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UNRAVELING THE MYSTERY OF TAKUTSUBO CARDIOMYOPATHY: A DESCENDANT OF COVID-19 HEART SYNDROME

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РАЗКРИВАНЕ НА МИСТЕРИЯТА НА КАРДИОМИОПАТИЯТА TAKUTSUBO: ПОТОМЪК НА СЪРДЕЧНИЯ СИНДРОМ НА COVID-19

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Abstract. Takutsubo, or stress cardiomyopathy (TCM) is one of the important cardiovascular disorders encountered during the COVID-19 pandemic. We performed a PubMed search of relevant articles and presented this review which included epidemiology, etiopathogenesis, diagnosis and treatment of this clinical disorder. Takutsubo is usually more common in women than men. COVID-19 infection or vaccination can incite severe emotional disorders such as anxiety and depression, which flames up impaired neural networks in the limbic system. This stirs up disorganized regulation of autonomic nervous system with predominance and excessive firing of sympathetic nervous system to the ventricular myocardium. Moreover, direct invasion and systemic effects of COVID-19 infection including hormonal influences, autoimmunity, cytokine storm and neighboring infections might also play a significant role in the manifestation of this disorder. It commonly presents signs and symptoms of left ventricular dysfunction. Although most cases are undergoing remission within a few weeks, complications such as LV outflow tract obstruction, thromboembolism and arrhythmias were also reported. Since clinical symptoms are non-specific, a high degree of clinical suspicion is warranted particularly with the co-existing COVID-19 infections. Clinicians often leaned upon battery of tests including ECG, echocardiography and CMR to rule out myocarditis and coronary artery disease. Supportive management including treatment of heart failure and any associated arrhythmias and thromboembolism. Recurrences are common, but the treatment of underlying psychiatric disorders, including relaxation techniques, is the key strategy to avoid future occurrences.

Key words: COVID-19, takutsubo cardiomyopathy, stress cardiomyopathy, emotional stress disorder, anxiety, depression, sympathetic over activity, left ventricular failure

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Резюме. Такуцубо, или стресовата кардиомиопатия (ТКМП), е едно от важните сърдечно-съдови заболявания, срещани по време на пандемията от COVID-19. Извършихме PubMed търсене на подходящи статии и представихме този преглед, който включва епидемиология, етиопатогенеза, диагностика и лечение на това клинично заболяване. Такуцубо обикновено се среща по-често при жените, отколкото при мъжете. Инфекцията с COVID-19 или ваксинацията срещу това заболяване може да предизвика тежки емоционални разстройства като тревожност и депресия, което разпалва увредените невронни мрежи в лимбичната система. Това предизвиква дезорганизирана регулация на автономната нервна система с преобладаване и прекомерно задействане на симпатиковата нервна система към вентрикуларния миокард. Освен това директната инвазия и системните ефекти на инфекцията с COVID-19, включително хормонални влияния, автоимунитет, цитокинова буря и съседни инфекции, също могат да играят значителна роля в проявата на това разстройство. Обикновено представлява признаци и симптоми на левокамерна дисфункция. Въпреки че повечето случаи са подложени на ремисия в рамките на няколко седмици, също се съобщава за усложнения като обструкция на изходния тракт на LV, тромбоемболия и аритмии. Тъй като клиничните симптоми са неспецифични, високата степен на клинично подозрение е оправдана, особено при съпътстващи инфекции с COVID-19. Клиницистите често разчитаха на набор от тестове, включително ЕКГ, ехокардиография и CMR, за да изключат миокардит и коронарна артериална болест. Поддържащо лечение, включително лечение на сърдечна недостатъчност и свързаните с нея аритмии и тромбоемболия. Рецидивите са чести, но лечението на основните психиатрични разстройства, включително техники за релаксация, е ключовата стратегия за избягване на бъдещи събития.

