TakoTsubo cardiomyopathy

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Abbreviations

ARs – Adrenoreceptors

HPA – Hypothalamo-pituitary-adreno

AMP – Adenosine monophosphate

ATP – Adenosine triphosphate

STEMI – ST elevation myocardial infract

TC – TakoTsubo cardiomyopathy

LV – Left ventricle

CNS – Central nervous system

SAH – Subarachnoid hemorrhage

TIA – Transient ischemic attack

ECG – Electrocardiography

CK MB – Creatine kinase-muscle/brain

EF – Ejection fraction

MRI – Magnetic resonance imaging

LVOT – Left ventricle outflow tract

IABP – Intraaortic ballon pump

HF – Heart failure

ACE – Angiotensin converting enzyme

CT – Computer tomography

NT-proBNP – N-terminal pro B-type natriuretic peptide

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1. SUMMARY

TakoTsubo Cardiomyopathy – Ragib Botonjić

Introduction: TakoTsubo cardiomyopathy is a complex pathological condition considered as a cardiomyopathy with multifactorial aetiology, where the decreased level of the estrogen in postmenopausal women contributes as an important risk factor.

Aim: To analyse risk factors for the development of TakoTsubo cardiomyopathy in our patient population and test if they are related with different myocardial damage severity which can be defined by blood level of troponin and N-terminal pro B-type natriuretic peptide as well as changes in left ventricular ejection fraction.

Materials and methods: In this retrospective study we included 49 patients that were consecutively hospitalized in the Department of cardiovascular diseases, University hospital centre Zagreb with the diagnosis of TakoTsubo cardiomyopathy in the period from 2007 till 2017. Statistical analysis was performed using SPSS statistical software. Categorical data are presented as absolute and relative frequencies, continuous variables as median with range.

Results: The analysis showed that 35 of 49 patients (70%) with the diagnosis of TakoTsubo cardiomyopathy were postmenopausal women. In our patients, 20,4% had an intracranial pathology. The average age in patients with TakoTsubo cardiomyopathy was 67,65 ± 12,62 years and there was no statistically significant difference in age between males and females (p=0,710). The average ejection fraction was 46% ± 11% and there was no statistically significant difference in EF between postmenopausal women and other patients (p=0,237). The average level of troponin was 593,28 ± 306,84 ng/L. There was no statistically significant difference in troponin level between postmenopausal females and other patients (p=0,278). There was a moderate negative correlation between troponin level and EF (p=0,021, r=-0,348). There was not any significant difference in the prevalence of intracranial pathology between postmenopausal and other patients (p=0,087). Mean serum NT-proBNP level was 2845 ± 1300,43 pg/mL with no significant difference between postmenopausal women and other patients (p=0,374).

Conclusion: The majority of patients with TakoTsubo cardiomyopathy in our population are postmenopausal women. However, there is no difference in the level of serum troponin, NT-proBNP as well as EF between postmenopausal women and other patients with this diagnosis. Although it increases the risk for the development, it seems that menopause doesn't affect the level of myocardial damage in TakoTsubo cardiomyopathy.

Key words: TakoTsubo, cardiomyopathy, troponin, postmenopausal, NT-proBNP, ejection fraction

1. SAŽETAK

Takotsubo Kardiomiopatija - Ragib Botonjić

Uvod: Takotsubo kardiomiopatija je kompleksno patološko stanje multifaktorijalne etiologije, pri čemu se smanjena razina estrogena u serumu kod žena u postmenopauzi smatra važnim rizičnim čimbenikom.

Cilj: Analizirati u našoj populaciji pacijenata različite rizične čimbenike za razvoj TakoTsubo kardiomiopatije i ispitati jesu li isti povezani sa različitim stupnjem oštećenja miokarda definiranim razinom srčanog troponina i N-terminalnog proB-tipa natriuretskog peptida u serumu bolesnika, te iznosom istisne frakcije (EF, engl. *ejection fraction*) lijeve klijetke.

Materijal i metode: U ovoj retrospektivnoj studiji smo uključili 49 pacijenata koji su bili za redom hospitalizirani u Klinici za bolesti srca i krvnih žila Kliničkog bolničkog centra Zagreb zbog dijagnoze TakoTsubo kardiomiopatije u periodu od 2007. do 2017. godine. Statistička analiza je urađena koristeći SPSS statistički program. Kategorički podaci su prikazani kao apsolutna i relativna učestalost, a kontinuirane varijable kao medijan s rasponom.

Rezultati: Analiza je pokazala da su 35 od 49 pacijenata (70%) s dijagnozom TakoTsubo kardiomiopatije bile žene u postmenopauzi. Kod naših pacijenata, njih 20,4% je imalo neku intrakranijalnu patologiju. Prosjek dobi kod pacijenata sa TakoTsubo kardiomiopatijom je bio 67,65 ± 12,62 i nije bilo statističke značajne razlike u dobi između muškaraca i žena. (p=0,710). Prosječna istisna frakcija je bila 46% ± 11% i nije bilo statističke značajne razlike između postmenopauzalnih žena i ostalih pacjenata (p=0,237). Prosječna razina troponina je bila 593,28 ± 306,84 ng/L. Nije bilo statističke značajne razlike u troponinu između postmenopauzalnih žena i ostalih pacjenata (p=0,278). Našli smo umjerenu negativnu povezanost između istisne frakcije lijeve klijetke i razine srčanog troponina u serumu (p=0,021, r=-0,348). Nije bilo nikakve statističke razlike u pojavnosti intrakranijalne patologije između postmenopauzalnih žena i ostalih pacijenata (p=0,087). Srednja serumska vrijednost NT-proBNP-a iznosila je 2845±1300,43 pg/mL, bez značajne razlike između postmenopauzalnih žena i ostalih pacijenata s ovom dijagnozom (p=0,374).

