ORIGINAL ARTICLE

Comparison of on-admission ST-segment elevation tako-tsubo patients and myocardial infarction women: in-hospital course and long-term follow-up

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Abstract

Background: Tako-tsubo cardiomyopathy (TTC) is an uncommon transient cardiomyopathy with a clinical and electrocardiographic (ECG) presentation similar to that of ST-elevation myocardial infarction (STEMI).

Aim: To compare clinical presentation, in-hospital course, and long-term outcomes in TTC female patients with on-admission ST-segment elevation and anterior STEMI female patients.

Methods: Consecutive TTC patients with on-admission ST-segment elevation were selected. Using a propensity score, a matching STEMI control group was put together. The patients were followed for a mean 1,002 ± 552 days. Major adverse cardiac events were defined as TTC recurrence, MI recurrence, heart failure requiring hospitalisation, percutaneous coronary intervention, coronary artery bypass grafting, stroke and death.

Results: Forty one TTC patients were enrolled, including 29 women with on-admission ST-segment elevation. The control group consisted of 46 STEMI women with left anterior descending occlusion. The ECG at presentation showed greater ST-segment elevation (6.0 ± 1.6 *vs* 2.0 ± 1.2 mm, $p < 0.01$) in the control STEMI patients than in the TTC group. Also, baseline CK-MB (16.2 ± 20.6 *vs* 66.0 ± 125.2 ng/mL, $p < 0.01$) and troponin-I levels (2.99 ± 5.36 *vs* 42.70 ± 64.79 ng/mL, $p < 0.01$) were significantly higher in the STEMI patients. Echocardiography showed higher follow-up ejection fraction in the TTC than in the STEMI group (57.0 ± 8.0 *vs* 49.5 ± 8.8%, $p < 0.01$). During follow-up, there was no significant difference in the major adverse cardiac events rate between the TTC and STEMI groups (–24.1% *vs* 41.3%, $p = 0.13$).

Conclusions: Although there is some diversity in ECG, laboratory, and ECHO parameters, none of these patterns alone can reliably distinguish TTC from MI in female patients. TTC and STEMI females have similar in-hospital and long-term outcomes.

Key words: tako-tsubo cardiomyopathy, myocardial infarction, STEMI

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INTRODUCTION

Tako-tsubo cardiomyopathy (TTC), characterised by a temporary left ventricular (LV) dysfunction, is a rare form of acute heart failure often mimicking an acute coronary syndrome (ACS) [1, 2]. TTC is triggered by stressful events. Electrocardiographic (ECG) and laboratory findings are similar to ST-segment elevation myocardial infarction (STEMI) due to left anterior descending (LAD) coronary artery occlusion [3–6]. A few studies have compared findings in TTC and MI patients, but no single pattern alone can reliably distinguish these two

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Table 1. Current Mayo Clinic criteria for tako-tsubo cardiomiopathy

1. Transient hypokinesia, akinesia, or dyskinesia in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that usually extend beyond a single epicardial vascular distribution; and frequently, but not always, a stressful trigger.
2. The absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3. New ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
4. Absence of pheochromocytoma and myocarditis.

To diagnose tako-tsubo cardiomyopathy, all four criteria must be fulfilled

Table 2. Medications used in TTC-STE and STEMI control patients

Medication	TTC-STE group (n = 29)	STEMI group (n = 46)	P
On admission and during hospital stay, n (%)			
Acetylsalicylic acid	26 (89.6)	46 (100)	0.02
Clopidogrel	23 (79.3)	46 (100)	< 0.01
Heparin	26 (89.6)	46 (100)	0.02
Beta-blockers	24 (82.7)	37 (80.4)	0.80
Angiotensin-converting enzyme inhibitors	24 (82.7)	41 (89.1)	0.43
Diuretics	13 (44.8)	24 (52.1)	0.53
Statins	26 (89.6)	46 (100)	0.02
Anxiolytics	6 (20.7)	3 (6.5)	0.06
Inotropic agents	3 (10.3)	8 (17.4)	0.40
Amiodarone	2 (6.9)	10 (21.7)	0.08
At discharge, n (%)			
Acetylsalicylic acid	23 (79.3)	46 (100)	< 0.01
Clopidogrel	10 (34.5)	46 (100)	< 0.01
Beta-blockers	29 (100)	42 (91.3)	0.10
Angiotensin-converting enzyme inhibitors	27 (93.1)	43 (93.5)	0.95
Statins	21 (72.4)	45 (97.8)	< 0.01
Diuretics	5 (17.2)	23 (50.0)	< 0.01

conditions [7, 8]. Therefore, we selected a group of TTC women from a single cardiology centre to compare their ECG, laboratory, and echocardiographic parameters to those of females with MI due to LAD occlusion.

