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COVID-19 and Takotsubo Cardiomyopathy: An integrative review

Luiz Mezencio Neto[1], Vinícius Batista Silva[2], Ney Ferreira de Sousa Filho[3], Haroldo da Silva Santana[4]

[1]Department of Medicine, Centro Universitário Municipal de Franca, Brazil
Email: netomluiz@hotmail.com
[2]Department of Medicine, Centro Universitário Municipal de Franca, Brazil
Email : vinicius.eb1@gmail.com
[3]Department of Medicine, Centro Universitário Municipal de Franca, Brazil
Email: neyferreira94@hotmail.com
[4]Department of Medicine, Centro Universitário Municipal de Franca, Brazil
Email: haroldo_santana3@hotmail.com

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***Abstract*—** *Coronavirus 2019 (COVID-19), Takotsubo cardiomyopathy (CT) stands out. Also known as broken heart syndrome, it is a rare dysfunction that affects the systolic function of the left ventricle, resulting from an abrupt and intense discharge of catecholamines, of a transient and reversible nature. However, the coexistence of CT and COVID-19 results in an intense cytokine storm, which makes the outcome not so favorable, with increased risks for cardiogenic shock, myocarditis, and cardiac tamponade. Thus, the objective of this study was to analyze scientific evidence on the relationship between COVID-19 and CT in healthy patients or patients with controlled systemic diseases (without complications). An integrative literature review was carried out in the MEDLINE database, with the strategies "Takotsubo Syndrome and COVID-19" and "Takotsubo Syndrome and SARS-Cov-2". Initially, a total of 194 references were obtained which, after critical analysis by the researchers, included 5 case reports in this review. The investigation of the cases did not identify specific patterns of clinical manifestations, laboratory tests or imaging in healthy patients or with controlled systemic diseases, but in general, the occurrence of cytokine storms with impacts on the coagulation cascade and on the patterns can be highlighted. of cardiac functioning. Thus, we emphasize the importance of including CT as a differential diagnosis in the face of the poor prognosis of the patient with COVID-19 and that studies continue to be carried out to better elucidate this issue which, although rare, can be fatal.*

I. INTRODUCTION

The 2019 Coronavirus (COVID-19) pandemic, caused by the spread of the new coronavirus (SARS-Cov-2), has different clinical presentations, including asymptomatic infections. Among the cardiovascular manifestations, the following were related: arrhythmias, pericardial effusion, thromboembolic phenomena, myocardial infarction with normal coronary arteries, myocardial injury, myocarditis, heart failure and Takotsubo cardiomyopathy (CT) [1]. In

terms of CT, its incidence has increased approximately five-fold, representing about 8% of acute coronary syndromes during the pandemic, versus 1% in the pre-pandemic period [2].

The word "Takotsubo" refers to a Japanese fishing vessel for catching octopus, which has a circular bottom and narrow neck and resembles the shape of a heart in CT. Also known as broken heart syndrome, it is a rare dysfunction that affects the left ventricular (LV) systolic function, resulting from an abrupt and intense discharge of catecholamines (triggered by physical or emotional stressors), of a transient and reversible nature [3,4]. Its clinical presentation is very similar to acute coronary syndrome, corresponding to approximately 2% of patients who present with acute chest pain and dyspnea, in addition to changes in the electrocardiogram and increase in biomarkers of cardiac injury, but on CT there is no significant coronary stenosis (no coronary artery disease) at the injured site.

Conditions such as overstimulation of the sympathetic system, abnormality of microvascular and myocardial tissue metabolism, and coronary artery vasospasm have been linked to CT. In addition, lower body mass index (BMI), previous mid-ventricular gradient, female gender, and temporal proximity to a first event were associated with the recurrence of this syndrome [3,4].

Case management is performed with supportive and symptomatic medication to improve left ventricular function, and treatment time is 3-4 weeks, generally with a good prognosis, although there is an approximate 2% risk of ventricular arrhythmias and in-hospital mortality [3].