Zaključak: Većina pacijenata s dijagnozom TakoTsubo kardiomiopatije u našoj bolesničkoj populaciji bile su žene u postmenopauzi. Nismo našli razliku u razini srčanog troponina i NT-proBNP u serumu, kao i istisnoj frakciji lijeve klijetke između postmenopauzalnih žena i ostalih pacijenata s ovom dijagnozom. Dakle, iako menopauza povećava rizik za razvoj TakoTusbo kardiomiopatije, čini se da ista ne utječe na težinu oštećenja miokarda.

Ključne riječi: TakoTsubo, kardiomiopatija, Troponin, Postmenopauza, NT-proBNP, istisna frakcija

3. PREFACE

3.1. TAKOTSUBO CARDIOMYOPATHY

3.1.1. EPIDEMIOLOGY

Before recognition of TakoTsubo syndrome as a specific type of cardiomyopathy, it was considered under different diagnosis. Since 1990. it has been recognised as a specific cardiac disease (1). Interestingly, TakoTsubo cardiomyopathy (TC) has been recognised in all races all over the world even though with lower prevalence among the Hispanics and African Americans (2).

Many of patients with TC went unrecognised in the past. Because of better awareness and availability of invasive coronary angiography, this disease is nowadays better recognised. Minhas et al. (3) showed increased incidence of the TC from 2006 till 2012. During this period there was an increase of TC diagnosis for 20 times. (Fig. 1)

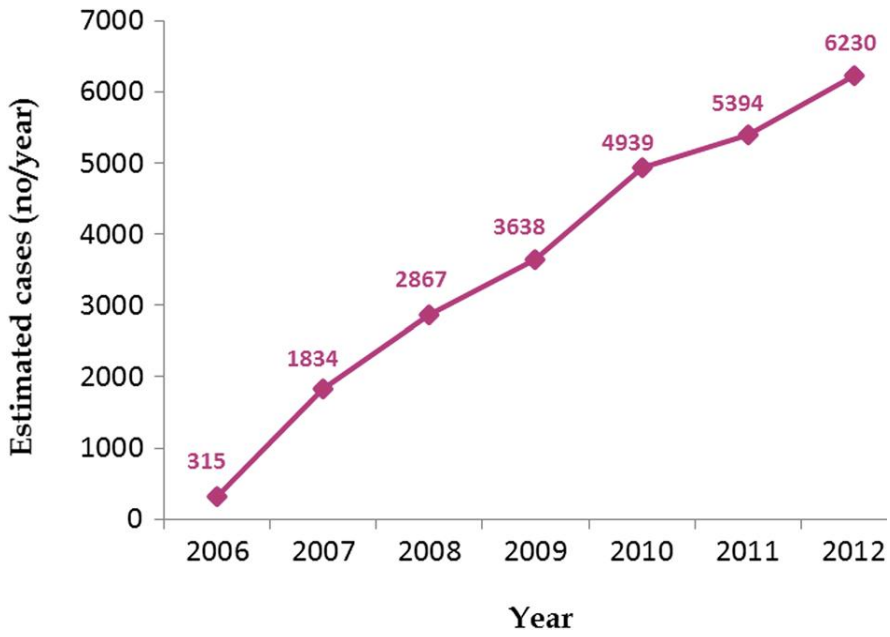

Figure 1.Trends in reported incidence of TakoTsubo cardiomyopathy from 2006 to 2012. Modified from a table by Minhas AS, Hughey AB, Kolias TJ (3)

According to different epidemiological studies it has been found that 90% of patients with TC are postmenopausal women, with similar prevalence across different ethnic groups (4). Another study among 1750 patients with TC showed that even 89.8% were women with a mean age of 67 years (5).

3.1.2. ETIOLOGY

TC is a multifactorial disease and we cannot separate only one factor responsible for the development of disease. The most common etiologies reported in the literature include: stressful situations, estrogen depletion (menopausal women), intracranial pathology (haemorrhage, brain tumors, different psychological diseases), some medications and pheochromocytoma. Despite of the different factors contributing to TC, they all have in common the increase of catecholamine levels in both circulation and myocardium.

3.1.3. PATHOPHYSIOLOGY

Majority of patients with TC have experienced some very stressful event (5) Stress is physiological response of the body which is responsible for different actions on target organs including heart. Structures in our body which are responsible for mediating stress are present in both autonomic as well as in the central nervous system. In such case stressors from outside are responsible for brain activation which in turn increases quantity as well as the bioavailability of the cortisol, epinephrine and norepinephrine. (6)

Suzuki et al measured brain activity defined as regional cerebral blood flow in patients with acute TC. Interestingly they found that during acute phase of TC, brain blood flow was increased in hippocampus, brainstem and basal ganglia while it was decreased in prefrontal cortex region. After the acute phase of TC, the blood flow in those regions started to decrease but still stayed increased even during chronic phase of TC when cardiac wall motion abnormalities disappeared. (7) Despite multiple studies showed that increase in the catecholamine level is responsible for the TC, we still do not know the exact pathophysiological mechanism (17).

Pathophysiology of TC consists of two phases where the first phase includes increased release of epinephrine and norepinephrine by the activation of hypothalamic-pituitary-adrenal (HPA) axis triggered by a given stress (HPA gain). At this axis epinephrine binds to the β1- and β2- adrenoceptors (ARs), whereas norepinephrine which is released from the sympathetic nerves acts predominantly via the β1-ARs on ventricular cardiomyocytes that results with positive inotropic effect. The second phase starts after the binding of catecholamines to the β1-ARs that initiates the receptor coupling with the Gs protein family. The receptor coupling with

Gs protein family will lead to increase of intracellular cycle AMP through well known enzyme adenyl cyclase.

Study by Akashi and colleagues showed correlation between TC and catecholamines. For the first time they reported elevated serum catecholamine levels in patients with TC. (8) In study by Wittstein et all it has been showed that in the acute phase of TC there is an increase in concentration of circulating plasma catecholamine (epinephrine, norepinephrine and dopamine) as well as stress-related circulating neuropeptides that are several times higher than in patients with ST-elevation acute myocardial infarction. They reported that those concentration remains elevated up to one week (9) (Figure 2.)

