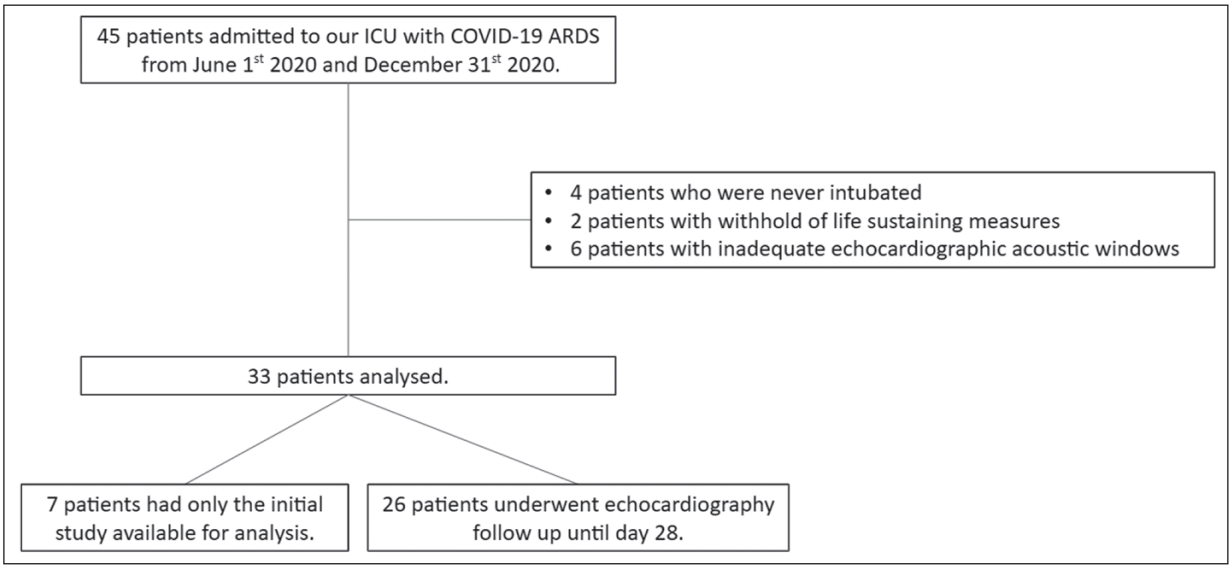

TABLE 1.– *Patients' characteristics and outcome (n: 33)*

Variables	Results
Males, n (%)	19 (57)
Age (years)	63.5 [60-80]
BMI (kg/m^2)	31 [25-36]
Chronic HTN	18 (54.5)
CHARLSON score[a]	1 [0-1]
SOFA score[a]	3 [3-6]
APACHE II score[a]	11 [9-12]
ARDS severity, no. (%)	
Mild	0 (0)
Moderate	22 (67)
Severe	11 (33)
ICU mortality, no. (%)	16 (48)
Mean arterial pressure (mmHg)[b]	102 [92-111]
PEEP (cmH_2O)[b]	14 [13-15]
PaO_2/FIO_2 ratio[b]	225 [181-249]
Plateau pressure (cmH_2O)[b]	24 [22-25]

HTN: hypertension; BMI: body mass index; SOFA: sequential organ failure assessment; APACHE II: acute physiologic assessment and chronic health evaluation II; PEEP: positive end-expiratory pressure; PaO_2: partial pressure of oxygen in arterial blood; FIO_2: inspired fraction of oxygen
Data are expressed either as frequency (percentage) or as median [interquartile range]
[a]Values refer to ICU admission
[b]Values refer to same day of first echocardiogram performed

TABLE 2.– *Main findings of the first echocardiogram performed in each of the 33 patients analyzed*

