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DERLEME/ REVIEW

TAKOTSUBO SENDROMUNA GÜNCEL BİR BAKIŞ

A CURRENT OVERVIEW OF TAKOTSUBO SYNDROME

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ÖZET

Takotsubo sendromu, kalbin sol ventrikülünün geçici işlev bozukluğu ile karakterize akut, geri dönüşümlü bir hastalıktır. Takotsubo sendromunun patogenezi tam olarak bilinmemektedir. Ancak Takotsubo sendromununpatogenezi ile ilgili çeşitli hipotezler ileri sürülmüştür. Takotsubo sendromunun patogenezi ile ilgili hipotezler; koroner mikrovasküler disfonksiyon, koroner arter spazmı, katekolamin kaynaklı miyokardiyal sersemleme, akut koroner sendromdan sonrası reperfüzyon hasarı, miyokardiyal mikroinfarktüs, endotel disfonksiyonu ve östrojen eksikliği ve kardiyak yağ asidi metabolizmasındaki anormallikler şeklinde adlandırılabilir. Takotsubo sendromu ile ilgili hipotez ve teoriler arasında en sık olarak katekolamin kaynaklı kardiyotoksisite ve koroner mikrovasküler disfonksiyon üzerinde durulmaktadır. Takotsubo sendromu bazı klinik semptom ve bulgularla kendini gösterir. Takotsubo sendromunda, başvuru sırasında görülen semptomlar, en yaygından en aza doğru göğüs ağrısı, nefes darlığı ve senkoptur. Klinik olarak akut göğüs ağrısı ve nefes darlığı gibi şikayetlere neden olduğu için akut miyokard enfarktüsü veya akut koroner sendrom ile karıştırılabilir. Bu nedenle bu hastalıklardan ayırt edilmesi önemlidir. Ayırıcı tanıda anamnez, fizik muayene, kardiyak troponin, kreatin kinaz, troponin, elektrokardiyografi (EKG), koroner anjiyografi kullanılır. Takotsubo sendromunun ayırıcı tanısında fiziksel veya duygusal stresin varlığı önemli bir rol oynar. Takotsubo sendromu için spesifik bir tedavi yoktur. Ancak tedavi akut ve kronik dönemler olarak ikiye ayrılabilir. Akut dönemde Takotsubo sendromuna bağlı gelişen komplikasyonlara yönelik tedaviler uygulanırken, kronik dönemde beta blokerler, anjiyotensin dönüştürücü enzim (ACE) inhibitörleri, anjiyotensin II reseptör blokerleri gibi ilaçlar kullanılmaktadır. Takotsubo sendromu yoğun bakım hastalarında da görülebilmektedir. Yoğun bakım hastalarında sıklıkla hemodinamik bozukluklar ve solunum yetmezliği ile kendini gösterir. Bu nedenle yoğun bakım hastalarında hemodinamik ve solunumsal değişiklikler gözlendiğinde Takotsubo sendromu düşünülmeli ve hastalar bu yönde takip edilmelidir.

ANAHTAR KELİMELER: Takotsubo Sendromu, Yoğun Bakım, Stres, Akut Hastalık.

ABSTRACT

Takotsubo syndrome is an acute, reversible disease characterized by transient dysfunction of the left ventricle of the heart. The pathogenesis of Takotsubo syndrome is not known precisely. However, various hypotheses regarding pathogenesis have been put forward. These hypotheses; coronary microvascular dysfunction, coronary artery spasm, catecholamine-induced myocardial stunning, reperfusion injury after acute coronary syndrome, myocardial microinfarction, endothelial dysfunction and estrogen deficiency, and abnormalities in cardiac fatty acid metabolism. Among these hypotheses and theories, catecholamine-induced cardiotoxicity and coronary microvascular dysfunction are most frequently emphasized. Takotsubo syndrome manifests itself with some clinical symptoms and signs. In Takotsubo syndrome, symptoms seen at presentation are chest pain, shortness of breath, and syncope, from the most common to the least. Clinically, it can be confused with acute myocardial infarction or acute coronary syndrome because it causes complaints such as acute chest pain and shortness of breath. Therefore, it is important to differentiate from these diseases. Anamnesis, physical examination, cardiac troponin, creatine kinase, troponin, electrocardiography (ECG), coronary angiography are used in the differential diagnosis. The presence of physical or emotional stress plays an important role in the differential diagnosis of Takotsubo syndrome. There is no specific treatment for Takotsubo syndrome. However, treatment can be divided into two parts as acute and chronic phases. While treatments for complications arising due to Takotsubo syndrome are applied in the acute phase, drugs such as beta blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers are used in the chronic phase. Takotsubo syndrome can also be seen in intensive care patients. In intensive care patients, it often manifests itself with hemodynamic disturbances and respiratory failure. Therefore, Takotsubo syndrome should be considered in intensive care patients when hemodynamic and respiratory changes are observed and patients should be followed up in this direction.