Ключови думи: COVID-19, кардиомиопатия takutsubo, стресова кардиомиопатия, емоционално стресово разстройство, тревожност, депресия, симпатикова свръхактивност, левокамерна недостатъчност

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Epidemiology

Takutsubo is a Japanese term which literally means an octopus pot and it is used to describe a narrow neck and ballooning of the apical portion of the left ventricle which is the most common presentation of stress cardiomyopathy noted so far. In a textbook description of this clinical entity, it is a typical left ventricular pumping abnormality which presents as congestive cardiac failure and typically manifests in the elderly women who had recently experienced a severe emotional stressor. The most common sites of occurrence include an apical ballooning form (75%), mid-ventricular ballooning form (10-20%), basal (< 5%) and biventricular form (0.5%) [1]. The incidence of TCM is roughly estimated to be around 10-15 cases out of 100,000 cases [1]. The average incidence of the TCM among patients with the COVID-19 patients is estimated to be around 2-4% [2]. TCM associated with the COVID-19 patients usually mimics acute coronary syndrome (ACS) and accounts for 1.2-2.2% of these ACS cases [3]. The percentage of acute coronary syndrome cases diagnosed with TCM before and during COVID-19 pandemic was 1.5% and 7.75% [4, 5]. Additionally, the median hospital stay of TCM cases diagnosed during the COVID-19 pandemic was substantially higher as compared to TCM cases diagnosed before pandemic [5]. The percentage of patients developing TCM following first and second dose of mRNA COVID-19 vaccination is approximately 50% [6]. Following COVID-19 vaccination, symptoms of TCM appeared within 2.62 days with most of these patients exhibiting left ventricular ejection fraction (LVEF) less than 50% [6]. In-hospital mortality rate, hospital discharge rate and 1-year mortality of TCM developing COVID-19 vaccination is 1.3%, 73.6% and 6.9% respectively [6].

Etiopathology

As of today, there are no specific etiological factors that can be specifically attributed to the causation of TCM. TCM is also called stress cardiomyopathy because it is mostly induced by a variety of stressors. Important risk factors that are implicated in the causation of TCM include postmenopausal women, diabetes, asthma and cannabis usage [1]. Both emotional (stress, fear, grief anxiety, depression, and anger) and physical stressors (stroke, seizure, schizophrenia, substance abuse, post menopause, encephalitis, meningitis, head trauma, and asthma) are widely implicated in its occurrence [7, 8]. Previous reports indicate that, TCM was demonstrated in 30-45% of cases without any emotional stressor [8].

It is not surprising to rationalize that COVID-19 infection and vaccination can serve as an important emotional stressor for inducing TCM. These emotional triggers are speculated to disrupt the neural pathways in the limbic part of the nervous system. As a result of this impairment, the autonomous nervous system which controls the blood flow and contractability of heart chambers is derailed resulting in the ultimate manifestation of this clinical entity. Furthermore, systemic complications and direct local action of the COVID-19 virus are also an important risk factors suspected for developing TCM.

Burrowing into the underlying mechanisms

Since the advent of the COVID-19 pandemic, patients presenting with new onset cardiovascular disorders are on the rise. This increased propensity to develop cardiovascular disorders was surprisingly substantial irrespective of their underlying clinical risk factor profile. It is without exacerbation that almost the entire medical community is astonished and dumbfounded at the advent of a spectrum of cardiovascular abnormalities including stress cardiomyopathy in the COVID-19 patients. Since then, the clinical researchers have delved into the underlying mechanisms that form the basis for initiation, evolution and clinical presentation of cardiovascular disorders in the COVID-19 patients. Based on these preliminary research studies, researchers speculated some systemic, immunological, hormonal, and neurological aberrations that might be potentially instrumental and propitious in the causation of multi-spectrum cardiovascular disorders in the COVID-19 patients