The coexistence of CT and COVID-19 has been related to a cytokine storm, with high levels of epinephrine and changes in microcirculation resulting from the inflammatory environment caused by the virus. In the heart, these molecules can change the function of the heart muscle, generating mechanical stress that, added to the other changes, favor the development of cardiomyopathy and hypercoagubility [1,5]. In this condition, the outcome of CT is no longer so favorable, as many patients had cardiogenic shock, myocarditis, and cardiac tamponade [6].

On the other hand, the emotional stress caused by the pandemic itself, such as deprivation of social life, economic impacts, and family losses, may be responsible for the hyper catecholaminergic state and, in turn, for cardiomyopathy [1].

In view of the above, it is important to pay attention to this possible cardiovascular complication triggered by SARS-Cov-2 infection and to carry out an adequate diagnosis and management, to reduce the morbidity and mortality of this group. In this sense, the present research aimed to analyze scientific evidence on the relationship between COVID-19 and CT in healthy patients or with controlled systemic diseases (without complications).

II. METHODS

This is an integrative literature review, which followed the six steps suggested by Souza, Silva and Carvalho [7], namely: 1) elaboration of the guiding question; 2) search or sampling in the literature; 3) data collection; 4) critical analysis of included studies; 5) discussion of the results and 6) presentation of the integrative review.

Based on the guiding question of this research, "what is the scientific evidence of the relationship between COVID-19 and CT in healthy patients or patients with controlled systemic diseases (without complications)?", the search strategy in the scientific literature was established, which occurred on December 27, 2021. The descriptors "Takotsubo Syndrome", "COVID-19" and "SARS-Cov-2" were selected, according to the Medical Subject Headings (MeSH), which were applied in the Medical Literature databases Analysis and Retrieval System Online (MEDLINE), whose possibility of containing scientific material relevance and level of evidence worldwide is greater. Two search strategies were used, namely "Takotsubo Syndrome and COVID-19" and "Takotsubo Syndrome and SARS-Cov-2", and the following inclusion criteria were adopted: full texts, published between the years 2019 and 2021, in English and to answer the guiding question. In addition, aiming at a better dialogue between the findings, we opted for articles with healthy patients or controlled systemic diseases (without complications), with a positive reverse transcriptase reaction test followed by a positive real-time polymerase chain reaction (RT-PCR). and presence of LV akinesia or hypokinesia on ECHO as evidence of CT. Editorials, theoretical reflection, dissertations, theses, and reviews were excluded.

Initially, a total of 194 references were obtained, which were imported into the Mendeley bibliography manager, which identified 42 duplicate articles, which were excluded. After reading the 152 titles and abstracts, 115 articles were excluded because they did not cover the research theme. Of the 37 studies selected for full reading, five were included in this review. Each selection step was first performed individually by the authors, who subsequently reached a consensus to ensure that the texts met the review question and the inclusion criteria.

For the analysis of the articles, a script was used including article title, author(s) name(s), year and month of publication, study objective, method, case description (age,

gender, clinical presentation, laboratory, and imaging tests), evolution, clinical outcome, and relevant observations. Subsequently, the data obtained was critically analyzed, with an emphasis on scientific evidence of the relationship between COVID-19 and CT.

The data were discussed through the interpretation and synthesis of the results, searching for possible gaps in knowledge and, finally, the review was presented.

III. RESULTS AND DISCUSSION

The articles selected for the discussion of this integrative review meet all the pre-established inclusion criteria and were reviewed by all authors. The five articles are case reports, published in 2020, and are described in Table 1, below.

Of the five case reports included in this review, three were male and two were female. The age of the participants ranged between 40 and 74 years, with a mean of 55 years; two were healthy and the others were hypertensive, dyslipidemic and had glycemic alterations (two diabetics and one with altered fasting glycemia).

Fever, cough (dry or productive) and dyspnea were the most prevalent early symptoms of COVID-19, followed by chest pain, fatigue, myalgia, and diarrhea. The worsening of the patients' clinical condition began with a drop in oxygen saturation (O2) requiring delivery therapy through cannula, continuous positive airway pressure (CPAP) and orotracheal intubation (OTI). The interval between the onset of COVID-19 symptoms and the need for O2 supportive therapy was three days to 14 days.

In the general population, studies carried out in European countries and in the United States suggest that TC predominantly affects women. Men represent only 10% of the patient population and are predominantly Asian but tend to have a greater need for catecholamine use, intubation, cardiogenic shock, and death compared to women [10,13].