METHODS

From January 2005 to June 2010, 6,190 patients with ACS underwent cardiac catheterisation in our institution. From that ACS group, 41 consecutive TTC patients underwent both urgent coronary angiography and ventriculography, and demonstrated the recent Mayo Clinic criteria for TTC (Table 1) [3]. We developed a dataset that included admission data, clinical characteristics, echocardiographic and ECG records, laboratory parameters, and the findings from the follow-up.

Clinical characteristics, including age, sex, stressful trigger, coronary risk factors, and a history of cardiac diseases, were recorded for each patient. The ST-segment elevation was defined as a deviation > 1 mm in ≥ 2 adjacent leads. A T wave inversion was present when it was observed in ≥ 2 contiguous leads with a change from a previous ECG tracing, if available. Furthermore, ST depression, QT interval (mean value from three measurements in II lead), and QRS duration, were included in the ECG characteristics. Left ventricular ejection fraction (LVEF) was assessed using transthoracic echocardiography during an acute phase, and again later after recovery. Laboratory measurements included myocardium necrosis markers. All patients were treated according to the current guidelines for ACS. The medications used during hospitalisation and at discharge are presented in Table 2. The following in-hospital complications were recorded: cardiogenic shock and arrhythmias.

Follow-up phone calls were made. If there was hospitalisation during the follow-up, additional data concerning hospital stay details were collected from each patient. The com-

posite major adverse cardiac events (MACE) were defined as TTC recurrence, MI recurrence, heart failure requiring hospitalisation, percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), stroke and death.

To compare a female TTC population to ST-segment elevation patients, a set of 29 TTC women with on-admission ST elevation (TTC-STE) was put together. Furthermore, we reviewed the 6,190 ACS patients database, and a control group of STEMI women with isolated LAD occlusion was selected. Using a propensity score matching (PSM) method 1-to-n nearest neighbour, caliper set to 0.0005 to reduce a selection bias, a set of control STEMI women was selected [9]. To evaluate the PSM, all on-admission parameters were included.

Statistical analysis

Data normality was assessed by the Kolmogorov-Smirnov test. Absolute values, frequencies and percentages were used to describe categorical variables. Continuous variables are presented as means ± SD and ranges, unless otherwise specified. Continuous and categorical variables were compared with the use of the χ^2 test, paired t-test, and unpaired t-test, as appropriate. Analyses were performed using the STATISTICA v. 8 software (StatSoft Inc.). The level of significance was set at $p < 0.05$.

RESULTS

Clinical characteristics of presentation

Clinical characteristics of TTC patients are listed in Table 3. Forty one TTC patients represented 0.66% of all patients admitted with ACS, and the majority of TTC patients were women aged 43 to 85 years. The commonest presenting cardiovascular symptoms were chest pain, exertional dyspnoea, and nausea or vomiting. Pre-existing heart disease risk factors in the TTC patients included hypertension, hyperlipidaemia, diabetes mellitus, tobacco use, and previous MI. In 80% of patients, careful history-taking identified significant stressful events in the 24 h before the TTC. Most of these events were regarded as emotionally mediated, or alternatively were due to a physical trigger. In some patients, no identifiable stressor was found.

On admission, the commonest ECG finding was ST-segment elevation mimicking acute anterior MI. The ECG findings in the remaining patients were diverse, and included ST-segment depression and isolated dynamic T-wave inversion. In one patient, there were no ECG changes.

Propensity score matching

The PSM was calculated from all on-admission clinical parameters that were estimated or measured during the first hours of hospitalisation, and which were indistinguishable in both TTC-STE and STEMI (Table 4). The PSM process selected all patients from the TTC group with ST-segment elevation, and 46 patients from the STEMI group (Fig. 1).

