ORIGINAL ARTICLE

Clinical presentation, treatment, and long-term outcomes in patients with takotsubo cardiomyopathy

Experience of a single cardiology center

Grzegorz Opolski, Maciej M. Pawlak, Marek F. Roik, Janusz Kochanowski, Piotr Ścisło, Radosław Piątkowski, Janusz Kochman, Grzegorz Karpiński, Robert Kowalik, Marcin Grabowski, Paweł Balsam, Krzysztof J. Filipiak

1st Department of Cardiology, Medical University of Warsaw, Independent Public Central Clinical Hospital, Warszawa, Poland

KEY WORDS

clinical characteristics, management, outcomes, takotsubo cardiomyopathy

ABSTRACT

INTRODUCTION Takotsubo cardiomyopathy (TTC) is a rare transient cardiomyopathy mimicking acute coronary syndrome (ACS).

OBJECTIVES The aim of the study was to retrospectively analyze the clinical course, treatment strategies, and follow-up of patients with TTC.

PATIENTS AND METHODS Among all patients hospitalized in the department between January 2005 and January 2010, we identified a group of patients who were fulfilling the modified Mayo Clinic criteria for the diagnosis of TTC. Clinical presentation, hospital course, and clinical outcomes were analyzed.

RESULTS A total of 31 patients with TTC were included into the study; women comprised 93.5% of the study population. The most common symptoms included chest pain and dyspnea caused by emotional or physical stress. Cardiogenic shock was present in 2 subjects and life-threatening ventricular arrhythmias in 3 other patients. Twenty-four patients had ST-segment elevation on the electrocardiogram. A mean left ventricular ejection fraction was 42 ±8.6% during contractility abnormalities, and it increased to 58 ±7.9% during recovery. Troponin I was positive in 30 cases with a mean peak level of 2.7 ±5.1 ng/ml. Follow-up data were available in 23 patients and a mean follow-up was 955 ±502.8 days. We did not observe a recurrence of TTC.

CONCLUSIONS TTC is observed mainly in postmenopausal women. Clinical presentation of TTC is almost indistinguishable from ACS, but its course is milder and the outcomes are better.

Correspondence to:
Prof. Grzegorz Opolski, MD, PhD,
I Katedra i Klinika Kardiologii,
Warszawski Uniwersytet Medyczny,
Samodzielny Publiczny Centralny
Szpital Kliniczny, ul. Banacha 1a,
02-097 Warszawa, Poland,
phone: +48-22-599-19-58,
fax: +48-22-599-19-57,
e-mail: grzegorz.opolski@wum.edu.pl
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INTRODUCTION Takotsubo cardiomyopathy (TTC), also known as stress cardiomyopathy or apical ballooning syndrome, is defined as a temporary left ventricular dysfunction caused mainly by stress, with left ventricular regional wall hypokinesis extending beyond a single coronary artery distribution and without any significant coronary lesions (FIGURE 1).[1,2] Clinical presentation of this severe cardiac disorder is indistinguishable from acute coronary syndrome (ACS),[3,4] but due to TTC pathophysiology, the American Heart Association classified this stress syndrome as a primary acquired cardiomyopathy.[5] To diagnose TTC and to differentiate it from ACS, Prasad et al.[1] proposed the modified Mayo Clinic criteria for the diagnosis of TTC:

1 transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or

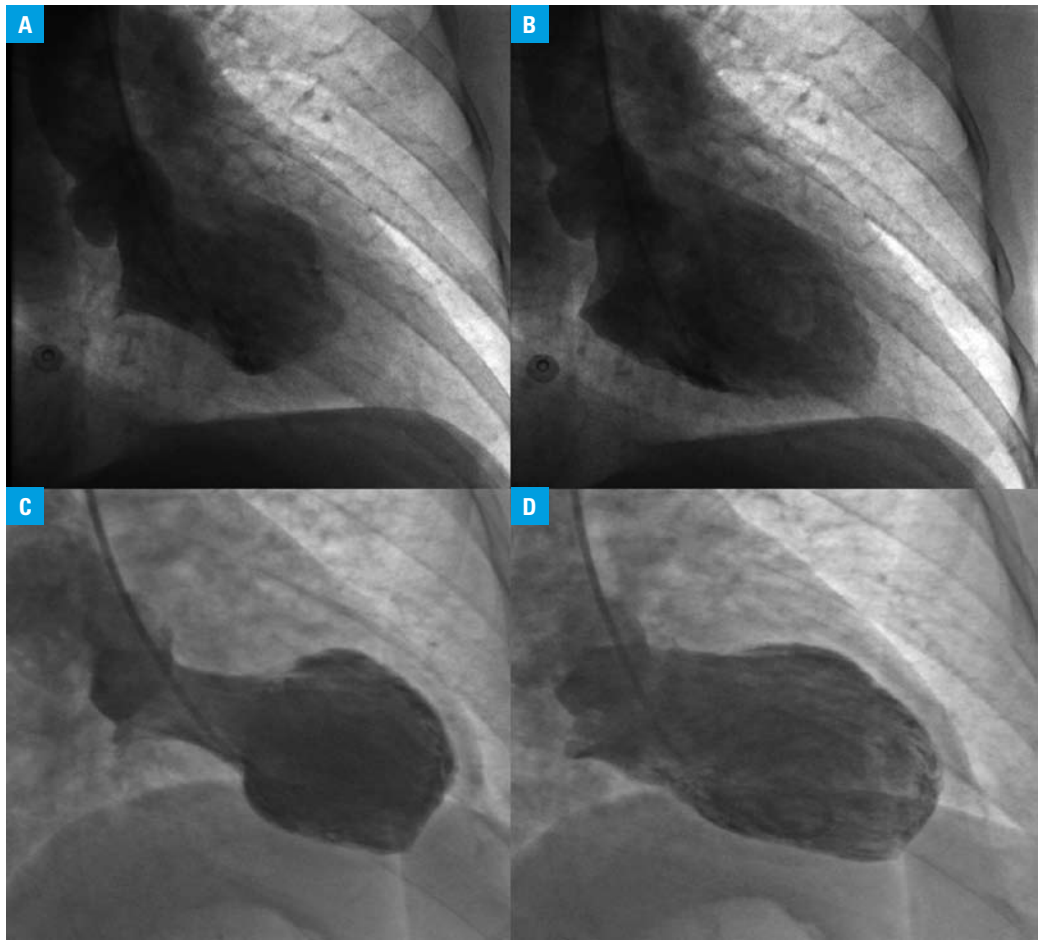

FIGURE 1 Left ventriculograms. Freeze frames from left ventriculograms show normal function at the apex and base during end-systole and (**A**) end-diastole (**B**) with akinesis of the mid segments – a midventricular ballooning variant. Second takotsubo cardiomyopathy variant with hyperdynamic basal contraction (apical ballooning variant) at end-systole (**C**) and (**D**) end-diastole.

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 artery disease or angiographic evidence of acute plaque rupture

3 new abnormalities on the electrocardiogram (ECG) (ST-segment elevation and/or T wave inversion) or modest elevation in cardiac troponin

4 the absence of pheochromocytoma and myocarditis.

All the 4 criteria must be fulfilled in order to diagnose TTC.

The aim of our study was to create a registry of patients with diagnosed TTC in order to learn more about the clinical characteristics, management strategies, and long-term outcomes of this rare cardiac disease.

PATIENTS AND METHODS The database of the 1st Department of Cardiology, Medical University of Warsaw, Poland, was reviewed in order to identify all patients with ACS (n = 5620) who were treated between January 2005 and January 2010. We included patients who underwent both emergent coronary angiography and ventriculography and who fulfilled the recent Mayo Clinic criteria for TTC.[1] We developed a dataset that included admission date, clinical characteristics, echocardiographic and electrocardiographic records, laboratory parameters, and the findings from the follow-up of patients with diagnosed TTC (n = 31).

Clinical characteristics, including sex, age, coronary risk factors, duration of chest pain, stressful trigger, and a history of cardiac diseases, were recorded for each patient.

On an ECG performed on admission, ST-segment elevation was defined as a deviation >1 mm higher than isoelectric line in ≥2 contiguous leads. T wave inversion was present when it was observed in ≥2 contiguous leads with change from a previous ECG tracing, if available. Additionally, ST depression, QT interval, and bundle branch blocks (BBB) were included in the ECG characteristics. Left ventricular ejection fraction (LVEF) was assessed using transthoracic echocardiography during an acute phase and within the next 24 hours after recovery. Laboratory measurements included creatine kinase and cardiac marker levels, including the peak level of troponin I and creatine kinase-MB fraction.