KEYWORDS: Takotsubo syndrome, Intensive care, Stress, Acute Disease.

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INTRODUCTION

Takotsubo syndrome (TCMP) (Stress-induced cardiomyopathy, Apical ballooning syndrome, Broken heart syndrome) is an acute disease characterized by transient left ventricular dysfunction (1, 2). It often causes reversible heart failure and resolves spontaneously within weeks (2 – 4). Patients often present with clinical signs such as acute chest pain and shortness of breath (2, 5). These complaints are similar to the presenting complaints of acute myocardial infarction or acute coronary syndrome. In addition, elevation of cardiac troponin and creatine kinase, ECG (Electrocardiography) changes (findings such as ST elevations in precordial leads) cause confusion with acute myocardial infarction and acute coronary syndrome in the early period of diagnosis (1). The fact that coronary stenosis is not observed in coronary angiography and there is a triggering emotional or physical stress in the anamnesis are helpful for TCMP (5, 6).

In TCMP, apical ballooning of the left ventricle is observed after systole (1). This is the classic pattern of left ventricular morphology. Apart from that, in TCMP; morphological features such as hypokinetic circumferential base (inverted Takotsubo variant), hypokinetic circumferential mid-ventricle (middle LV –Left Ventricule- variant), and focal variations can be traced (7 – 11).

An association between emotional or physical stress and cardiovascular events was recognized long ago. Stressful situations in population level cause a surge in cardiovascular mortality. Major non-cardiac surgeries, sepsis and subarachnoid hemorrhage increase cardiovascular mortality without an apparent coronary artery obstruction or cardiac structural abnormalities (12). One of the reasons for this increased cardiovascular mortality is Takotsubo syndrome. After the central Niigata Prefecture earthquake in Japan in 2004, a raised incidence of TCMP was reported (13).

Takotsubo syndrome can also be observed in intensive care patients. Most of the patients who are followed up in the intensive care unit initially present with serious diseases that lead to major stress such as respiratory distress, sepsis, convulsions and shock. Therefore, many of the patients followed up in the intensive care unit potentially have Takotsubo syndrome. This is why Takotsubo syndrome is not uncommon in intensive care. It is associated with particularly significant haemodynamic and respiratory instability in intensive care patients (14). Respiratory and hemodynamic deterioration with new onset arrhythmias are a warning for Takotsubo syndrome in intensive care patients. Therefore, when such conditions develop in patients followed in intensive care, patients should be followed up in terms of Takotsubo syndrome.

There is no specific treatment for Takotsubo syndrome. The treatment of Takotsubo syndrome is different in the acute phase and in the chronic phase and recurrence. In the acute phase, complications arising from Takotsubo syndrome are treated. In the chronic phase and recurrence, agents such as beta-blockers, angiotensin converting enzyme (ACE) inhibitors, Angiotensin II receptor blockers are used(1, 12).

EPIDEMIOLOGY

Takotsubo CMP (TCMP) is usually known as a disease that affects the older Asian women. While this assumption is mostly accurate, patients from all age groups have been reported, including a 2 years old girl with a malignancy (15). Several studies from Western countries reported that 90% of the patients were women between the ages 65-70 (15, 16). One study from Japan also reported the average age of the patients as 74 (15).