Ochani et al. (2021) [14] pointed out as the most common complaints of COVID-19 fever, cough and dyspnea, and, less frequently, gastrointestinal symptoms. According to the authors, the age group from 65 years is at greater risk of developing the infection, especially due to established comorbidities. However, younger adults are also being hospitalized with serious illness, albeit less frequently, as in the cases presented by this study. It is also important to note that most patients will develop a mild disease, and only a minority will develop severe hypoxia, requiring hospitalization and mechanical ventilation, but the reasons are not clear.

The investigation of the cause of clinical worsening in these patients was carried out based on laboratory tests (Table 2) and imaging tests (Table 3), shown below.

Observing Table 2, laboratory alterations are observed in several parameters, suggestive of an ongoing inflammatory response, cardiac alterations, as well as coagulation and myocardial damage. These facts support increasing evidence of the association between COVID-19 and an exacerbated inflammatory response, with abnormal activation of the coagulation cascade, which results in a worse prognosis [15,16]. Patients with cardiac injury are more likely to have more non-invasive ventilation and invasive mechanical ventilation, with higher mortality [17].

The radiographic findings presented suggest pneumonia or interstitial inflammatory lung disease, congruent with the patterns presented by COVID-19. On the electrocardiogram, the most common presentations were ST-segment elevation and sinus tachycardia, but they were concomitant in only one case [11]. Other changes were nonspecific or diffuse ST segment and T wave abnormalities in precordial leads, poor R progression, mild diffuse PR interval depressions, low atrial ectopic rhythm, and reciprocal ST depression in V4–V6 and QTc 452 ms with U waves. diffuse.

As for ECHO, hypokinesia or akinesia were identified, especially in the middle and apical segments of the VC and hyperkinesia of the basal segments. Dilation was found in three cases [8,9,11] and left ventricular ejection fraction (LVEF) ranged from 15 to 43%. One of the cases [8] presented partial obstruction of the LV outflow tract, with two large apical thrombotic formations. In the others, ECHO did not show LV outflow tract obstruction, thrombus, or pericardial effusion.

LV obstruction by thrombus is considered a rare complication of CT. This fact can be observed through altered coagulation test results, which guide the use of parenteral anticoagulant medication (such as unfractionated heparin or low molecular weight heparin) in order to reduce hospital stay and mortality [18].

Table 1 - Presentation of articles included in the integrative literature review by author, year of publication, age and sex of participants, clinical presentation, and time between onset of COVID-19 and Takotsubo cardiomyopathy

Author & year	Age & sex	Medical history	Clinical presentation	Time between COVID-19 onset and clinical worsening
BERNARDI et al., 2020 [8]	74, M	SAH, dyslipidemia, and altered fasting glucose	Fever up to 38 °C, dyspnea and cough that progressed to respiratory failure requiring CPAP	Five days after admission
FAQIHI et al., 2020 [9]	40, M	Healthy	Dry cough, chest pain, myalgias and fatigue for four days, which in 2 hours progressed to respiratory failure requiring a high-flow nasal cannula	Four days from symptom onset
FUJISAKI et al., 2020 [10]	60, M,	SAH, dyslipidemia, and T2DM	Fever and dyspnea for two weeks that evolved with 75% SpO2 in 15 L of oxygen and bilateral crackles and tachycardia, with severe respiratory distress and need for intubation	Two weeks from onset of symptoms
MINHAS et al., 2020 [11]	58, F	SAH, dyslipidemia, and T2DM	Productive cough, fatigue, fever, and diarrhea for five days that progressed to respiratory distress requiring a 5 L nasal cannula and, shortly thereafter, intubation	Five days from symptom onset
SALA et al., 2020 [12]	43, F	Healthy	Oppressive chest pain and dyspnea for three days, which progressed to oxygen desaturation (SpO2 89%) and need for CPAP	Three days from symptom onset

CPAP, continuous positive airway pressure; F, feminine; M, masculine; SAH, systemic arterial hypertension; SpO2, oxygen saturation; T2DM, Type 2 diabetes mellitus