Variables	Results n (%)
Acoustic window	
Adequate	20 (61)
Suboptimal	13 (39)
LV ejection fraction	
> 80%	2 (6)
80-55%	25 (76)
< 55%	6 (18)
LV regional wall abnormalities	
Yes	4 (12)
No	29 (88)
Mitral doppler	
E peak velocity (cm/s)	73 [65-88]
E/A ratio	1.32 [1-1.60]
Tissue doppler	
Septal e' peak velocity (cm/s)	8 [7.20-10]
E/e' ratio	8 [7-10]
LV outflow tract VTI (cm)	
<13 (low stroke volume)	0
13-17 (undetermined stroke volume)	5
>17 (normal stroke volume)	21
RVOT acceleration time (ms)	
≤ 85	3
> 85	10
Pulmonary systolic Pressure (mmHg)	
≤ 40	8
> 40	2
RV dilation	13 (39)
Mild enlargement (>75% of LV diameter)	12 (36)
Moderate/severe enlargement (≥100% of LV diameter)	1 (3)
TAPSE (mm)	
< 17	2
≥ 17	25

LV: left ventricle; RV: right ventricle; VTI: velocity time integral; RVOT: right ventricular outflow tract; TAPSE: tricuspid annular plane systolic excursion
Data are expressed either as frequency (percentage) or median [interquartile range]

status (both patients with E peak velocity below 60cm/s, E/A ratio ≤ 1, E/e´≤ 10, LVEF ≥ 65% and low end systolic volume) and 1 corresponded to the previously mentioned left atrial thrombosis with obstructive shock.

Discussion

RV enlargement, pulmonary hypertension and new or dynamic LV global and regional contractility abnormalities were our main findings.

Transthoracic echocardiography is not always possible in critical patients with ARDS under mechanical ventilation. This may be influenced by patient position (prone ventilation), patient's subcutaneous edema, high positive end expiratory pressure with pulmonary areas of hyperinflation and patient's thoracic anatomy. When plausible, it may be time consuming. Even so, the method is useful in most patients and brings reliable information, sometimes with immediate therapeutic implications.

The most frequent finding was RV enlargement (43%) considering not only the initial assessment, but all echocardiograms from the 28-day follow-up for each patient. The known association between this and mechanical ventilation has been well described by Vieillard-Baron and colleagues[17]. While Vieillard´s assessment was made by a LV end diastolic diameter to RV end diastolic diameter ratio greater than 0.6, our RV dilation definition only included those with a ratio greater than 0.75 (an index of 0.6 would have overestimated our results). We did not contemplate the septal motion in a short axis for RV dilation diagnosis (although an important physiological finding for a better interpretation, it was not considered in our setting). RV enlargement higher incidence could be explained by a high

level of PEEP used in our patients (median 14 cmH_2O) although plateau pressure was always less than 30 cmH_2O (same parameter used by Vieillard for defining protective ventilation). Furthermore, this finding could also be associated with hemodynamic or thrombotic changes in pulmonary circulation generated by COVID-19 ARDS and hypoxemia. However, every patient with dilated RV and/or elevated PSAP underwent a simultaneous venous doppler of the lower limbs: no thrombotic events were found.

LV global and regional wall motion abnormalities, including Takotsubo, have also been well described in critically ill patients, especially in sepsis[18]. This could be explained in our series by the presence of Systemic Inflammatory Response Syndrome (SIRS) generated by COVID-19 and the consequent stress response. 1 of the 3 patients with TakoTsubo at the initial echocardiogram showed a total recovery by the second week assessment. However, during 2 posterior septic events within his ICU stay, myocardial involvement was reproduced showing the high risk of these patients to repeat contractility deterioration when re-exposed to stress.

Only 1 confirmed thrombotic complication was found in our series. It is noteworthy that all patients included received high dose chemoprophylactic with low weight heparin (1 mg/kg of enoxaparin) from day 1 of ICU admission.

Another frequent finding was hypercontractility with low end systolic left ventricular volume. This may be due to restrictive fluid management strategies in ARDS patients, to the presence of SIRS or to the development of tachycardiomyopathy or arrhythmic complications (the latter was not evaluated in our study).

Among chronic structural abnormalities, mild LV myocardial hypertrophy was the main finding. This may respond to the high prevalence of chronic arterial hypertension in our population (54.5%).

In conclusion, transthoracic echocardiography is not always plausible in critical patients with ARDS under mechanical ventilation. However, it continues to prove its usefulness in most patients and brings reliable information, sometimes with immediate therapeutic implications. Although echocardiography is available bedside and with no harm or risk for the patient, it has proven to be time consuming for the attending physician.

Conflict of interest: None to declare

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