It is hard to detect the true incidence of TCMP, as it is a newly recognized disease, the information and clinical experience available is rapidly increasing. It should be noted that as the recognition of the disease increases, yearly incidence also increases. Minhas et al. reported a 20 fold increase in the incidence of TCMP between 2006 and 2012 (17). This is mostly due to the increased awareness of clinicians to the disease. This trend in the increased incidence was also reported in several other studies. For example, one center from Minneapolis reported an increased incidence in the last decade, with an incidence of 50 patients in the year of 2009 (15). Another study reports that 2% of the patients who were admitted with a suspected acute coronary sy-

ndrome were eventually diagnosed with TCMP. Annual incidence of TCMP in United States (US) may be estimated around 7000-14000 cases (13).

One of the large-scale studies about the epidemiology of TCMP comes from the United States of America (US). ⅕ of the US community hospitals were included in the study, and the incidence of TCMP was found to be 6,837 in 2008. The same cohort also emphasized that 70% of the patients were white and only 1% of them were Asian. This skew towards the Caucasians may be caused by the distribution of the sample population, however, this study shows that the TCMP is not restricted to Asians and may be seen in Caucasians too. As the reports and case series demonstrate, the incidence of TCMP is lower in Hispanics and African Americans. The recurrence rate of the disease varies between 0-22% in different patient groups (18). Additionally, recurrence rate was detected as 17.7% in patients with pheochromocytoma triggered TCMP (19).

There are no large scale epidemiological studies that correlate the combined incidence of neurological diseases and TCMP. However, several case series emphasize the causative relationship between neurological diseases and TCMP. One study from Italy reports that emotional triggers were seen in 27.7% of the cases, while physical triggers were seen in 36% of them. 7.8% of the patients had both physical and emotional triggers. Additionally, 55.6% of the patients had an acute or past history of the neurological or psychiatric diseases (20). In rare cases, TCMP may be triggered by viral diseases. there are 4 cases of TCMP triggered by viral gastroenteritis (21).

Takotsubo syndrome is not rarely observed in intensive care units. In a study conducted by Muratsu et al., 5 of the 5084 patients admitted to the intensive care unit were diagnosed with Takotsubo syndrome and 19 with clinical Takotsubo syndrome. The most common primary disease among the patients was sepsis (n=10), and secondary was subarachnoid hemorrhage (n=5), (22).

In the study conducted by Doyen et al., 13 of 280 patients admitted to the intensive care unit were diagnosed with Takotsubo syndrome using Mayo clinical criteria. Takotsubo syndrome was later confirmed by European Society of Cardiology (ESC) Heart Failure Association criteria. 69.2% of the patients diagnosed with Takotsubo syndrome were found to be female. In addition, the study found that Takotsubo syndrome is associated with high morbidity (14).

In another study from Korea, surprisingly high numbers of TCMP cases in Internal Care Unit (ICU) settings were reported. In a sample group of 92 patients, 28% were found to have TCMP (23). Rowell et al. reported only 4 cases of TCMP in their sample of 116 patients. In the same study, all of the patients were women (24). Lastly Oras et al. reported the incidence of 5% in a retrospective study in which more than 1000 patients were included (25).

Another article by Salah et al. presents 10 cases of TCMP in Coronavirus Disease-19 (COVID-19) patients. The mean age was 64.6 and 9 of the patients presented were women (26).

Also, after the COVID-19 pandemic, the rate of TCMP has increased in patients with initial diagnosis of acute coronary syndrome. As stated in this chapter, before the pandemic, this rate was near 2%, however after the start of the pandemic, this rate has risen to 7.75% (27). This significant increase is also supported by the study of European Association of Cardiovascular Imaging. In their study, 1216 COVID-19 positive patients were evaluated and 2% of them were diagnosed with TCMP (28). In another study, 118 COVID-19 positive patients were evaluated with clinically indicated transthoracic echocardiography and 4.2% of them were diagnosed with TCMP (29).

PATHOPHYSIOLOGY

The pathogenesis of TCMP is not known precisely (2, 30, 31). However, various hypotheses regarding pathogenesis have been put forward. These hypotheses; coronary microvascular dysfunction, coronary artery spasm, catecholamine-induced myocardial stunning, reperfusion injury after acute coronary syndrome, myocardial microinfarction, endothelial dysfunction and estrogen deficiency, and abnormalities in cardiac fatty acid metabolism (2, 31). Among these hypotheses and theories, catecholamine-induced cardiotoxicity and coronary microvascular dysfunction are most

frequently emphasized. Myocarditis is another theory about the pathophysiology of the TCMP, however, it is extremely unlikely due to absence of myocarditis in biopsies and absence of delayed gadolinium hyperenhancement with Cardiac magnetic resonance imaging (MRI).