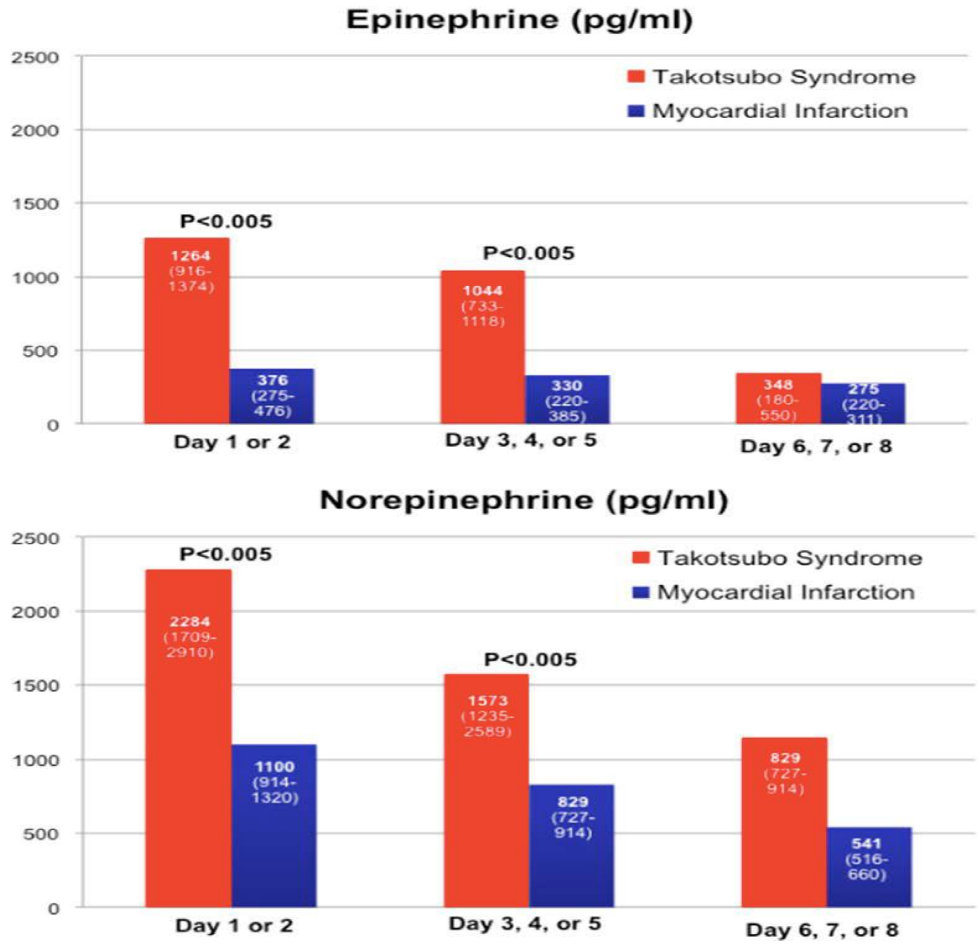

Figure 2. Plasma Catecholamine levels in patients with TakoTsubo Cardiomyopathy and patients with myocardial infraction Massachusetts Medical Society 2005

Another study of Eitel at al showed that there is increased exposure of the β2 receptors on the apex of the heart which are responsible for the apical myocardial dysfunctions. (18) At

another study it has been found that supraphysiological level of catecholamine may trigger the β2 receptor conversion from stimulatory (Gs) to inhibitory (Gi) pattern resulting in the depression of the myocardial contractility and typical presentation of the apical hypocontractility on echocardiography. (19)

At acute phase of TC in addition to the increased serum level of catecholamines there is increased concentration of catecholamine in the local myocardial tissue (10) The increased release of the norepinephrine on the local level is caused by the well known mechanism of exocytosis of the catecholamine from the presynaptic clefts of the local sympathetic neurons while at same time there is decreased re-uptake of norepinephrine by terminal nerve axons throught the specific uptake-1 transporter. (11) This process was well described by the iodine-123 meta-iodo-benzyl-guanidine, which act as a γ-emitting norepinephrine analog used to image myocardial sympathetic nerve terminals with single-photon emission computed tomography.

Recent data showed that endothelial dysfunction is common in patients with the TC which could lead to epicardial as well as microvascular coronary artery vasospasm. This may be the second major pathophysiological mechanism in TC. (12) Endothelial dysfunction is an endothelial disbalance between vasoconstrictor and vasodilative factors. (12) In patients with TC we can assume increased concentration of vasoconstrictors which leads to transient myocardial ischemia and typical transient LV dysfunction. (12) The link between coronary artery endothelial dysfunction and TC may also explain why postmenopausal women are more prone to development of TC. In this period women have both age-related and estrogen deficiency–related coronary vasomotor abnormalities. (13) Under normal circumstances estrogen improves the microvascular coronary supply to myocardium by dependent as well as independent mechanisms. (14) Due to decreased concentration of estrogen, women in menopause have increased sympathetic drive as well as increased endothelial dysfunction. (15)

Another evidence of estrogen role in the pathogenesis of TC is presented in animal experimental study where it has been shown that stress-induced LV apical ballooning can be prevented by pretreatment with α- and β-adrenoceptor blockers and estrogen. This is explained by estrogen ability for both endothelial protection as well as for attenuation of the stress-induced hypothalamo-sympatho-adrenal outflow from the central nervous system to the target organs. Nevertheless, estrogen upregulates the cardio-protective substances such as atrial natriuretic peptide and heat shock protein 70. (16) It seems that estrogen level has utmost

importance in the pathogenesis of TC by direct cardiac effect as well as by indirect effect through regulation of sympathetic surge on heart.