All patients were treated according to the current guidelines for ACS. The medications included acetylsalicylic acid (ASA), angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and statins. The following complications were recorded: cardiogenic shock, arrhytmias, and use of inotropes.

Follow-up phone calls were made. If there was hospitalization during follow-up, additional data concerning discharge from hospital were collected from each patient.

Data normality was assessed by the Kolmogorov-Smirnoff test and summarized as mean ±1 stan-

TABLE 1 Baseline clinical characteristics of the study population (n = 31)

age, yrs ±SD	67 ±11
women, n (%)	29 (93.5)
hypertension, n (%)	24 (77.4)
hyperlipidemia, n (%)	20 (64.5)
previously reported ACS, n (%)	8 (25.8)
diabetes, n (%)	7 (22.5)
smoking, n (%)	6 (19.3)
chronic obstructive pulmonary disease, n (%)	2 (6.4)

Abbreviations: ACS – acute coronary syndrome, SD – standard deviation

TABLE 2 Clinical presentation along with electrocardiographic, echocardiographic, and laboratory parameters (n = 31)

clinical presentation	
chest pain, n (%)	29 (93.5)
dyspnea, n (%)	12 (38.7)
vomiting, n (%)	7 (22.5)
symptoms duration, h	11.5 ±9.4
cardiogenic shock/vasopressors, n (%)	2 (6.4)
ventricular fibrillation, n (%)	1 (3.2)
sustained ventricular tachycardia, n (%)	2 (6.4)
physical trigger, n (%)	2 (6.4)
emotional trigger, n (%)	13 (41.9)
electrocardiographic parameters	
ST-segment elevation, n (%)	24 (77.4)
in precordial leads, n (%)	21 (67.7)
in inferior wall leads, n (%)	3 (11.5)
ST-segment depression, n (%)	1 (3.2)
isolated T wave inversion, n (%)	3 (9.6)
additional T wave inversion, n (%)	21 (67.7)
left bundle branch block, n (%)	1 (3.2)
right bundle branch block, n (%)	1 (3.2)
QRS duration, ms	95 ±19
QT interval, ms	420 ±57
echocardiographic parameters	
initial left ventricular ejection fraction, % (n = 23)	42 ±8.6
left ventricular ejection fraction after acute phase, % (n = 21)	58 ±7.9
laboratory data	
creatine kinase, IU/l (n = 29)	201.8 ±208.5
creatine kinase-MB fraction, ng/ml (n = 25)	13.9 ±21.7
peak troponin I, ng/ml (n = 30)	2.7 ±5.1
white blood cells, × 10^3/µl	8.6 ±2.6

Data are presented as mean ±SD

Abbreviations: see TABLE 1

dard deviation unless otherwise stated. Frequencies and percentages were used to describe categorical variables. Analyses were performed using the STATISTICA 8 software (StatSoft Inc., Poland). The level of significance was set at $P < 0.05$.

The study was approved by the local Ethics Committee.

RESULTS During a 5-year period, 5620 patients with ACS were admitted to our department. Based on the predefined diagnostic criteria for TTC, 31 patients with TTC (0.5%) were included into our analysis. All patients had angiographically normal coronary arteries. The apical ballooning variant with regional wall motion including apical and midventricular akinesis with sparing of the base was present in 16 cases (51.6%). The midventricular balooning variant with midventricular akinesis and preserved contraction of the apex and base was present in 15 patients (48.4%). Baseline clinical characteristics are presented in TABLE 1. The study included 29 women (93.5%); a mean age at presentation was 69 ±11 years (range, 43–85 years); 27 women (93.1%) were aged >55 years. Hypertension was observed in 24 (77.4%), and hyperlipidemia in 20 patients (64.5%). Eight patients (25.8%) had previously diagnosed ACS, 7 (22.5%) – diabetes mellitus, and 2 (6.4%) – chronic obstructive pulmonary disease. Six patients (19.3%) were smokers.

The details of clinical presentation are shown in TABLE 2. The mean time from symptom onset to cath-lab procedure was 11.5 ±9.4 hours. The most common symptoms included chest pain (93.5%) and dyspnea (38.7%). Seven patients (22.5%) suffered from nausea and vomiting. Two patients (6.4%) presented with cardiogenic shock requiring inotrope agents, 1 had ventricular fibrillation, and 2 more (6.4%) had sustained ventricular tachycardia treated with intravenous amiodarone. Use of diuretics was necessary in 14 cases (45.1%).