1. Catecholamine-Induced Myocardial Stunning

It has been found that patients with TCMP experience an emotional loss or trauma before the diagnosis when questioned (2, 32). As a result of this study, it was suggested that excessive catecholamine release due to stress in TCMP leads to left ventricular dysfunction (30, 33 – 35). Various studies have been done to support this theory. One study found that patients with TCMP had higher circulating catecholamine levels compared to normal values (36, 37) and these levels persisted for 7-9 days after the initial presentation. Moreover, in a study of patients with TCMP (37), serum catecholamine concentrations were found to be two to three higher than in patients with myocardial infarction. This situation reveals that serious emotional stress is an accelerating factor in the development of TCMP. However, exogenous catecholamines, subarachnoid hemorrhage and pheochromocytoma have been reported to cause typical TCMP features such as wall motion abnormalities and depressed ejection fraction. (38, 39).

In addition to these, another study demonstrated that patients with hemodynamically unstable TCMP have a higher risk of heart attack when catecholamine supplementation is given, different complications associated with TCMP occur, and the risk of death is higher (1). Also, rat models showed that ST-segment elevations and apical ballooning may be prevented by the administration of alpha and beta receptor antagonists. These studies support the catecholamine theory.

Also, a study by Muratsu et al. demonstrated that subarachnoid hemorrhage was the second most frequent complication in ICU patients who had TCMP (22). This finding supports the hypothesis that sympathetic nervous system activation may induce TCMP. There is catecholamine-induced endothelial dysfunction in TCMP (40).

2. Endothelial Dysfunction and Estrogen Deficiency

Recent studies have shown that endothelial dysfunction is common in patients with TCMP (2). These studies are thought to explain the epicardial and/or microvascular coronary artery spasm seen in TCMP (2). Both age-related and estrogen deficiency coronary vasomotor abnormalities have been demonstrated in TCMP (41 – 43). This may explain the prevalence of TCMP in postmenopausal women. In physiological conditions, estrogen is beneficial on coronary microcirculation by various mechanisms (endothelium-dependent and endothelial-independent) and has a positive effect on coronary blood flow (43). In a study, it has been shown that stress-induced left ventricular apical ballooning can be prevented with estrogen supplementation (44). This situation supports the role of estrogen deficiency in the development of TCMP.

3. Coronary Microvascular Dysfunction

The majority of patients who undergo imaging for TCMP have normal coronary arteries or non-obstructive coronary artery disease on angiography (45). Therefore, obstructive coronary disease was excluded in the etiology of TCMP. Therefore, microvascular causes are thought to play a role in pathophysiology. Based on this, the theory of coronary microvascular dysfunction has been put forward. As a result of imaging methods performed for this theory, there are data in the literature indicating that microvascular dysfunction has a place in TCMP (40). However, coronary angiography is not used to visualize coronary microcirculation. Other focused methods such as thrombolysis in myocardial infarction (TIMI) frame count, corrected TIMI frame count (CTFC), TIMI myocardial perfusion grade (TMPG), and coronary flow reserve (CFR) have shown conflicting results. However, the limited imaging methods make it difficult to reveal new data.

CLINICAL PRESENTATION

Takotsubo syndrome constitutes approximately 1-2% of patients presenting with acute coronary syndrome (3, 46, 47). The majority of patients with Takotsubo syndrome are women (48). In the early stages of Takotsubo syndrome, ele-

ctrocardiographic findings and biomarkers are generally similar to acute coronary syndrome (3, 32, 49 – 52). In Takotsubo syndrome, symptoms seen at presentation are chest pain, shortness of breath, and syncope, from the most common to the least (48, 50, 53). Since chest pain and shortness of breath are common in acute myocardial infarction, Takotsubo syndrome may be confused with acute myocardial infarction. However, the severity of symptoms in Takotsubo syndrome is generally less severe than in acute myocardial infarction (53). Pulmonary edema can be observed in Takotsubo syndrome (48). However, cardiac arrest, cardiogenic shock, and severe arrhythmias are rarely observed at the onset of the disease (out-of-hospital settings) (48, 53). Apart from these symptoms, nonspecific symptoms such as weakness, cough and fever have also been reported (3, 32, 49, 51, 54, 55).