Table 3. Tako-tsubo patients' clinical characteristics (n = 41)

Age [years]	69 ± 11.56
Women	39 (95.1%)
Hypertension	33 (80.4%)
Diabetes mellitus	9 (21.9%)
Hyperlipidaemia	26 (63.4%)
Tobacco use	8 (19.5%)
COPD or asthma	2 (4.8%)
Previously reported MI	8 (19.5%)
Precipitating factors:	
Emotional	27 (65.8%)
Physical	6 (14.6%)
No identifiable stressor	8 (19.5%)
Presenting symptoms:	
Chest pain	38 (92.6%)
Dyspnoea	14 (34.1%)
Nausea/vomiting	8 (19.5%)
Electrocardiography:	
ST-segment elevation	29 (70.7%)
ST-segment depression	4 (9.7%)
Dynamic T-wave changes only	7 (17.0%)
No changes	1 (2.4%)

COPD — chronic obstructive pulmonary disease; MI — myocardial infarction

The mean ± SD of propensity score was 0.422 ± 0.09 in the TTC-STE patients, and 0.413 ± 0.08 in the STEMI control group ($p = 0.87$). Thus, the baseline clinical characteristics were similar in the TTC-STE group compared to control patients (Table 4).

Electrocardiographic findings

Of the 41 TTC patients, 70.7% had anterior ST-segment elevation on the ECG at admission (TTC-STE), 9.7% had ST-segment depression, 17.0% had dynamic T-wave changes, and one (2.4%) had no ECG changes. All TTC-STE patients were women. A comparison between TTC-STE and STEMI patients in on-admission ECG is presented in Table 5. The mean time from symptom onset to first ECG recording was 11.3 ± 9.6 h for TTC-STE patients, compared to 3.7 ± 2.8 h for STEMI patients ($p < 0.01$). This longer period might be explained by atypical symptoms and transient chest pain reported in the TTC female patients. From all precordial leads, ST elevation was commonest in lead V_3 in both the TTC-STE and STEMI patients, and both groups differed significantly with regard to the maximal ST segment elevation (Fig. 2). There was no difference in the QRS duration between the TTC-STE and STEMI groups; however, the average QT interval was significantly shorter in the patients with LAD occlusion than in those with TTC (Table 5).

Table 4. Characteristics of propensity-matched female patients

	TTC-STE group (n = 29)	STEMI group (n = 46)	P
Killip class	1 ± 0.82	1 ± 0.80	0.77
Heart rate [bpm]	80 ± 15.54	80 ± 15.47	0.49
Systolic blood pressure [mm Hg]	130 ± 33.76	120 ± 25.60	0.42
Diastolic blood pressure [mm Hg]	80 ± 13.05	70 ± 12.37	0.75
Chest pain	27 (93.1%)	46 (100%)	0.07
Dyspnoea	11 (37.9%)	21 (45.6%)	0.51
Nausea/vomiting	7 (24.1%)	7 (15.2%)	0.33
Age [years]	68 ± 12.18	68.5 ± 11.42	0.43
Hypertension	23 (79.3%)	38 (82.6%)	0.79
Diabetes	7 (24.1%)	14 (30.4%)	0.55
Atrial fibrillation	5 (17.2%)	13 (28.2%)	0.27
Hyperlipidaemia	19 (65.5%)	18 (39.1%)	0.02
Tobacco use	7 (24.1%)	15 (32.6%)	0.43

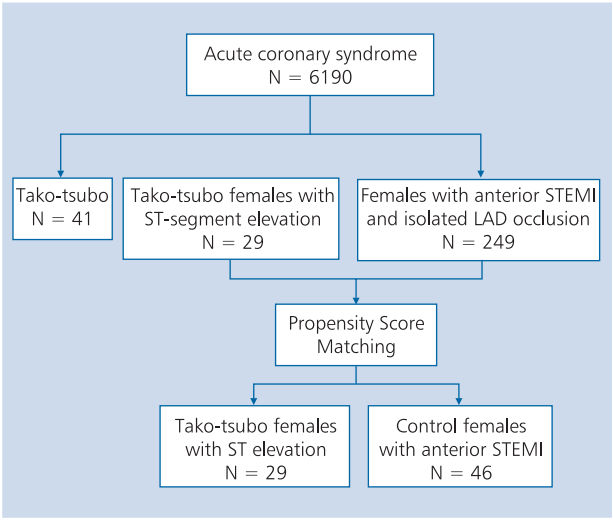

Figure 1. Propensity Score Matching process flowchart; STEMI — ST-elevation myocardial infarction; LAD — left anterior descending coronary artery

Echocardiographic values

Echocardiography was performed during the acute phase, and repeated after one to three months. Table 5 shows the echocardiographic results in both groups. There was no significant difference in the LVEF value at presentation between the TTC-STE and STEMI groups. However, the follow-up LVEF was significantly greater in the TTC-STE patients compared to controls. All parameters measured by echocardiography were comparable in both groups, except for the intraventricular septum diameter, which was significantly greater in STEMI than in TTC-STE women (Table 5).