A stressful event was reported in 15 patients (48.3%): 2 of them (6.4%) had experienced physical stress, and 13 (41.9%) – emotional stress. No stressors were identified in the remaining 16 patients (51.6%).

ECG abnormalities were present in all except 1 patient (96.7%). Twenty-four patients (77.4%) were admitted with ST-segment elevation, of whom 21 patients (67.7%) had ST-segment elevation in precordial leads, and 3 in inferior wall leads. ST-segment depression was observed in 1, isolated T wave inversion in 3, left BBB in 1, and right BBB in 1 patient. Additional T wave inversion was noted in 21 patients (67.7%). The mean QRS duration was 95 ±19 ms, and the mean QT interval was 420 ±57 ms. A typical ECG with ST-segment elevation performed in a TTC patient on admission and at discharge is shown in FIGURE 2.

ECG during acute phase was performed in 23 (74.1%), and after recovery in 21 patients (67.7%). The mean baseline LVEF was 42 ±8.6%, and increased to 58 ±7.9% during recovery. The laboratory parameters were measured on admission. Troponin I levels were positive in 30 patients (96.7%) with a mean peak troponin level of 2.7 ±5.1 ng/ml (range, 0.2–22 ng/ml). The levels of creatine kinase were measured in 29 patients (mean, 201.8 ±208.5 IU/l), and of creatine kinase-MB fraction in 25 patients (mean, 13.9 ±21.7 ng/ml [range, 0.2–78 ng/ml]); white blood