This syndrome may also develop in intensive care unit (ICU) patients. Usually first signs include pulmonary edema and ischemic changes in ECG. Cardiac biomarkers may also be elevated. In contrast with the other patients, most patients in the ICU are unable to experience chest pain due to continuous sedation or overlapping symptoms of other conditions. This makes the diagnosis more challenging. In a study by Haghi et al. 5 out of 6 patients were unable to report chest pain and for these 5 patients, hemodynamic deterioration was the key diagnostic clue (56). Another study by Doyen et al. reported that 69.2% of the ICU patients who developed TCMP presented with shock, 46.2% presented with arrhythmias and 92.3% presented with acute respiratory failure (14). In a study by Giustino et al. 118 laboratory-confirmed COVID-19 patients underwent a clinically indicated Trans-thoracic echocardiography and the results of 5 of them (4.2%) were found to be compatible with TCMP. The median age was reported to be 66 and all of them were men. At the time of the admission, 4 of them had shortness of breath and the other patient had chest pain (29).

One case report from Chicago describes a COVID-19 positive patient with rapid deterioration of cardiorespiratory status in her 4th day of hospitalization (57). It should be noted that during the hospital course, COVID-19 positive patients may experience symptoms that are consistent with TCMP.

DIAGNOSIS

Takotsubo CMP, manifests very similarly to acute coronary syndrome (ACS). In most cases, acute presentations are approached like ACS. In this section, diagnostic approaches and different criterions are explained. Firstly, ECG manifestations of TCMP mimic ACS and commonly cause misdiagnosis **(Figure 1)**.

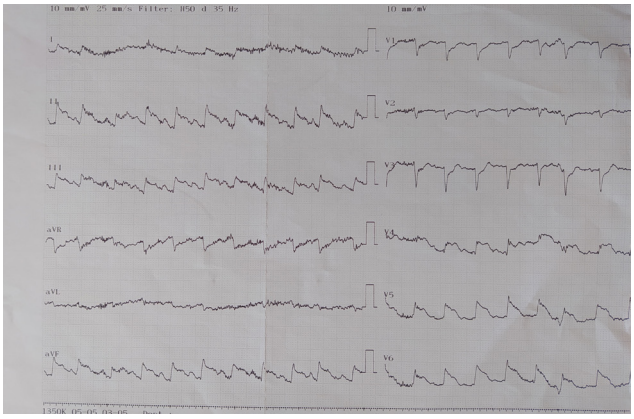

Figure 1: Takotsubo Syndrome Mimicking Acute Coronary Syndrome (Inferior MI) ECG Findings

Just like ACS, ST-segment elevations in precordial, inferior or lateral leads may be seen in TCMP. Elevations are most commonly seen in precordial leads, around 40-50% of the cases. Also, in some patients, new onset bundle branch blocks or non-specific T wave abnormalities may be detected. It is important to note that in the initial presentation, normal ECG findings don't rule out TCMP. In the following 2-3 days, ST-segment elevations tend to resolve and are replaced by diffuse deep T-wave inversions and QT-segment prolongation (57). Also, in some rare cases, transient pathological Q waves may be seen. Usually, these abnormalities are expected to resolve in 3-6 months (13).

In the acute settings, troponin level is usually measured for the ACS. Similarly to ACS, cardiac biomarkers are elevated in TCMP too, contributing to misdiagnosis. In 90% of the patients, at the initial presentation, the markers are found to be elevated (15). Compared to the ACS, peak troponin levels are usually found to be lower and creatine kinase (CK) level doesn't exceed 500 U/L (58). In contrast, brain natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) levels peak around the 48 hour (h) after the initial presentation and are usually 3-4 folds greater than the levels found in ACS (59). However, 24 times higher than normal biomarker levels were also reported (60).