The exact mechanisms that are involved in the materialization of Takotsubo cardiomyopathy secondary to COVID-19 infection are very unclear. Nevertheless, clinicians speculated and formulated few hypotheses for its emergence, and they range from prolonged hibernation, exaggerated sympathetic tone, immunological mimicry, cytokine storm, hormonal imbalances, fibrosis and hyperinflammation [9-11] (Figure 3) Other possible mechanisms proposed include myocarditis, hypoxia and coronary artery disease all of which would subject the ventricular myocardium to undue stress thereby instigating ultrastructural changes that are susceptible to the development of stress cardiomyopathy [3] (Figure 1). It is demonstrated that excessive emotional stressors tend to derail the neural networks in the limbic system specially in the following regions including the amygdala, insula, anterior cingulate cortex, prefrontal cortex and hippocampus (Figure 3) [6]. This impairment of neuronal networks is believed to activate the sympathetic nervous system leading to release of the catecholamines through the activation of the hypothalamic-adrenal-pituitary axis [6]. These released catecholamines tend to act on the alpha-1 (α-1) receptors causing vasoconstriction, increased blood pressure,

increased afterload, micro-vessel spasm, microvascular dysfunction, direct myocardial injury, and coronary ischemia [6, 12]. At the same time, stimulation of beta-adrenergic receptors causes impairment of myocardial contractability, increased oxygen demand, obstruction of left ventricular outflow, and increased mechanical wall stress [12] Excess spilling of catecholamines into the blood will also trigger the β2-adreoreceptor in the apical part of the cardiac tissue to switch from Gs to Gi coupling resulting in negative inotropic effects and cardiac pump failure [2, 13].

Previous reports indicates that, the COVID-19 virus persists in the systemic tissues in a subset of patients known as long haulers [14]. These long haulers experienced prolonged symptoms, a trend that can be rationalized by end-organ damage, altered immunity and low grade inflammation [11]. Cardiac manifestations in the long-term COVID-19 haulers include labile heart rate, myocarditis, pericarditis, congestive cardiac failure, coronary artery aneurysm, arrhythmias and sudden cardiac death [11]. In the long haul, we can ruminate that the COVID-19 virus hibernates and takes refuge in the left ventricular myocardium for a prolonged duration in a non-symbiotic relationship. During its sojourn in the ventricular myocardium, it can inflict low-grade inflammation of the cardiomyocytes resulting in a host of structural alterations ranging from apoptosis, necrosis, endothelial dysfunction, pericyte damage, extracellular matrix digestion, gap junction impairment and fibroblast activation.

Unlike other viruses, the ability of COVID-19 to infect every cell in the myocardium including cardiomyocytes, cardiac fibroblast, endothelial cell, pericyte and extracellular matrix and thereby cellular abnormalities is widely discussed and speculated [15-17] (Figure 1). These cellular and extracellular aberrations provoked by COVID-19 could add together to instigate ventricular thinning and dilation of the ventricular myocardium, a key pathological finding in Takotsubo Cardiomyopathy.

Cardiac Tropism of COVID-19 virus: impact on Cardiomyocytes, pericytes, endothelial cells and fibroblasts (Figure 2).