Laboratory parameters

Troponin-I (Tn-I) values on admission were elevated in all TTC patients. The median Tn-I level was 2.99 ± 5.36 ng/mL in the TTC-STE group compared to 42.70 ± 64.79 ng/mL in the STEMI patients ($p < 0.01$). The mean CK-MB level was 16.2 ± 20.6 ng/mL in the TTC-STE patients compared to 66.0 ± 125.2 ng/mL in controls ($p < 0.01$); however, no differences in the median CK-MB level were found (141.0 ± ± 212.0 ng/mL *vs* 278.0 ± 636.9 ng/mL, $p = 0.06$).

Medications

Table 2 lists the preadmission and discharge medications for the TTC-STE patients and the control group. TTC mimics an ACS, thus initial management was directed towards the treatment of myocardial ischaemia with administration of loading doses of acetylsalicylic acid (ASA) and clopidogrel. In the control group, every patient received loading doses of antiplatelet drugs, which was significantly more often than in the TTC patients. On-admission heparin was given in 26 TTC-STE patients, and in 46 STEMI patients. During hospitalisation, no significant differences were observed in the rate of diuretics and angiotensin-converting enzyme inhibitors (ACE-I) administration. The β-adrenergic blockading agents use at baseline was also balanced between the TTC-STE and control groups, but statins use was significantly lower in the TTC-STE group. The usage of inotropic agents, amiodarone, and anxiolytic agents was similar in both groups. However, at discharge, diuretics were given significantly less frequently in the TTC-STE patients. Statins were prescribed less often after the TTC-STE than in STEMI patients. Beta-blockers were given to all TTC-STE women and to more than 90% of control patients. ACE-I use was balanced be-

Table 5. Electrocardiographic and echocardiographic parameters in TTC-STE and STEMI female patients

	TTC-STE group (n = 29)	STEMI group (n = 46)	P
Electrocardiographic parameters			
QRS duration [ms]	90.0 ± 18.6	91.5 ± 13.0	0.2
Maximum ST elevation [mm]	2.0 ± 1.2	6.0 ± 1.6	< 0.01
Maximal ST elevation in V_3	16 (55.1%)	25 (54.3%)	0.94
QT duration [ms]	400 ± 61.6	340 ± 49.6	0.01
Echocardiographic parameters			
Ejection fraction at presentation [%]	42.0 ± 7.5	42.0 ± 8.0	0.57
Ejection fraction at follow-up [%]	57.0 ± 8.0	49.5 ± 8.8	< 0.01
Left ventricular diastolic diameter [mm]	45.0 ± 4.2	46.5 ± 5.4	0.24
Left atrial diameter [mm]	36.0 ± 3.9	37.0 ± 5.5	0.27
Aorta diameter [mm]	28.0 ± 3.7	30.8 ± 4.8	0.1
Right ventricular diameter [mm]	23.0 ± 3.3	23.0 ± 3.3	0.43
Intraventricular septum diameter [mm]	11.0 ± 1.3	11.9 ± 1.3	< 0.01

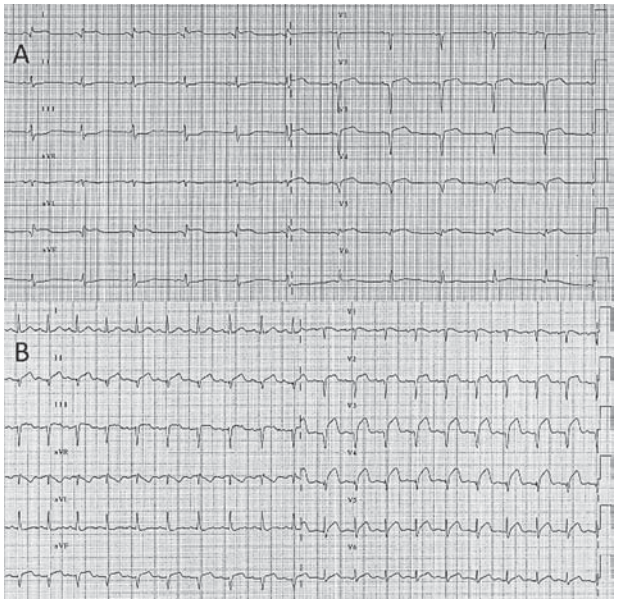

Figure 2. Representative examples of on-admission 12-lead ECGs in a patient with tako-tsubo cardiomyopathy (**A**), and in a patient with ST-segment elevation myocardial infarction (**B**). Paper speed 25 mm/s, calibration 1 cm = 1 mV

tween the TTC-STE and STEMI groups. Dual antiplatelet therapy was continued in both groups, with significant differences in ASA and clopidogrel usage.