Ideally, patients with ACS should undergo angiography after the initial diagnosis. TCMP patients usually undergo angiography because of the initial misdiagnosis of ACS. During the angiography, no obstructions are detected in TCMP patients (61). However, in cardiac imaging, ventricular wall motion abnormalities are seen in these patients. These abnormalities are differentiated from ACS by their distributions. 3 different abnormal Left Ventricule (LV) contraction patterns are identified to be associated with TCMP. Most common type is apical ballooning type (75%) followed by mid ballooning type (25%) (15). Basal ballooning is seen very rarely (<1%), which is also called ''inverted TCMP"(18,62).

30% of the patients also show signs of right ventricular wall abnormalities(13, 61). These patients tend to develop congestive heart failure and have worse prognosis compared to patients with no right ventricular abnormalities (13).

In order to accurately diagnose TCMP, a detailed history must be obtained. As emphasized previously, different physical or emotional factors may trigger this syndrome. Also, it should be noted that TCMP may manifest in chronically ill patients who are admitted to the ICU for a long term. ICU patients who develop left ventricular systolic dysfunction in association with 1 or more of the factors such as hemodynamic compromise, pulmonary edema, troponin elevation, or ECG evidence of ischemia or infarction should be investigated for TCMP (23).

Also, it should be noted that ACS and TCMP may coexist and are not mutually exclusive (18).

Currently, there no universal diagnostic approach to TCMP. However, 4 different diagnostic criterions are used commonly **(Box 1 - 4)**.

Box 1: Mayo clinic criteria (63)

1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.

2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.

3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.

4. Absence of:
Pheochromocytoma, Myocarditis

Box 2: Swedish criterion (64)

Transient hypokinesis, akinesis, or dyskinesis in segments of the left ventricle, and frequently a stressful trigger (psychological or physical)

■ Absence of other pathological conditions (for example, ischemia, myocarditis, toxic damage, and tachycardia) that might more credibly explain the regional dysfunction

■ Slight or no increase in cardiac troponin levels (disparate with the amount of myocardial dysfunction)

Box 3: Italian criteria (65)

Typical transient LV wall-motion abnormalities extending beyond one epicardial vascular distribution, with complete functional normalization within 6 weeks

■ Absence of potentially culprit coronary stenosis or angiographic evidence of acute plaque rupture, dissection, thrombosis, or spasm

■ New and dynamic ST-segment abnormalities or T-wave inversion

■ Onset of transient or permanent left-bundle-branch block

■ Mild increase in myocardial injury markers (creatine kinase MB <50 U/L)

■ Clinical and/or instrumental exclusion of myocarditis

■ Postmenopausal woman (optional)

■ Antecedent stressful event (optional)

Box 4: MRI-based criteria from US and Europa (66)

■ An acute cardiac event typically presenting with chest pain and/or dyspnea

■ Transient systolic dysfunction with marked left ventricule(LV) contraction abnormality (akinesia or dyskinesia of the LV apical and/or midventricular or basal segments)

■ Absence of severe (>50%) obstructive coronary artery disease or angiographic evidence of acute plaque rupture

■ Electrocardiographic abnormalities (ST-segment elevation or T-wave inversion)

■ Slightly raised cardiac troponin level

■ Absence of pheochromocytoma

■ Absence of myocarditis or typical ischemic transmural late gadolinium enhancement on cardiovascular MRI (if available)

TREATMENT

Treatment in Acute Phase

There is no specific treatment for Takotsubo syndrome (67). Current treatment modalities applied in the acute phase are supportive therapies aimed at reducing the complications of Takotsubo syndrome (68).

In the acute phase of Takotsubo syndrome, serious cardiological complications occur in approximately 20% of patients (39). The most common complication in the acute phase is systolic heart failure (51, 52, 69). Complications occurring during this period can be confused with acute coronary syndrome (33).

When patients with Takotsubo syndrome present to the hospital, all patients should be followed up by ECG for at least 24 hours (70). However, patients with corrected QT interval (QTc) prolongation should also be followed up by ECG because of the increased risk of ventricular arrhythmias (58, 70).

