

Takotsubo Syndrome during the COVID Era: More Stressful Events or an Unclear Bond?

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Abstract

'Takotsubo syndrome' is a cardiomyopathy characterized by a temporary wall motion abnormality of the left ventricle which shares common features with acute coronary syndrome. During the COVID-19 pandemic acute coronary syndrome can be one of the initial presentations of COVID-19 infection, ranging from a ST elevation myocardial infarction to Takotsubo cardiomyopathy. We elaborate a review of the existing literature until the April 27, 2021, in order to analyze and explore the connections between Takotsubo Cardiomyopathy and the COVID-19 pandemic. We selected twenty-seven case reports/case series and three studies. The analyzed cases include 53 patients, 19 male (36%). Shared clinical features are hypertension, diabetes mellitus and dyslipidemia. The majority were COVID-19 positive, 23 requiring mechanical ventilation. A recovered cardiac function has been described in 20 patients. In COVID-19 patients, therapy involves the use of hydroxychloroquine in 15 subjects and chloroquine in one of them. Coronary angiography was not ever performed, according to clinical instability and less-probably different diagnosis. The most type of Takotsubo syndrome was the typical one, even if inverted, biventricular and atypical were reported. The overall analysis shows a higher prevalence of male patients compared to the known literature and higher rates of clinical features such as hypertension, diabetes mellitus and dyslipidemia. An increased psychological distress, the cytokine storm, augmented adrenergic responses and microvascular dysfunction have been hypothesized playing a role. Our study explores what the existing literature offers and clarify the importance of an accurate and immediate recognition of Takotsubo syndrome during a stressful period like the COVID pandemic.

Keywords: Takotsubo and COVID-19 • Stress cardiomyopathy and coronavirus • Stress cardiomyopathy and COVID-19

Introduction

'Takotsubo Syndrome' (TTS) refers to a cardiomyopathy characterized by a temporary wall motion abnormality of the Left Ventricle (LV) which shares common features with Acute Coronary Syndrome (ACS) specifically in terms of a microvascular ACS form. TTS includes a wide spectrum of emotional or physical triggers resulting also in left ventricular dysfunction. The term 'Takotsubo' recalls the Japanese word for octopus trap, due to the shape of the LV at the end of systole visible at echocardiographic investigation [1]. Different diagnostic criteria have been proposed among whom the Inter TAK Diagnostic Score was developed by the International Takotsubo Registry to assess the likelihood of TTS diagnosis. A coronary angiography with left ventriculography is generally performed even if obstructive coronary lesions may occasionally be present concomitantly. Currently different TTS sub-types are known to be possible: apical ballooning type also known as the typical TTS form, midventricular, basal or inverted and focal wall motion patterns. The prevalence of TTS is estimated to be approximately 2%-3% in all

patients presenting with suspected ACS and women who are 55 years old had 10.7 times higher odds for developing TTS when compared with men of similar age group according to an American database.

COVID-19 Pandemic

On March 11th, 2020, the World Health Organization (WHO) declared the pandemic infection of SARS-CoV-2 (COVID-19). By then about 160 000 000 cases had been reported and more than 3000000 deaths had been recorded. During the COVID-19 pandemic myocardial injury (defined as elevation in cardiac troponin concentration above the 99th percentile of upper reference limit) has been observed in 8%-12% of hospitalized COVID-19 patients and ACS can be one of the initial presentations of COVID-19 infection, ranging from a ST Elevation Myocardial Infarction (STEMI) to Takotsubo cardiomyopathy. Several triggers during the COVID-19 era could be related to Takotsubo syndrome. We performed a narrative review aiming at a better insight into connections between the

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Received: 06 September, 2021; **Accepted:** 20 September, 2021; **Published:** 27 September, 2021

COVID-19 pandemic and Takotsubo cardiomyopathy, focusing on its features and possible causes [2].