In addition to neurological effect by the sympathetic nervous system on the development of TC, it is well recognized that pathological changes in the cranium are responsible for the development of the TC. That is why in many cases the term "neurogenic stunned cardiomyopathy" is often used for the diagnosis of TC. CNS disorders which are the most commonly associated with TC include SAH, seizure and ischemic stroke, while other disorders like ALS, bacterial, viral or immune-mediated encephalitis/meningitis or traumatic brain or spinal injury have been rarely described as triggers. (21) The exact prevalence of the TC in the patients with the CNS diseases are not known because patients with the CNS diseases do not routinely get ECG or echocardiography. (22) In the study of Kilbourn KJ at al it has been found that 20% of patients with SAH develop cardiac wall-abnormalities. (20)

Development of TC has been shown in another retrospective study of 2276 patients with diagnosis of the non-traumatic SAH. This study has been performed at neurological intensive care unit of Emory University Hospital in Atlanta, Georgia, from 2005. to 2011. and it has been estimated that the incidence of TC after SAH was 0.8% (according to the Mayo Clinic Criteria). All patients were women, white race with mean age 45 ± 11 years; 21.1% patients had the apical sparing reverse TC type, with significantly higher troponin-I levels compared to patients with the typical apical ballooning pattern (23). Another well documented study provide evidence that ischemic stroke is a risk factor for the development of the TC.(24) In the largest study of 24,071 TC patients 655 (2.7%) of them were reported to have had stroke/TIA as the underlying disease.(25)

The most important myocardial abnormality which occurs in TC is a transient ventricular wall dysfunction. As it is stated before overactive adrenoceptor signalling in the presence of the elevated catecholamine concentration might be trigger of the LV dysfunction. (26) Today it is well known that catecholamine through β-receptors mediate positive inotropic, chronotropic and lusitropic cardiac functions. Regional myocardial differences in the distribution of the adrenoceptors might explain regional cardiac wall abnormalities in TC.

In recent experimental data it is stated that β2-receptors are more frequently expressed at apical region of the heart comparing to the basal region while β1-receptors and sympathetic nerve terminals of the neuro-cardiac axis are much frequently present at base of the heart. (27)

We can conclude that both epinephrine and norepinephrine exert positive inotropic effect through β1-receptors and Gs-coupling proteins. However, they have different function when bind to the β2-receptors. This happens when patient has supraphysiological level of epinephrine in blood that triggers β2-receptors to change from the Gs to Gi coupling. (28) The change of Gs coupling to the Gi coupling will result with negative inotropic effect which will cause pathological change in the cardiac myocardium. This change will result into apical ballooning of myocardium. Although it explains pathology, this change may be considered as cardiac protective mechanism. It is well recognized in the experimental study where the high dose of epinephrine can induce direct cardiomyocyte depression and cardioprotection in Gi-dependent manner.(29)

In a study on the rat model it has been described that IV injection of high epinephrine dose produced characteristic cardiac depression of the apical region while the same amount of norepinephrine did not produce any kind of the apical depression(30). One can conclude that the mechanism of myocardial dysfunction in TC is related to epinephrine but not to norepinephrine cardiac surge because dysfunction was not present in region where norepinephrine-releasing sympathetic nerve terminals are of the highest density (31).

3.1.4. DIAGNOSIS

Criteria for the diagnosis of the TakoTsubo cardiomyopathy have been described by several centres worldwide using various diagnostic references (Table 1.) (32) General consensus has not yet been established. The possibility that TC and coronary artery disease can coexist is very important to consider because not all patients with the TC will have normal coronary arteries on coronary angiography. Differentiation of TC from acute coronary syndrome is a real challenge because many clinical symptoms and signs, echocardiography and ECG findings are very similar, such as cardiac chest pain, ST-segment elevation and regional wall abnormalities. (33) TC is diagnosed during coronary angiography when we find no coronary arteries obstruction and cardiac wall abnormalities extend beyond single coronary artery territory.

ST-segment elevation is generally present on ECG of the TC patients as well as deep T-wave inversion which develop over time after symptom onset which is distinguished from the STEMI where ECG changes are recognised immediately. However this can be challenging to distinguish TC from STEMI. (34) It has been reported that TC and anterior STEMI can be differed by ECG changes where most patients with anterior STEMI have ST-elevation in leads V2-V4 by contrast to the patients with TC where ST-segment elevation is present most frequently in leads II, III, aVF, aVR and V5-V6. The myocardial wall motion abnormalities are rarely seen in V1 lead region. This criteria has 90% specificity and sensitivity but has not be still been applied in clinical practice for differentiation of anterior STEMI from TC (35).

Gothenberg (Sweden)	**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, ischaemia, 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)**
Italina network (Italy)	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 - Clinical and/or instrumental exclusion of myocarditis - Postmenopausal woman (optional) - Antecedent stressful event (optional)
Mayo Clinic (USA)	Transient akinesis or dyskinesis of LV wall-motion abnormalities (ballooning) with chest pain: - Electrocardiographic changes (ST-segment elevation or T-wave inversion) - No substantial obstructive epicardial coronary artery disease - Absence of pheochromocytoma or myocarditis
MRI-based (USA and Europe)	-An acute cardiac event typically presenting with chest pain and/or dyspnoea - Transient systolic dysfunction with marked 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 - Absence of pheochromocytoma - Absence of myocarditis or typical ischemic transmural late gadolinium enhancement on cardiovascular MRI (if available)

Table 1. Diagnostic Criteria for TakoTsubo Cardiomyopathy

3.1.5. MANAGEMENT

Approximately 10% of patients with TC develop cardiogenic shock (36). Their management depends whether LVOT obstruction is present or not. This is why the patients with cardiogenic shock should be sent urgently for the echocardiography to assess for the presence of the LVOT obstruction. (37)