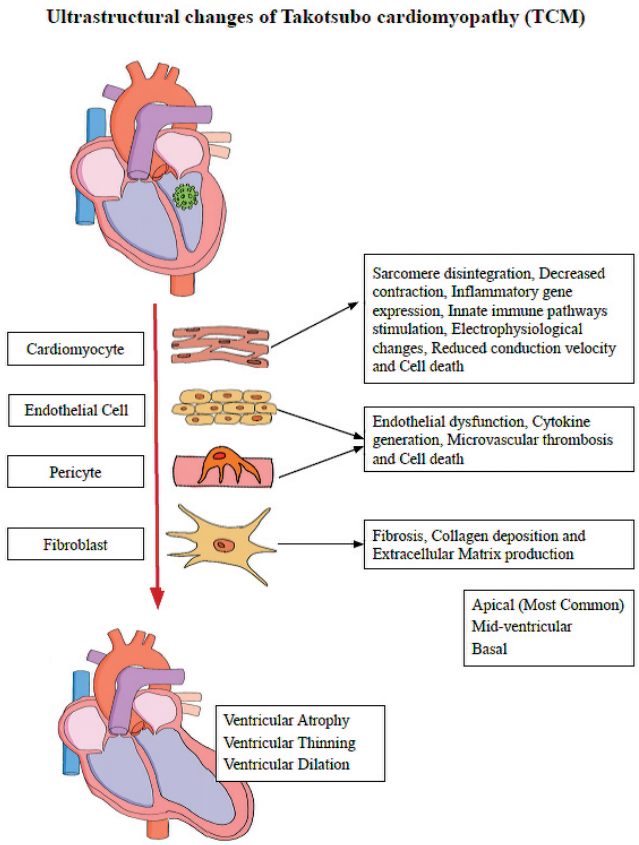

Fig. 1. Ultrastructural changes in Takotsubo cardiomyopathy (TCM): Direct invasion of ventricular myocardium by COVID-19 virus can stir up some cellular changes which might be the underlying basis for developing Takubsubo cardiomyopathy in these patients. Cardiomyocyte, endothelial cells, pericytes and fibrocyte infection with COVID-19 virus can induce various pathological aberrations and changes that ultimately makes the apical part of ventricular myocardium vulnerable to thinning, dilation and atrophy, features characteristic of stress cardiomyopathy seem in COVID-19 patients

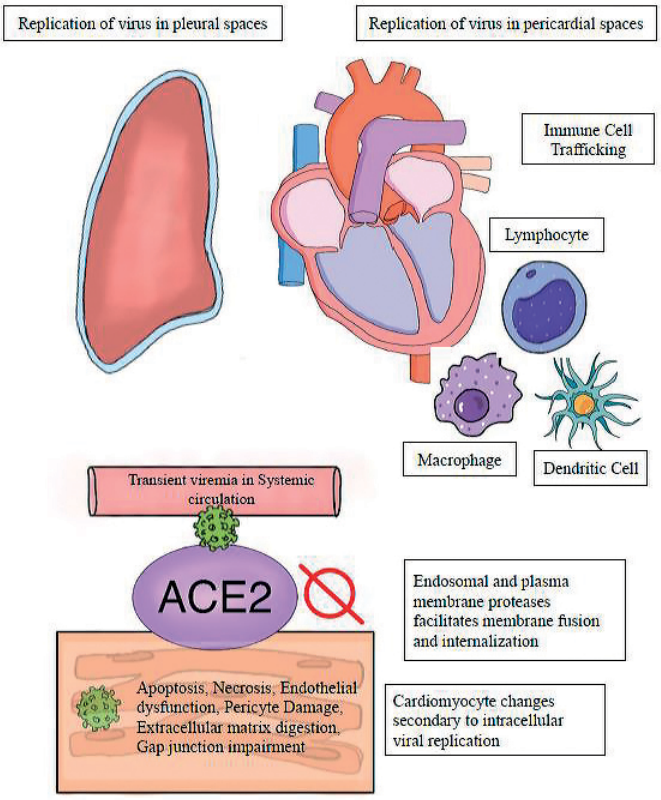

Fig. 2. Cardiac tropism of COVID-19 virus: Some of the factors that favor cardiotropism during COVID- 19 infection include replication of virus in pleural & pericardial spaces, immune cell trafickking and ACE2 expression in cardiomyocytes. Spike protein of COVID-19 virus binds to ACE2 receptors expressed on cardiomyocytes. Endosomal and membrane protease facilitate internalization of COVID-19 virus thereby instigating changes including apoptosis, necrosis and other changes that predispose the ventricular myocardium for development of TCM