Outcomes and follow-up

Every patient survived initial hospitalisation. During that time, cardiogenic shock requiring inotropic agents was present in three TTC-STE patients, and in five STEMI patients. There was no difference in the occurrence of ventricular fibrillation or sustained ventricular tachycardia. During follow-up (1,002 ± 552 days) there was one documented TTC recurrence, and three new MI in the control group. Heart failure requiring hospitalisation was balanced between both groups, although repeat revascularisation (PCI/CABG) was required significantly more often in STEMI patients. Other complications occurred in a similar rate in both groups. The composite MACE tended to be more often observed in the STEMI patients, but the difference was not significant (Table 6).

DISCUSSION

Tako-tsubo cardiomyopathy, also called transient LV apical ballooning syndrome, is an acute cardiac condition that involves transient LV dysfunction. As previously reported, with some diversity of ECG patterns, patients with TTC usually have ST-segment elevation in precordial leads, with a rate 59% to 100% [10–13]. In our TTC group, the ST-segment elevation at baseline ECG was present in almost 71% of women. The TTC and the matched STEMI patient groups had comparable ischaemic changes at baseline ECG, and the highest ST-segment elevation was in V_3; however, the average magnitude of the ST-elevation was significantly lower in the TTC than in the STEMI patients. Also, the QT interval measured at on-admission ECG was different. Similar ECG changes in the TTC patients were previously reported, and it was mostly explained by transient myocardial stunning [14].

Peak troponin and CK-MB values were significantly lower in the TTC patients, although initial LV dysfunction was similar in both groups. Moreover, during follow-up in all TTC women, LV function returned to normal, and in STEMI women impaired LV contraction persisted. Abnormal LV contraction observed in the TTC women is believed to be the

Table 6. Major adverse cardiac events (MACE) during follow-up

Events	TTC group (n = 29)	STEMI group (n = 46)	P
TTC recurrence	1 (3.4%)	0	0.20
MI recurrence	0	3 (6.5%)	0.16
HF requiring hospitalisation	5 (17.2%)	6 (13.0%)	0.76
PCI/CABG	0	6 (13.0%)	0.03
Stroke	0	1 (2.2%)	0.39
Death	1 (3.4%)	3 (6.5%)	0.49
Follow-up MACE (sum)	7 (24.1%)	19 (41.3%)	0.13

TTC — tako-tsubo cardiomyopathy; STEMI — ST elevation myocardial infarction; MI — myocardial infarction; HF — heart failure; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting

result of an apical portion vulnerability to increased plasma catecholamines that affects endocardial endothelial cells [15]. Additionally, due to increased vasoconstriction, and uneven β receptors distribution with the majority at $\beta 2$ receptors in the apical myocardium, TTC postmenopausal women are more likely to demonstrate apical suppression with basal sparing [16]. With increased sympathetic dominance, smaller size, and highest surface-to-volume ratio of apical part of the heart in TTC women, LV can easily become stunned [14, 15]. Conservative management resolves acute heart stunning, thus restoring regular LV contractions with apical myocardium perfusion uptake normalisation up to three months [15]. Hence, although some ECG, ECHO and laboratory patterns might be helpful in distinguishing TTC from STEMI, the exclusion of haemodynamically significant obstructive coronary disease can be difficult, and these two acute cardiac conditions should be initially treated with the same dual antiplatelet treatment [2–4]. However, after performing coronary angiography, TTC patients received significantly less frequently ASA, clopidogrel, and heparin. This pharmacological algorithm is believed to be the treatment with the lower exposure to unnecessary risks including bleeding events. The optimal TTC management has not been established, but supportive therapy including β-blockers and ACE-I leads to spontaneous LV recovery [4, 15].