Hypotensive patients without LVOT obstruction and significant pulmonary congestion should be treated with fluid resuscitation. Due to LV systolic dysfunction these patients may require inotropic therapy with dobutamine or dopamine as a temporary measure. Inotropic therapy may induce LVOT obstruction (38). Inotropic therapy however should be discontinued in patients who develop moderate to severe LVOT obstruction while change in the management is not necessary in patient with the mild LVOT obstructions. Mechanical circulatory support is the preferred therapy when there is marked LV dysfunction which is accompanied with the severe shock.(39)

Patients with hypotension associated with moderate to severe LVOT obstruction should not be treated with inotropic agents because this can worsen obstruction. In this case we should use beta blockers. In patients without significant pulmonary congestion, preload should be increased by leg elevation and fluid resuscitation.(40) In patients with LVOT obstruction and severe hypotension who do not tolerate or do not respond adequately to beta blockers, an alpha agonist such as phenylephrine should be added with close monitoring. In patients with LVOT obstruction and severe hypotension where initial medical therapy is not effective it is suggested to use mechanical circulatory support. However, in patients with LVOT obstruction use of the IABP may worsen the degree of the obstruction (41) and because of this , the LVOT gradient should be evaluated (42)

We should treat those patients with standard approach which include supplemental oxygen and ventilation as needed, intravenous diuretics and vasodilator therapy as needed to correct elevated filling pressure and/or LV afterload. However vasodilators therapy should be avoided in patients with LVOT obstruction.

Today we do not have specific randomized trial to define the optimal medical treatment for Takotsubo cardiomyopathy. However, hemodynamically stable patients are treated with

standard therapy for HF which includes betablockers, ACE inhibitors, MRA and diuretics as necessary to treat volume overload. (43)

4. HYPOTHESIS

TakoTsubo cardiomyopathy in our patients is also more often diagnosed in postmenopausal women. Postmenopausal women with TakoTsubo cardiomyopathy may develop more severe myocardial damage compared to other patients with this diagnosis, measured as the maximal level of serum troponine, NT-proBNP as well as left ventricular ejection fraction.

5. OBJECTIVES

We have performed retrospective analysis of 49 consecutive patients with the diagnosis of Takotsubo cardiomyopathy that were hospitalized in our department in the period from 2007. till 2017. to explore the presence of different etiological factors known to be related with the development of TC.

Another objective of this study was to detect if severity of myocardial damage in patients with TC is related to different clinical background, i.e. to detect if the level of myocardial damage in TC depends weather the patient is a postmenopausal woman or not.

6. MATERIAL AND METHODS

In this retrospective study we included all consecutive patients with the diagnosis of TakoTsubo cardiomyopathy in the Department of cardiovascular diseases University hospital centre Zagreb in the period from 2007 till 2017.

In this study we included only patients with definitive diagnosis of the TakoTsubo cardiomyopathy which was diagnosed by echocardiography and coronary angiography. Clinical criteria for the diagnosis of the TakoTsubo cardiomyopathy were as follow:

1. Detailed history of chest pain, dyspnoea and/or other signs of heart failure;
2. Laboratory analysis with elevated cardiac troponin T and NT-proBNP;
3. ECG changes (ST-segment elevation or depression, T wave depression);
4. Coronary angiography excluded coronary artery occlusion
5. Left ventriculography showed characteristic morphological pattern of "apical ballooning";
6. Echocardiography showed characteristic apical hypocontractility together with hypercontractility of the basal segments.

In order to confirm definitive diagnosis of TC it was preferred that patient had all five clinical criteria.

Categorical data are presented as absolute and relative frequencies, continuous variables as median with range. Results were presented in form of tables and graphs. Statistical significance was set at $P<0,05$. For statistical analysis of the of data we used application SPSS for Windows 17.0 and Microsoft Excel (version 11 Microsoft Corporation, Redmond, WA, SAD)

7. RESULTS

Using above-mentioned clinical criteria for definitive diagnosis of TakoTsubo Cardiomyopathy, we have detected 49 patients in the period from 2007. – 2017. We found that 35 out of 49 patients (70%) with the diagnosis of TakoTsubo cardiomyopathy were postmenopausal women.

The average age in patients with TakoTsubo cardiomyopathy was 67,65 ± 12,62 years. The youngest patient was 52 years old and the oldest was 90. Exactly 50% of patients were between 61 and 75 years old. There was no statistically significant difference in age between males and females (p=0,710, t=-0,374).