Table 2 - Results of laboratory tests to investigate the clinical condition

Author & year	Troponin T	Troponin-I	CK	NT-proBNP	WBC	CRP	Ferritin	D-dimer
BERNARDI et al., 2020 [8]	775 ng/l	N/A	26,8 µg/l	8.999 ng/l	12.870/µl	14,2 mg/l	1.580 µg/l	2.931 ng/ml
FAQIHI et al., 2020 [9]	N/A	4,7 ng/ml	422 units/l	N/A	$0,55 \times 10^9$/l	82,5 mg/l	3101 ng/ml	No high levels
FUJISAKI et al., 2020 [10]	N/A	2,69 ng/ml and peak at 2,77 ng/ml	N/A	N/A	Lymphopenia	281 mg/l	N/A	13,8 µg/ml
MINHAS et al., 2020 [11]	N/A	Negative, but peaked at 11,02 ng/ml	N/A	N/A	Leukopenia	N/A	N/A	N/A
SALA et al., 2020 [12]	Curve was 135–107–106 ng/l	N/A	N/A	512 pg/ml	N/A	18 mg/l	N/A	N/A

CK, creatine kinase; CRP, C-reactive protein; N/A, not applicable; N-terminal pro–B-type natriuretic peptide; WBC, white blood cell;

Two case reports shared cardiac magnetic resonance (CMR) results. According to Bernardi et al. [8], increased end-systolic volume with severe systolic dysfunction, hypokinesia of the midapical segments of the left ventricle with a typical pattern of apical ballooning and myocardial edema in the midapical segments of the left ventricle were observed. Sala et al. [12] presented CMR on the seventh day, which showed recovery of systolic function (from 52% by CTA to 64%), but with persistence of mild hypokinesia in the basal and middle segments of the left ventricle and, in the same places, diffuse myocardial edema.

Table 3 - Results of imaging tests to investigate the clinical condition

Author & year	Radiography chest	Electrocardiogram	Echocardiogram
BERNARDI et al., 2020 [8]	Diffuse hazy densities	ST segment elevation in anterolateral leads	Dilated LV with akinesia of the mid and apical segments, hyperkinesia of the basal segments and severe systolic dysfunction (LVEF: 30%); first degree diastolic dysfunction; partial LV outflow tract obstruction and two large apical thrombotic formations
FAQIHI et al., 2020 [9]	Interstitial infiltrates and consolidations	Sinus tachycardia and nonspecific ST segment and T wave abnormalities in precordial leads	Basal and mean LV akinesia with apex preservation (LVEF: 30%) and decreased cardiac output (2.8 L/min)
FUJISAKI et al., 2020 [10]	Diffuse opacities in all lung fields	ECG recorded 1 day before showed atrial fibrillation, poor R progression and negative T waves in leads I, aVL and V2-V6. On presentation, sinus tachycardia, poor progression R	LV apical and mid-biventricular segments were severely hypokinetic, while the LV and RV bases were contracting normally. LVEF: 15%
MINHAS et al., 2020 [11]	Bilateral infiltrates with lower lobe predominance	Sinus tachycardia and ST-segment elevation of 1 mm in leads I and aVL, mild diffuse PR interval depressions, and diffuse ST-T wave changes	Anterior mid-distal, anteroseptal, anterolateral and apical akinetic segments, moderately hypokinetic inferolateral mid and distal segments, and hyperdynamic basal segments. Apical ballooning was also observed. LVEF: 20%. The free wall of the distal or apical third of the RV was akinetic, with hyperdynamic movement of the RV basal wall. RV function has been slightly reduced
SALA et al., 2020 [12]	Subtle bilateral opacities	Low atrial ectopic rhythm, mild ST-segment elevation in leads V1–V2 and aVR, reciprocal ST depression in V4–V6 and QTc 452 ms with diffuse U waves	Mild left ventricular systolic dysfunction (LVEF 43%) with inferolateral wall hypokinesia

ECG, electrocardiogram; LV, left ventricle; LVEF, left ventricular ejection fraction; RV, right ventricle