In previously reported studies, TTC patients had milder in-hospital course and better outcomes [2, 15], but according to our findings there is no significant difference between in-hospital outcomes in the TTC and STEMI patients. Both groups were comparable in in-hospital cardiogenic shock rate, a similar number of patients had ventricular fibrillation, and only sustained ventricular tachycardia tended to be less frequently observed in the TTC than in the STEMI patients. In TTC patients with cardiogenic shock, the use of inotropes is questionable, because of the circulating catecholamines increase, meaning that an intra-aortic balloon pump is required [17]. In TTC patients with LV outflow obstruction, additional calcium channel blockers may reduce the outflow gradient. Although all MACE, except heart failure, were more often seen in STEMI women than in TTC, a significant difference was seen only for invasive revascularisation procedure rates. What is important is that almost 20% of TTC patients had a history of previous MI.

During follow-up, only one TTC patient died, and only one had TTC episode recurrence. The sum of MACE events was higher in STEMI women than in TTC cardiomyopathy patients. Despite corresponding in-hospital complications, TTC has a more favourable long-term outcome than MI [15, 18, 19].

Limitations of the study

The analysed group represents a single cardiology department set, so it is relatively small. Additionally, analysis was partially retrospective.

CONCLUSIONS

Although there is some diversity in laboratory, ECHO, and ECG findings, none of these parameters alone can reliably distinguish TTC from acute MI in females. To establish the proper diagnosis, coronary angiography is necessary. With a similar in-hospital course, TTC female patients have better long term outcomes than STEMI women.

Conflict of interest: *none declared*

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Porównanie przebiegu klinicznego i wyników obserwacji odległej u pacjentów z kardiomiopatią tako-tsubo oraz u pacjentek z zawałem serca z uniesieniem odcinka ST

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Streszczenie

Wstęp: Kardiomiopatia tako-tsubo to rzadka postać odwracalnej niewydolności serca imitująca zawal serca z uniesieniem odcinka ST (STEMI).

Cel: Celem pracy było porównanie objawów, przebiegu klinicznego i obserwacji odległej w grupie pacjentów z kardiomiopatią tako-tsubo z uniesieniem odcinka ST i w grupie pacjentów ze STEMI.

Metody: Do badania włączono chorych z rozpoznaną kardiomiopatią tako-tsubo. Na podstawie metody *propensity score* stworzono grupę kontrolną STEMI.

Wyniki: Do badania włączono 41 pacjentów z kardiomiopatią tako-tsubo, u 29 obserwowano uniesienie odcinka ST przy przyjęciu. Grupę kontrolną stanowiło 46 osób ze STEMI ściany przedniej. W badaniu EKG przy przyjęciu stwierdzono wyższe uniesienie odcinka ST (6,0 ± 1,6 *v.* 2,0 ± 1,2 mm; $p < 0,01$) w grupie kontrolnej w porównaniu z grupą badaną. Wykazano różnicę w stężeniu CK-MB (16,2 ± 20,6 *v.* 66.0 ± 125.2 ng/ml; $p < 0,01$) i troponiny-I (2,99 ± 5,36 *v.* 42,70 ± ± 64,79 ng/ml; $p < 0,01$) w obu grupach. W badaniu ECHO u pacjentów z grupy kardiomiopatii tako-tsubo zaobserwowano zwiększenie wartości frakcji wyrzutowej lewej komory w obserwacji odległej (57,0 ± 8,0 *v.* 49,5 ± 8,8%; $p < 0,01$) w porównaniu z grupą kontrolną STEMI. Częstość występowania poważnych zdarzeń sercowo-naczyniowych (nawrót kardiomiopatii tako-tsubo, dorzut zawału, ostra niewydolność serca wymagająca hospilizacji, przezskórna anigioplasyka/pomostowanie aortalno-wieńcowe, udar, zgon) podczas trwania obserwacji odległej (1002 ± 552 dni) nie różniły się istotnie między grupami kardiomiopatii tako-tsubo i STEMI (24,1% v. 41,3%; $p = 0,13$).

Wnioski: Istniejące różnice w badaniach laboratoryjnych, EKG i ECHO między pacjentami z kardiomiopatią tako-tsubo oraz pacjentami ze STEMI nie pozwalają jednoznacznie rozróżnić obu opisywanych ostrych stanów kardiologicznych. Przebieg kliniczny i wyniki obserwacji odległej u osób z kardiomiopatią tako-tsubo w porównaniu z chorymi ze STEMI są podobne.

Słowa kluczowe: kardiomiopatia tako-tsubo, zawał serca, STEMI

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