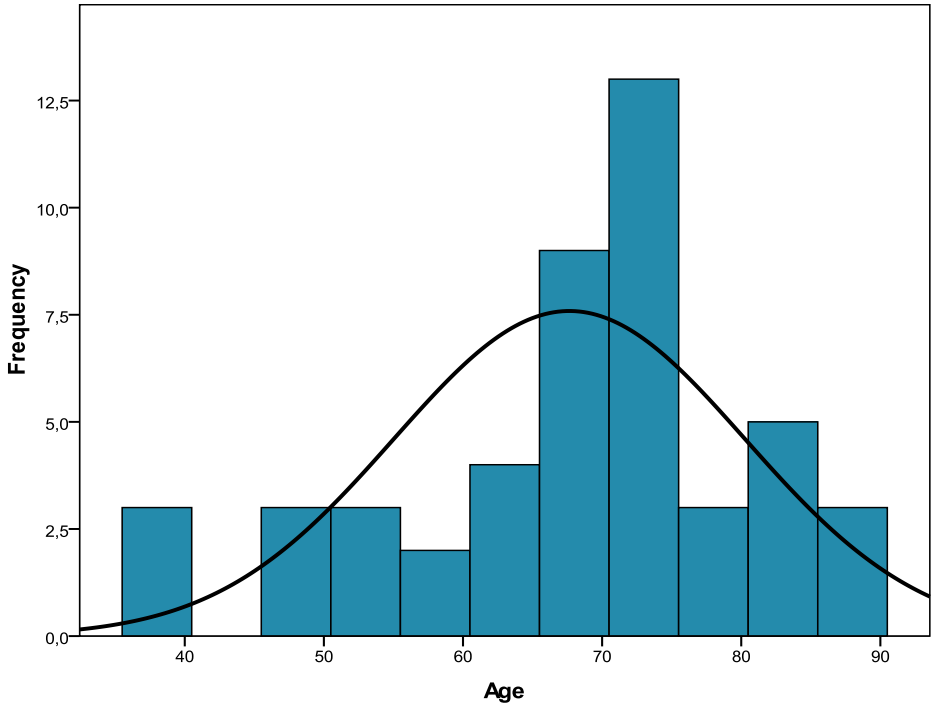

Figure 3. Age distribution of TakoTsubo Cardiomyopathy

The average ejection fraction in patients with Takasubo cardiomyopathy was 46% ± 11%. The lowest EF was 15% and the highest was 67%. Half of patients had EF between 40% and 55%. Only 31,81% of patients had normal EF, while others had reduced EF (LVEF<55%) (figure 4.). We showed that there was no significant difference in EF between postmenopausal women and other patients with TC (p=0,237, t=-1200).

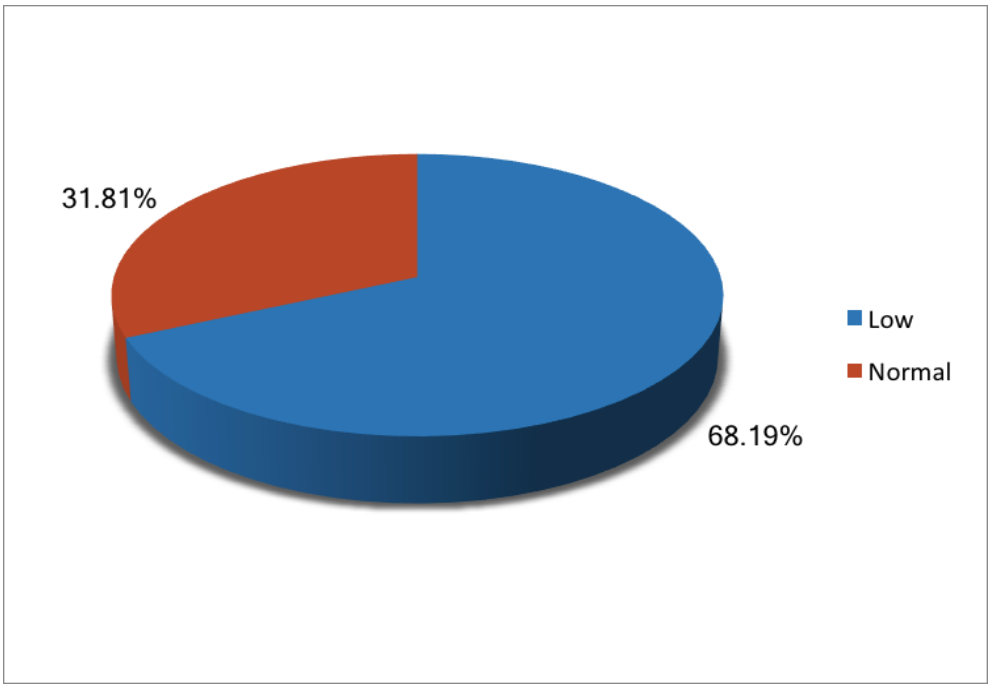

Figure 4. Ejaction fraction in 49 patients with TC

The average level of cardiac troponin was 593,28 ± 306,84 ng/L. The lowest level of troponin was 120 ng/L and the highest was 1983 ng/L with 50% of patient had troponin between 416 and 734 ng/L. There was no statisticaly significant difference in cardiac troponin levels between postmenopausal women and other patients (p=0,278, t=-1,098).

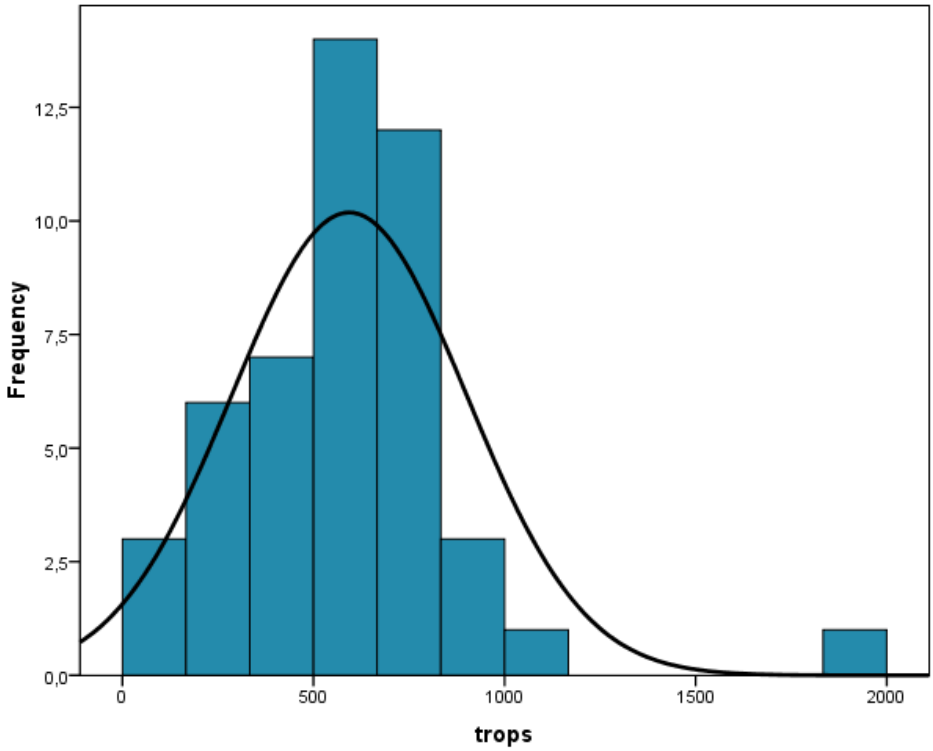

Figure 5. Troponin distribution among patients with TC

As expected the analysis of correlation between the level of troponin and ejection fraction in patients with TakoTsubo cardiomyopathy showed a moderate negative correlation between these two variables (p=0,021, r=-0,348) which means the higher troponin level is related to lower EF (Figure 6.)