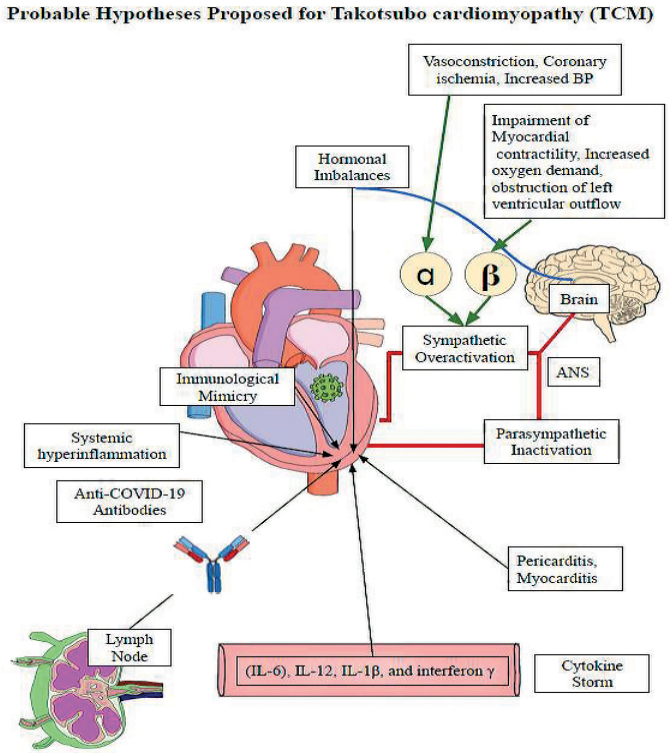

Fig. 3. Systemic changes induced by COVID-19 virus relevant to TCM: Systemic complications witnessed during COVID-19 infections such as hyperinflammation, cytokine storm, anti-COVID-19 antibodies, pericarditis, myocarditis, hormonal imbalances and overstimulation of sympathetic nervous system were all implicated together in manifestation of TCM

Although Cardiac tropism of COVID-19 virus is poorly understood, initial reports indicate that transient viremia in the systemic circulation, immune cell trafficking, replication of the virus in the pleural & pericardial spaces are partly alleged for COVID-19 virus journey towards myocardial tissues [16]. Once it reaches the myocardial tissues, the spike protein of the virus conveniently binds to ACE2 (angiotensin converting enzyme 2) expressed on the cardiomyocytes to initiate its internalization [15, 16]. (Figure 2). In a similar fashion, the COVID-19 virus houses in the pericytes, fibroblasts and endothelial cells utilizing ACE2 [15, 16]. Interaction of the spike protein of the virus with ACE2 is followed by membrane fusion and subsequent internalization, a process which should be aided by endosomal / plasma membrane proteases [15, 16] (Figure 2). Rapid replication within the cardiomyocytes paves the way for the pathological derangements ranging from sarcomere disintegration, decreased contraction, inflammatory gene expression, innate immune pathways stimulation, electrophysiological changes, reduced conduction velocity and cardiomyocyte cell death [15, 16]. Neighboring endothelial and pericyte involvement with COVID-19 causes endothelial dysfunction, cytokine generation, microvascular thrombosis and cell death [16]. Pro-inflammatory cytokines, transforming growth factor-beta 1 (TGFβ-1) and angiotensin II (Ang II) secreted by replication of COVID-19 viruses might signal the metamorphosis of cardiac fibroblast into myofibroblast [17]. Under physiological conditions, myofibroblasts are mainly functional in the production of collagen, deposition of extracellular matrix (ECM) and pro-modelling factors that are essential for tissue healing [17]. It is likely that COVID-19 induced cellular aberrations tend to create a microenvironment where myofibroblasts tend to be immortal so that fibrosis and ECM deposition occur at an heightened rate in the ventricular myocardium [17]. Lastly, the COVID-19 virus binding to ACE2 in the vascular smooth muscle of the coronary arteries causes accumulation of Ang-II leading to excess catecholamine surge, vasoconstriction, coronary ischemia, oxidative stress and inflammation [6, 12].

We surmise that, these spectrums of cellular and ultrastructural aberrations can form the pathological basis for thinning and dilation of the ventricular myocardium that can subsequently present phenotypically as TCM. Another important point to note is that the most common sites of ventricular dilation of TCM are apical followed by mid-ventricular, basal and bi-ventricular [10]. Unique myocardial structure and preferential oxygen supply might be the probable explanations for the COVID-19 colonization at the apical myocardium as compared to basal myocardium [18].