It is important to determine the presence of hemodynamically significant left ventricular outflow tract obstruction in patients with Takotsubo syndrome who develop complications of cardiogenic shock. Inotropic agents should be discontinued immediately in the presence of left ventricular outflow obstruction to prevent an increase in obstruction (67, 70). Because left ventricular outflow tract obstruction is associated with basal hypercontractility in patients with Takotsubo syndrome (38, 70 – 72). In such patients, in the absence of severe heart failure, short-acting intravenous (IV) Beta-blockers may be used. However, attention should be paid to the use of catecholamines as well as inotropes in the treatment of patients with Takotsubo syndrome who develop cardiogenic shock without left ventricular outflow tract obstruction. Because it is thought that catecholamines are also involved in the pathogenesis of Takotsubo syndrome (36, 37). Levosimendan can be used as a positive inotrope for maintaining catecholamine levels (73). However, its use is controversial due to the lack of evidence. Therefore, early evaluation of mechanical support is necessary in patients with low cardiac output. Mechanical support devices such as a microaxial blood pump can be used in patients with Takotsubo syndrome who develop cardiogenic shock (50, 70). Afterload does not increase in microaxial blood pump treatment. This is one of the advantages of microaxial blood pump therapy. In patients with Takotsubo syndrome with refractory shock, extracorporeal membrane oxygenation and temporary left ventricular assist devices can be used if there are no contraindications (70, 74).

In patients with Takotsubo syndrome who develop congestive heart failure, diuretics or treatments such as nitroglycerin can be used to reduce preload (32, 37). ACE inhibitors or angiotensin II receptor blockers can be used in the presence of congestive heart failure, wall motion abnormality and impaired left ventricular ejection fraction. In the acute phase of Takotsubo syndrome, the use of Beta-blockers is beneficial in reducing in-hospital mortality, regardless of the presence of left ventricular outflow tract obstruction (75).

Another complication of Takotsubo syndrome is intraventricular thrombus. Intraventricular thrombus is especially seen in patients with severe apical ballooning and low left ventricular ejection fraction and is seen in approximately 2-5% of patients (66, 76). In order to prevent intraventricular thrombus formation, the use of prophylactic anticoagulants in patients with Takotsubo syndrome with impaired left ventricular ejection fraction is recommended by some experts until left ventricular ejection fraction is recovered (68, 70, 71, 77, 78). The prolongation of the QTc interval in Takotsubo syndrome is associated with the development of ventricular arrhythmia (58). Therefore, the use of drugs that cause QT prolongation in patients with Takotsubo syndrome should be avoided.

The prognosis of the TCMP is reported to be benign in most patients. This is also true for ICU patients. Despite the accompanying comorbidities, Haghi et al. reported that only 1 out of 6 patients died due to other conditions.

Treatment in Recurrence and Chronic Phase

Beta-blockers are used to prevent recurrence in Takotsubo syndrome (12, 67). Beta-blockers may protect against stress triggers and the ensuing catecholamine surges (67). Therefore, Beta-blockers are most frequently prescribed after discharge in patients with Takotsubo syndrome (67). However, recent studies have shown that post-discharge beta blocker use has no beneficial effect on mortality after 1 year of follow-up (50). In addition, two meta-analyzes did not confirm the hypothesis that beta blockers are useful in preventing the recurrence of Takotsubo syndrome (79, 80). However, the use of ACE inhibitors or angiotensin II receptor blockers in the chronic phase of Takotsubo syndrome is associated with decreased relapse rate in Takotsubo syndrome or improved survival at 1-year follow-up (50, 80). This association can be explained by the reduction of sympathetic activity or the anti-inflammatory effect on the myocardium via the renin-angiotensin system of ACE inhibitors and Angiotensin II receptor blockers (67).

Takotsubo syndrome is a disease with acute, transient left ventricular dysfunction (1, 2). Patients often present with shortness of breath and chest pain. Therefore, it can be confused with acute myocardial infarction(MI) and acute

coronary syndrome. Therefore, ECG, cardiac troponin and creatine kinase levels are important in the differential diagnosis (1). However, no stenosis is observed in the coronary angiography in Takotsubo syndrome. In addition, patients often have a history of emotional and physical stress.

There is no specific agent in the treatment of Takotsubo syndrome. Besides, treatment is divided into two: acute phase and chronic phase-recurrence. Symptomatic treatment is applied for complications in the acute phase. In the chronic phase and recurrence, agents such as beta-blockers, ACE inhibitors, angiotensin II receptor blockers are used. However, the exact effectiveness of these treatments has not been fully established. Therefore, further studies are needed for the treatment of Takotsubo syndrome.

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