Sala et al. [12] also presented results of basal chest scintigraphy and endomyocardial biopsy. Scintigraphy identified bilateral irregular ground-glass opacities and showed no aortic dissection, pulmonary embolism, or coronary artery disease. Dynamic 3D volume rendering reconstruction demonstrated evident hypokinesia of the mid and basal segments of the left ventricle, with normal apical contraction, suggesting a reverse ST pattern. Endomyocardial biopsy, in turn, documented diffuse inflammatory infiltrates of T lymphocytes (CD3+ >7/mm2) with significant interstitial edema and limited foci of necrosis. Replacement fibrosis was not detected, suggesting an acute inflammatory process. Molecular analysis showed the absence of the SARS-CoV-2 genome in the myocardium. No contraction band necrosis or CT-associated microvascular abnormalities were observed.

Differential diagnoses of CT included acute myocardial infarction, myocarditis, coronary embolism, aortic dissection, coronary artery disease, and right ventricular dysfunction [8-10]. The compilation of

alterations from laboratory and imaging tests presented evidence the diagnostic complexity of CT, which occurs through the exclusion of other possible causes, mentioned above. Thus, three diagnostic criteria that can be used after exclusion of more common pathologies in medical practice, namely, 1) transient LV dysfunction at ECHO, 2) COVID-19 as a physical trigger, and 3) elevated cardiac biomarkers [10].

The treatment of CT is directed to the clinical manifestations presented by the patients. Thus, the maintenance of vital signs, hemodynamic stability and the treatment of possible complications are prioritized. Thus, in the face of COVID-19, in the absence of a standardized treatment, empirical treatment was performed. In three cases, there was an association of azithromycin with hydroxychloroquine [8,10,11]. However, hydroxychloroquine was later discontinued in one of them due to the possible risk of worsening cardiomyopathy and QT interval prolongation [11]. Two others used antivirals (lopinavir/ritonavir), and one opted for the combination with hydroxychloroquine [9,12].

Four cases intervened in coagulability disorders, with antiplatelet drugs and/or anticoagulants, to modify laboratory and imaging changes as well as prevent complications related to both COVID-19 and CT, especially the occurrence of thrombotic events [8-11].

Vasopressors have been used in arterial hypotension or cardiogenic shock [8-10]. In one of the cases [9] the use of dobutamine was considered, but its performance as an exogenous catecholamine was considered an aggravating factor for stress-induced cardiomyopathy. Thus, an infusion of milrinone was performed, which did not improve cardiogenic shock and generated tachyarrhythmia. Esmolol was started, titrated to a heart rate $\leq$ 95 beats/min, but was discontinued due to bronchospasm. In this case, given the possibilities of the service, therapeutic plasma exchange (TPE) was performed, and the plasma was replaced by 5% albumin, with the aim of rescuing the critically ill patient after failure of inotropic therapy [9].

Corticosteroids have been used as an adjuvant treatment during TPE [9] and in an attempt to reduce unwanted inflammatory effects [8,10]. Broad-spectrum antibiotics and atorvastatin were also associated [10].

According to scientific evidence, the evolution and outcome of the reported cases were quite satisfactory from the cardiac point of view: changes in the LV, measured by LVEF, regressed and three of the investigated patients were discharged in good condition [8,9,12], after an interval between 13 and 21 days after admission. One of the patients [10] showed normalization of the ECG and ECHO, but required hemodialysis during hospitalization, as he developed acute renal failure (ARF), and was discharged with subacute rehabilitation in a general practice outpatient clinic. Despite the improvement in cardiac function, another patient maintained respiratory distress and remained hospitalized, requiring venovenous extracorporeal membrane oxygenation [12].

IV. FINAL CONSIDERATIONS

From the present research, it can be noted that both the clinical presentation and imaging parameters and laboratory tests on CT were different in healthy patients or patients with controlled underlying disease, and the presentation of COVID-19 that preceded this syndrome was also varied between the clinical cases presented. However, in general, the occurrence of a cytokine storm can be highlighted, with impacts on the coagulation cascade and on the patterns of cardiac functioning, revealed by laboratory and imaging tests.

Thus, we emphasize the importance of including CT as a differential diagnosis in the face of the poor prognosis of the patient with COVID-19 and that studies continue to be carried out to better elucidate this issue which, although rare, can be fatal.

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