A Literature Insight: Takotsubo Cardiomyopathy during the COVID-19 Pandemic

We elaborate a review of the existing literature until the April 27, 2021, in order to analyze and explore the connections between Takotsubo Cardiomyopathy and the COVID-19 pandemic. The research was retrospectively conducted through two databases of scientific literature, PubMed and Scopus, using the keywords 'Takotsubo and COVID-19' and 'Stress Cardiomyopathy and Coronavirus or COVID-19'. All the articles found to be relevant, analyzing incidences of Takotsubo syndrome during the COVID-19 pandemic or showing new cases of Takotsubo Cardiomyopathy during the COVID era or in patients affected by COVID-19 were included. We selected twenty-seven case reports/case series and three studies [3]. A retrospective cohort study including 1914 patients at the final analysis and report a significant increase in the incidence of stress cardiomyopathy in patients presenting with ACS during the COVID-19 period (incidence proportion 7.8%). All patients were negative for COVID-19 and no significative differences in mortality and 30-day rehospitalization were reported. This is the only large cohort study conducted heretofore, making more concrete the suspect of a strict relation between stress-cardiomyopathy and COVID-19 era, even if none of the subjects was affected by SARS-COV-2infection. A contemporary prospective international survey of 1216 patients with presumed or confirmed COVID-19 analyzing echocardiography findings found a 2% of concomitant takotsubo cardiomyopathy, above the rate in general population. A variegated lists of case reports could be found in literature search: we selected twenty-six among them. The analyzed cases include 53 patients, 19 male (36%). Shared clinical features are hypertension, diabetes mellitus and dyslipidemia. The majority were COVID-19 positive, 23 requiring mechanical ventilation. A recovered cardiac function has been described in 20 patients. In COVID-19 patients, therapy involves the use of hydroxychloroquine in 15 subjects and chloroquine in one of them. Coronary angiography was not ever performed, according to clinical instability and less-probably different diagnosis. The most type of TTS was the typical one, even if inverted, biventricular and atypical were reported [4].

Different Gender Distribution and Clinical Features

Our search in scientific literature found several examples of Takotsubo cardiomyopathy among COVID-19 patients or during the COVID-19 pandemic, especially in patients who underwent mechanical ventilation: this could possibly be associated to a more severe SARS-COV-2 infection related disease or to the stressful events connected to intubation. The diagnosis was commonly made around the time of intubation. The overall analysis shows a higher prevalence of male patients compared to the known literature and higher rates of clinical features such as hypertension, diabetes mellitus and dyslipidemia. It is comprehensible if we consider that men account for a higher percentage in the sex distribution of this

disease. Among comorbidities, hypertension and diabetes are also found among patients presenting poor outcomes. Less is certain regarding the pathophysiology of TTS in COVID-19 patients: the exact mechanism is far to be clear, but several hypotheses have been proposed. A direct influence of COVID-19 infection through the induction of psychological distress, cytokine storm, augmented adrenergic responses and microvascular dysfunction has been hypothesized playing a role (Figure 1). A cytokine storm in COVID-19 infection is well known with a heightened release into the bloodstream of pro-inflammatory cytokines and chemokines, namely tumor necrosis factor- α , IL-6, and IL-1 β .

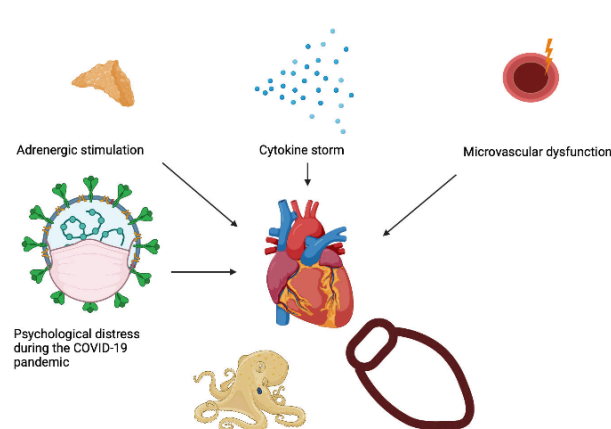


Figure 1: Pathophysiology of TTS in COVID-19 patients: Possible etiologies.

An increased adrenergic stimulation through a catecholamine-induced myocardial stunning has also been hypothesized, while a microvascular dysfunction noticed to be related to COVID-19 emerged as a physiological mechanism followed by TTS. The increased perspective stress could be related to quarantine and isolation adding negative elements to traditional risk factors for cardiovascular disease [5]. Quarantine has consequences on mental health in terms of anxiety, fear, anger, loneliness, and several studies have underlined that quarantine and isolation are associated with psychological and behavioral factors that could increase the risk of developing cardiovascular disease and among them TTS. The patients had a situation of physical and psychological exhaustion close to the period of the pandemic onset, and the additional burden of COVID-19 contributed to trigger TTS. TTS was also previously associated to natural disaster such as 2004 Japan earthquake and 2011 Joplin tornado.

Conclusion

A relationship between TTS and the COVID pandemic seems to be present and quite strong, even if the exact mechanism behind the etiology is less certain. Every hypothesized explanation could find support among scientific literature and several case reports. Our study explores what the existing literature offers and clarify the importance of an accurate and immediate recognition of TTS during a stressful, psychological and/or physical, period like the COVID pandemic, especially regard its being a transient cardiomyopathy in several cases.

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How to cite this article: Barbieri Lucia, Gentile Domitilla, Tumminello Gabriele, Conconi Barbara. "Takotsubo Syndrome during the COVID Era: More Stressful Events or an Unclear Bond?." *J Clin Res* 5 (2021) : 136