Risk factors and clinical presentation

Some of the important risk factors that were encountered in the TCM cases include hypertension, diabetes mellitus, older age and women [4]. Out of these, hypertension is regarded as the most important risk factor for developing TCM in the COVID-19 patients [19]. In COVID-19 patients, women (69.5%) are more likely to develop TCM as compared to men (30.5%) which can be explained by hormonal imbalances [20]. The age of presentation of TCM in the COVID-19 patients and non-COVID-19 patients is approximately 58.9 and 53.8 years respectively [19].

Following a stressful trigger, hypokinesis of the left ventricular myocardium in the absence of structural heart disease along with the appearance of new electrocardiographic changes is suspected to be conclusive of TCM according to Mayo Clinic [https://www.mayoclinic.org/diseases-conditions/broken-heart-syndrome/symptoms-causes/syc-20354617]. Clinical symptoms can range from chest pain (75%), dyspnea (50%), dizziness (25%), syncope (5-10%), tachyarrhythmias, sudden cardiac arrest and mitral regurgitation [1, 12, 21]. From the appearance of clinical symptoms, average time it takes for the COVID-19 patients with TCM to get admitted to the hospital is approximately 7.2 days [20]. It is important to understand that the most common apical TCM is usually associated with left ventricular outflow tract obstruction and apical thrombus formation [8].

In the setting of COVID-19 disease, the most common presentation is acute left ventricular dysfunction along with mixed cardiogenic and septic shock [11]. In other cases, it

might present as hypoxic respiratory failure requiring oxygen support and mechanical ventilation [22]. The clinical course of TCM can be complicated by congestive cardiac failure, shock, LV outflow tract obstruction, systemic thromboembolism, intramyocardial hemorrhage, myocardial rupture and arrhythmias [1, 22]. Interestingly as compared to conventional TCM, COVID-19 patients with TCM presented with dyspnea needing mechanical ventilation and were likely to develop cardiogenic shock eventually [20].

Diagnosis

Since TCM is mostly asymptomatic and non-specific, it might only be suspected by electrocardiogram (ECG) displaying grossly negative T-waves in the precordial leads along with QT prolongation [3]. According to a recently conducted meta-analysis, the most common ECG findings in the COVID-19 patients with TCM include ST elevation (50%), T-wave inversion (50%), and prolonged QT interval (50%) [20, 23]. Important cardiac biomarkers that are widely prevalent in the COVID-19 patients with TCM include CK (Creatine kinase) (18%), CK-MB (creatine kinase-myocardial band) (12%), cardiac troponin (17%) and BNP (28%) [20, 24]. In another recent study by Singh et al, cardiac troponin is the most common biomarker that is upregulated in 91% of the COVID-19 patients developing TCM. Although these biomarkers can relay the clinical suspicion of TCM, further diagnostic modalities such as cardiac imaging need to be performed to confirm the diagnosis of TCM.

Along with these signs, the appearance of apical wall ballooning (58.3%) and hypokinesis (33.3%) along with basal wall hyperkinesis in the trans thoracic echocardiogram (TTE) is diagnostic of TCM [3, 23]. In addition, reduced left ventricular ejection fraction (LVEF) (36.4%) was demonstrated by echocardiography in the COVID-19 patients developing TCM [23]. Sometimes it is hard to differentiate between TCM and myocarditis, so clinicians often lean upon cardiac magnetic resonance (CMR) and endomyocardial biopsy to rule out myocarditis [6]. It is also necessary to perform coronary angiography to rule out obstructive coronary artery disease or acute plaque rupture [6]. Moreover, coronary angiography is regarded as a gold standard modality for ruling out acute coronary syndrome or acute plaque rupture from TCM [25, 26]. CMR is usually necessary to rule out myocarditis in which case highlights the presence of myocardial edema (basal, lateral and sub-epicardial), inflammation and scarring along with delayed gadolinium enhancement (DGE) [8].