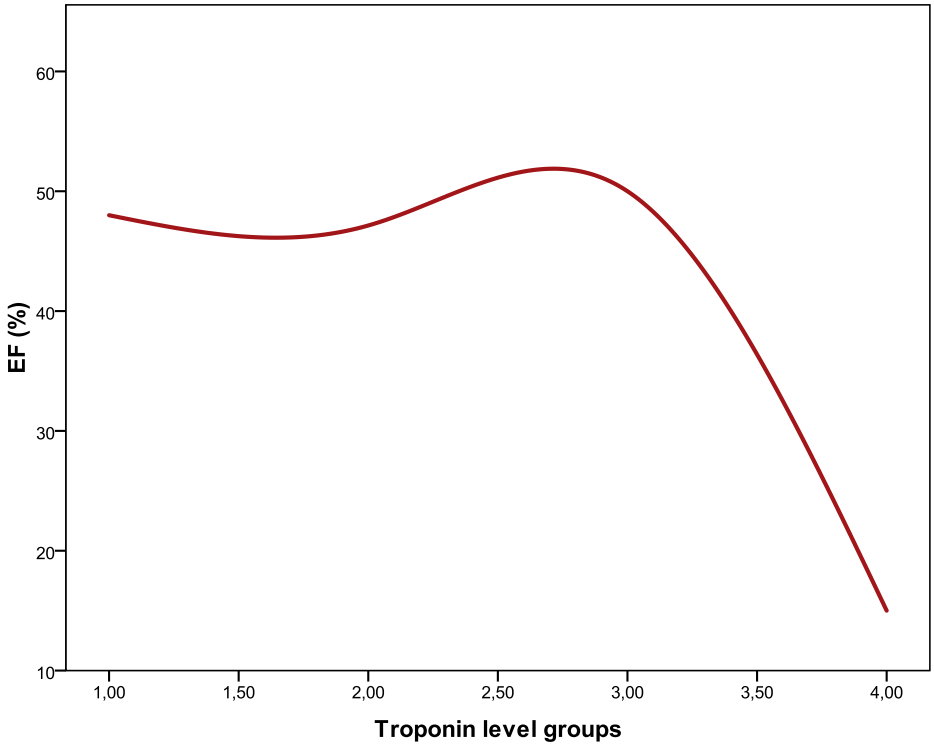

Figure 6. Correlation of EF and Troponin level

In our patient population, 20,4% had some intracranial pathology diagnosed by CT or MRI scan. Statistical analysis showed that there was no significant difference in the occurrence of intracranial pathology between postmenopausal and other patients with TakoTsubo cardiomyopathy (p=0,087) (Figure 7.)

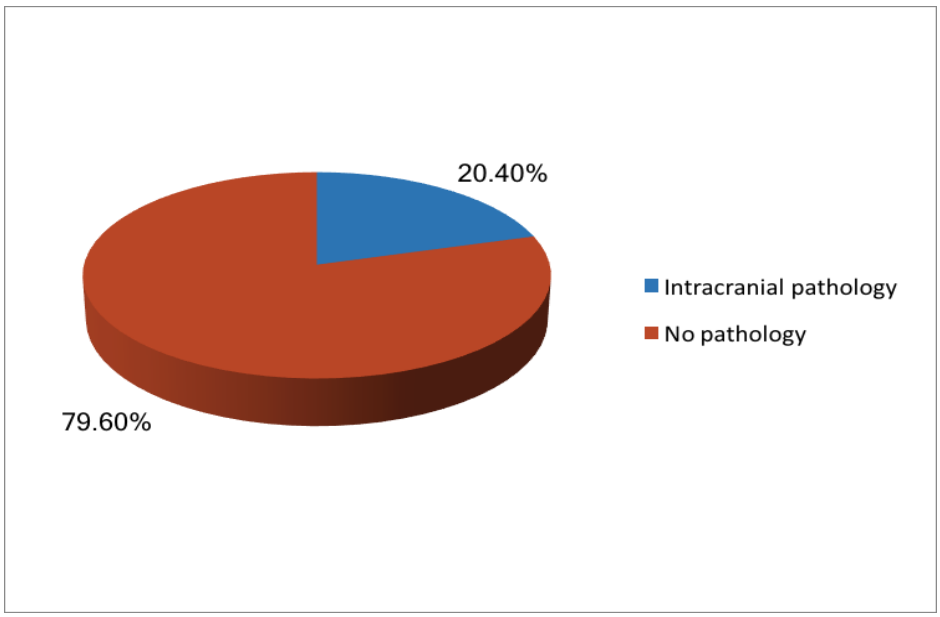

Figure 7. Prevalence of intracranial pathology in patients with Takotsubo Cardiomyopathy

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Mean NT-proBNP level measured in our patients was 2845 ± 1300,43 pg/mL and half of patients had NT-proBNP between 1561,25 pg/mL and 3808,5 pg/mL. (Figure 8) The level of NT-proBNP showed a strong negative correlation with age, which means that younger patients had higher level of this marker (p=0,008, r=-0,679. We haven't shown significant difference in the level of NT-proBNP between postmenopausal women and other patients with diagnosis of TakoTsubo cardiomyopathy (p=0,374).

