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Letter to Editors

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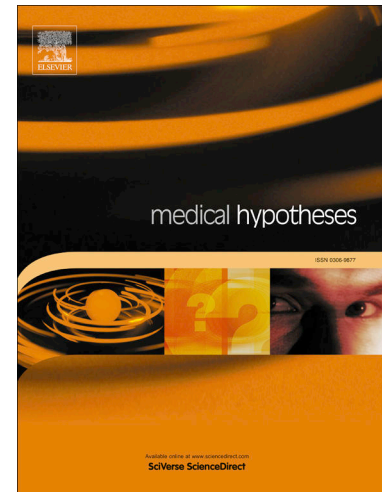
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## Correlation between Takotsubo cardiomyopathy and SARS-CoV-2 infection

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### Abstract:

Takotsubo cardiomyopathy (TTS), known as stress cardiomyopathy, is a rare disorder characterized by acute and transient left ventricular systolic and diastolic dysfunction, often associated with a stressful, emotional or physical event. TTS may be closely related to SARS-CoV-2 infection and the ongoing pandemic. The enormous emotional stress caused by the pandemic and respiratory infections caused by SARS-CoV-2 could be potential triggers for TTS. The case series cited above implicates that TTS should be considered in the differential diagnosis across the entire spectrum of myocardial injury in SARS-CoV-2 infected patients. Myocardial damage associated with SARS-CoV-2 infection is usually attributed to sepsis, hypoxemia, coronary artery disease, and myocarditis. We hypothesize that TTS may also play a role among these lesions.

To the Editor,

Takotsubo cardiomyopathy (TTS), known as stress cardiomyopathy, is a rare disorder characterized by acute and transient (<21 days) left ventricular (LV) systolic (and diastolic) dysfunction, often associated with a stressful, emotional or physical event, most commonly found in the days leading up to (1 to 5 days). The syndrome defines the presence of regional abnormalities in the mobility of the LV wall, characteristically extending beyond a single division of the epicardial coronary artery and with symptoms imitating acute coronary syndrome, in the initial stage of which it is treated as such by doctors during patient management. A typical pattern of regional abnormalities of the LV wall is hypokinesia, akinesia, or apical dyskinesia (apex ballooning) with basal hyperkinesia [1]. Recently, more and more reports have appeared about both the relationship of TTS with SARS-CoV-2 infection, and TTS in people not infected with SARS-CoV-2 due to the extreme mental, social, and economic stress created in the society under the influence of the pandemic. Hence, we hypothesize that SARS-CoV-2 pandemic may increase the incidence of TTS both directly by triggering myocardial injury, and indirectly by increasing the stress level in society. To support our hypothesis, a cohort study conducted at two Ohio hospitals showed a significant increase in the incidence of TTS during the SARS-CoV-2 pandemic period. The study included 1,914 patients with the acute coronary syndrome to compare patients reporting during the SARS-CoV-2 pandemic with patients in the four periods before the pandemic and found a significantly increased 7.8% incidence of TTS during the SARS-CoV-2 pandemic, compared to the pre-pandemic periods, where the proportion ranged from 1.5% to 1.8% [2]. Researchers at Leipzig University Hospital and Community Hospital Halle (Saale) conducted echocardiography in April, in patients infected with SARS-CoV-2 with both mild symptoms and severely ill health. The most common observation they noticed was reduced longitudinal strain, observed mainly in more than one primary segment of the left ventricle, in 71% of patients. This pattern resembled the "reverse tako-tsubo" morphology, which is not typical of other viral myocarditis [3]. In his work, Giustino described a study conducted between March and April 2020, during which he examined 118 laboratory-confirmed SARS-CoV-2 infected patients with clinically indicated echocardiography, of which 5 (4.2%) had features consistent with TTS. Of the five patients with TTS, four patients had regional wall abnormalities typical of TTS, including peripheral hypokinesia or akinesia of the apical and medial wall segments, while one patient had peripheral basal wall hypokinesia (consistent with inverse TTS) [4]. Dweck, in his international study, analyzed the results of echocardiography in patients with presumed or confirmed COVID-19 between April 3 and 20, 2020. The study ultimately included 1,216 patients from 69 countries on six continents, of whom TTS were detected in 2% of people [5].

In Geneva, Switzerland, an 83-year-old woman was observed who also had a confirmed case of SARS-CoV-2 infection. Echocardiography revealed left ventricular apical ballooning with hyperkinetic basal segments. Coronary angiography showed insignificant changes with typical TTS pictures in ventriculography [6]. Researchers at Johns Hopkins University presented a case of a 58-year-old woman who was admitted to the hospital with symptoms of SARS-CoV-2 infection. The patient then developed mixed shock, and the echocardiogram showed hypokinesia of the left ventricle and the ballot apex, which are typical of Takotsubo cardiomyopathy. Over the next few days, her LV function improved, further supporting the reversibility of the broken heart syndrome [7]. Another case that was described is the case of a 67-year-old woman who had upper respiratory symptoms and confirmed SARS-CoV-2 infection. She was diagnosed with large hemorrhagic pericardial effusion with echocardiographic signs of tamponade and mild left ventricular impairment. The patient was again diagnosed with TTS [8]. In Italy, an 87-year-old female patient was admitted to the clinic at a hospital in Brescia, in whom a nasopharyngeal swab was positive for SARS-CoV-2, and the x-rays showed pathognomonic pneumonia. The patient developed tachycardia, and an

echocardiogram showed changes in the LV - apical ballooning and hypokinesia of middle ventricular segments with a slightly reduced systolic function. The clinical, laboratory and the radiological picture was diagnostic for the TTS [9]. The next reported case is a 71-year-old woman diagnosed with COVID-19 undergoing a coronary angiogram showing significant changes in the proximal anterior descending artery and first oblique arteries. Ventriculography revealed a regional wall motion abnormality unrelated to coronary lesions, indicating typical Takotsubo cardiomyopathy [10].

In the case of a 50-year-old male confirmed by the PCR- SARS-CoV-2 test, coronary angiography showed normal coronary arteries. LV angiography showed basal segment akinesia and middle apex segment hyper-contraction at elevated diastolic pressure. Based on this finding, a diagnosis of reverse TTS was made [11]. A 59-year-old woman diagnosed with SARS-CoV-2 infection was admitted for dyspnea, ECG showed sinus tachycardia, delayed intraventricular conduction, and widespread negative T-wave repolarization changes in DIII and aVF. Given the lack of evident changes consistent with myocardial infarction on the ECG, the patient had an episode of acute chest pain after 12 hours in which the ECG showed lateral ST-segment elevation with lateral giant symmetrical anterior negative T waves and prolonged QT. The patient, therefore, underwent emergency coronary angiography, which showed that the coronary artery was free from significant changes. The subsequent echocardiogram showed apical akinesia with an "apex balloon" and a moderate reduction in systolic function (ejection fraction 40-45%), indicating symptoms of TTS [12].

In summary, the above cases allow to hypothesize that TTS may be closely related both to SARS-CoV-2 infection and the ongoing pandemic. The enormous emotional stress caused by the pandemic and respiratory infections caused by SARS-CoV-2 could be a potential trigger for TTS. The case series cited above suggest that TTS should be considered in the differential diagnosis across the entire spectrum of myocardial injury in SARS-CoV-2 infected patients. Myocardial damage associated with SARS-CoV-2 infection is usually attributed to sepsis, hypoxemia, coronary artery disease, and myocarditis. We hypothesize that TTS may also play a role among these lesions.

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