Treatment and prognosis

Patients with TCM usually need in-hospital admission for supportive management of heart failure and left ventricular outflow tract obstruction and close monitoring of any complications [25]. Treatment should be focused on the treatment of COVID-19 infection, mental relaxation techniques and usage of drugs including beta blockers and angiotensin-converting enzyme (ACE) inhibitors for improving the left ventricular dysfunction [2, 25]. Appropriate precaution needs to be taken to manage coexistent arrhythmias and thromboembolism for optimal survival rate [8, 25]. Previous reports indicate that in most cases, LV systolic function usually returns to normal levels within a few weeks [25, 26]. In contrast, TCM developing in the COVID-19 patients is life threatening with higher mortality ranging from 23.3 to 36.3% [20]. Men seem to have higher mortality as compared to women in the patients with TCM and COVID-19 [27]. According to a recent study, most of the COVID-19 patients with TCM are at a high risk of developing complications such as cardiac tamponade, heart failure, myocarditis, hypertensive crisis, septic shock, and cardiogenic shock [23]. Even after complete recovery, the risk of recurrence of TCM is estimated to be 2-20% within the first 10 years [1]. Studies indicate that long term recurrences can be prevented by administration of the calcium channel blockers (CCBs) and concurrent treatment of mental health comorbidities such as anxiety and depression [8]. Compared to the control population, patients with TCM are more likely to experience symptoms such as fatigue, shortness of breath, chest pain, palpitations and exercise intolerance in a long term basis [1].

Conclusion

Stress cardiomyopathy or TCM is reversible and transient acute left ventricular decompensation presenting in the women particularly after a recent episode of an emotional stressor such as COVID-19 infection. Both systemic complications and direct myocardial invasion due to COVID-19 infection are partly responsible for the manifestation of this clinical entity. Its presentation is non-specific, and it can range from chest pain, dyspnea, dizziness, and syncope. It should be mainly differentiated from acute coronary syndrome and myocarditis by ECG, echocardiography, CMR and coronary angiography. Management should be limited to the treatment of COVID-19 infections, heart failure, and any associated complications. Treatment and prevention of associated psychiatric disorders are very much essential to prevent any recurrences.

Future directions

Further research should be focused on the relationship between COVID-19 infection and sympathetic activation. Characterization of catecholamine induced cell signaling mechanisms post activation of beta-1 adrenergic receptors in the cardiomyocytes is needed. In addition, COVID-19 induced effects on pericytes, fibroblasts and extracellular matrix in the myocardium needs more work as it sheds light on their aberrations and their role in the manifestation of TCM. Furthermore, since postmenopausal women

are more likely to be inflicted, role of the testosterone and estrogen induced effects on cardiomyocytes, endothelial cells and their effects on blood flow, muscle contraction should be elucidated. Moreover, the cellular effects of anti-COVID-19 antibodies and cytokines which are more prevalent in the COVID-19 infections in the myocardial milieu need further investigation. It is entirely enigmatic how the presence of systemic inflammation provokes cellular changes in the cardiomyocytes, endothelial cells, pericytes and fibroblasts, a line of research which needs further attention. Previously, some researchers hypothesized that pericarditis and myocarditis might predispose to the occurrence of TCM, and it is still not entirely clear how does the presence of coexistent neighboring infection influences the initiation and clinical progression of TCM. It would also be worthwhile to characterize how the continuous presence of emotional stressors in the long-term influences the pathological mechanisms at the cellular level to make the patients susceptible to recurrent stress cardiomyopathy. Taken together, it is important to assess how all these multiple risk factors converge, coordinate, and inflict the cytopathic effects on myocardial cells which becomes the underlying pathophysiological basis for the occurrence of this clinical disorder.

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Author contributions

Conceptualization, S.H.K.; Writing – Original Draft Preparation, S.H.K.; Writing – Review & Editing, S.H.K. and P.J.S.; Figures, S.H.K. and P.J.S.; Final Approval, S.H.K. and P.J.S.

Conflicts of interest

None of the authors has any conflict of interest.

Data availability

No data is available. Data sharing is not relevant because no datasets were created and/or analyzed for this study.

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