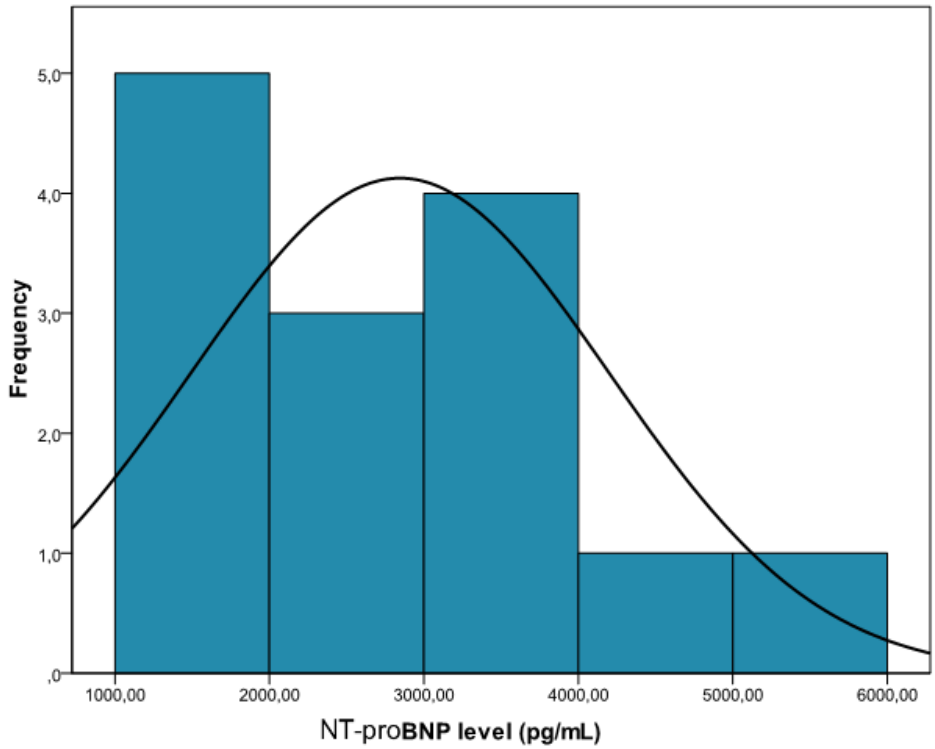

Figure 8. Distribution of level of NT-proBNP among patients with TC.

8. DISCUSSION

TakoTsubo cardiomyopathy is characterised for transient left ventricular dysfunction in the absence of coronary artery obstruction and occurs most commonly after strong emotional or physical stress. Interestingly, this disease is most commonly present in postmenopausal females. This has raised an interest into possible effect of estrogen on the development of the Takotsubo cardiomyopathy (44,45,46,47,48).

This investigation showed that the majority of our patients with the diagnosis of Takotsubo cardiomyopathy were postmenopausal women like it was previously reported in larger clinical trials.

The link between TakoTsubo cardiomyopathy and postmenopausal females was investigated by the study of Bruce T. Kuo and others. In their study of 18 cases of Takotsubo cardiomyopathy sixteen were postmenopausal women (89% of patients) which support our hypothesis that TC in our patients occurs more often in postmenopausal women as well (49,50,51).

The most of our patients with the diagnosis of TC were older than 65 years, with the average age of 67,65 ± 12,62 years. This is very similar to previous report by Fridolin et al where the average age for TC was 64.7 ± 11,5 years (52). We have not showed statistically significant difference in age between male and female patients (p=0,710, t=-0,374). This is different from the observation of Murakami et al. who concluded that male patients were younger than the female patients (72 years vs. 76 years) (53).

Average LV ejection fraction in patients with TC in our study was 46% ± 11%. Christian Templin et al reported somewhat lower left ventricular ejection fraction on admission (mean LVEF was 40.7) (54). We have also compared ejection fraction between females and males and found out that there was no statistically significant gender related difference in EF (p=0,237, t=-1200). We compared these results with study of Tsutomu Murakami, Tsutomu Yoshikawa and others (53) where they found out that there were no differences in gender distribution of EF in patients with diagnosis of TC.

We have also analysed cardiac troponin level in our patients with TC. There was no statistically significant difference in troponin level between postmenopausal and other patients

(p=0,278, t=-1,098). Study from Birke Schneider et al (54) showed that troponin level was significantly higher in males than females which do not match with our results. When we consider troponin as a diagnostic tool for TC we found out that mean troponin in patients with TakoTsubo cardiomyopathy was 593,28 ± 306,8 and 50% of our patients had troponin level between 416 and 734. Analysis of correlation between troponin level and LV ejection fraction in patients with TakoTsubo cardiomyopathy showed a moderate negative correlation between these two variables (p=0,021, r=-0,348), which means that higher troponin level is associated with lower the ejection fraction as expected. This is concordant with the results of study from Radhakrishan Ramaraj et al (56).

The serum level of NT-proBNP in our patients with TC showed a strong negative correlation with age, which means that younger patients had higher level of NT-proBNP. There was no significant difference in the level of NT-proBNP between postmenopausal women and other patients with TC (p=0,374). This is in discordance with the study from Murakami et al (53) who showed higher BNP level among male than in female patients.

9. CONCLUSIONS

1. Postmenopausal women are at highest risk for the development of TC. It seems that hormonal changes are one of the major risk factor for the development of TC.
2. The decrease of LVEF in patients with TC does not depend on whether patients were postmenopausal women or not.
3. The increase of cardiac troponin level in patients with TC does not depend on whether patients were postmenopausal women or not
4. The increase of NT-proBNP level in patients with TC does not depend on whether patients were postmenopausal women or not.
5. In conclusion, although menopause presents a high risk for the development of TakoTsubo cardiomyopathy, it does not affect the level of myocardial damage.

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Because of interest in music especially playing guitar, Ragib attended Art School in Bihać. During this period Ragib participated in several guitar playing competitions where he won several awards for his performances.

During his studies, Ragib was involved in many extracurricular activities where most important activities were participations on several medical elective courses on prestigious Universities such as McGill University in Canada as well as University of Texas in USA.

Ragib is fluent in Bosnian, Croatian, English, Turkish and German.