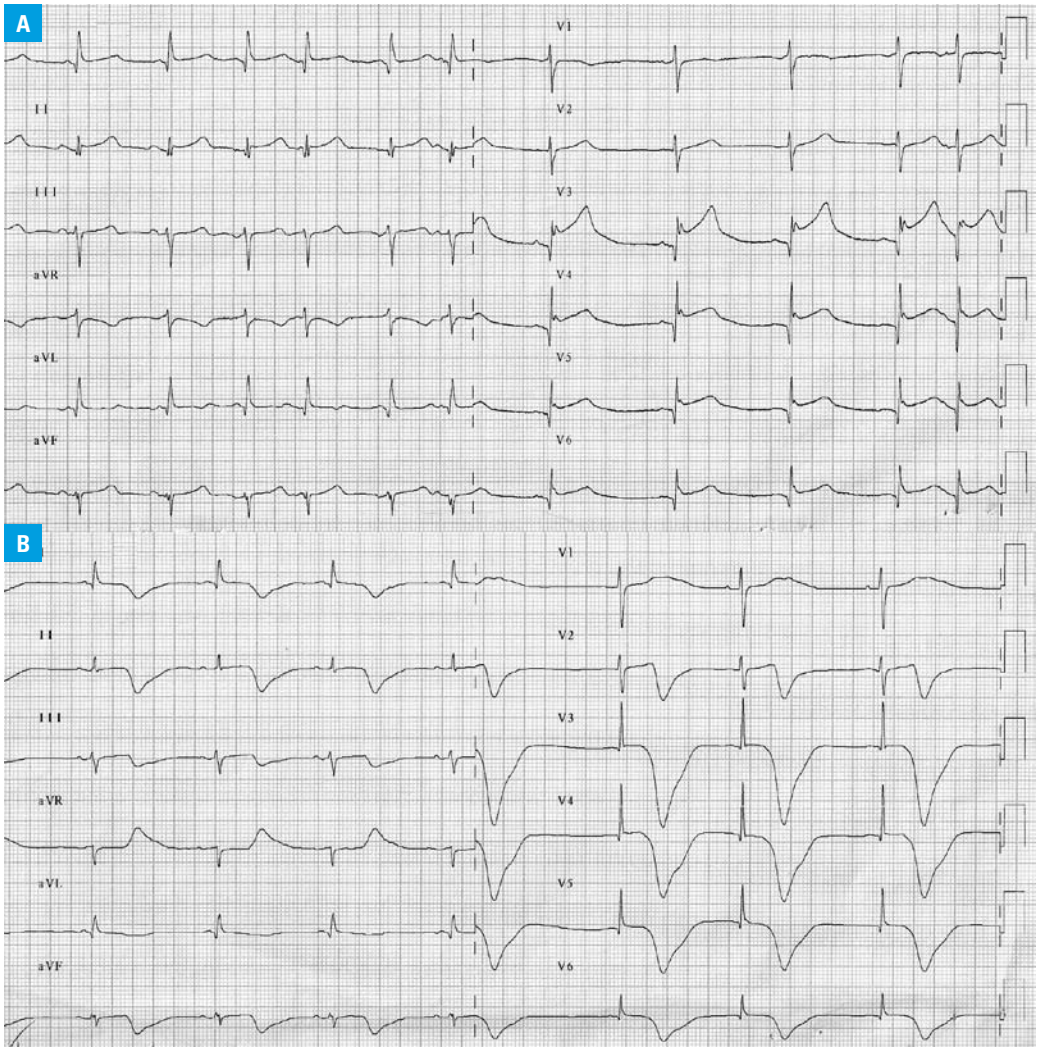

FIGURE 2
A Electrocardiogram (ECG) during acute phase demonstrating diffuse ST-segment elevation in I, II, aVL, aVF, and V3 to V6 leads
B ECG at discharge showing deep T wave inversion in previously ST-segment elevated leads

cell count was measured in all patients (mean, 8.6 ±2.6 × 10^3/μl).

All medications used during hospitalization are listed in TABLE 3. On-admission antiplatelet treatment with ASA and clopidogrel loading doses was used in the majority of patients: 26 (83.8%) received both antiplatelet drugs and 3 (9.6%) – only ASA. Twenty-six patients received β-blockers (83.8%), 25 (80.6%) – ACE inhibitors, and 11 (35.4%) – unfractionated heparin.

After discharge, ASA was continued in 26 patients (83.8%), and 12 patients (38.7%) received additional clopidogrel treatment. β-blockers were prescribed in all except 1 patient (96.7%), ACE inhibitors in 29 patients (93.5%), statins in 20 (64.5%), and diuretics in 6 (19.3%).

Follow-up data were available in 23 patients (74.1%) (mean time, 955 ±502.8 days): 1 patient died from bone cancer, 1 had stroke with hemiplegia, and 2 were hospitalized – 1 due to high blood pressure, and the other due to recurrence of chest pain. In our dataset of clinical outcomes no recurrence of TTC was observed.

DISCUSSION To our knowledge, this case series represents the largest TTC study report in the Polish population. The prevalence of TTC in our department was found to be 0.5%, which is in line with the previous studies (0.36%–2%).[4,6-9] The incidence of TTC might be underestimated because ventriculography was not performed in patients with previously diagnosed ACS and normal coronary arteries. Our study group comprised mainly postmenopausal women with numerous cardiovascular risk factors. In the Rhode Island Takotsubo Cardiomyopathy Registry described by Regnante et al.,[6] cardiovascular risk factors were uncommon. However, in our group, 25.8% of patients had a history of ACS, and we believe that it might have been the actual onset of TTC misdiagnosed as an acute myocardial ischemia.

The mean time between the onset of symptoms and the cath-lab procedure was 11.5 ±9.4 hours. In line with the findings of other meta-analyses, the most common symptoms of TCC were chest pain and dyspnea.[7,8,10] However, we noticed a high rate of vomiting and nausea – symptoms that were unusual in other studies on TCC. The severity of the disease at presentation varied. In most cases, the clinical manifestation of TCC was mild, but 2 patients developed cardiogenic shock, and in another 2 patients life-threatening arrhythmia was present. Stress as a causative factor was identified in half of the patients; in 41.9% it was emotional stress, and in 6.4% physical stress. Stress-induced catecholamine surge is believed to be a causative agent in TTC.[7] The observation that TTC resembles pheochromocytoma

TABLE 3 Medications used in patients with takotsubo cardiomyopathy

on admission and during hospital stay, n (%)	
β-blockers	26 (83.8)
ACE inhibitors	25 (80.6)
ASA	29 (93.5)
clopidogrel	26 (83.8)
diuretics	14 (45.1)
inotropic agents	2 (6.4)
amiodarone	2 (6.4)
unfractionated heparin	11 (35.4)
benzodiazepines	5 (16.1)
hydroxyzine	2 (6.4)
at discharge, n (%)	
ASA	26 (83.8)
clopidogrel	12 (38.7)
β-blockers	30 (96.7)
ACE inhibitors	29 (93.5)
statins	20 (64.5)
diuretics	6 (19.3)

Abbreviations: ACE – angiotensin-converting enzyme, ASA – acetylsalicylic acid

cardiomyopathy confirms this hypothesis.[11] ST-segment elevation in precordial leads present on admission has been observed by other authors.[12] Unlike the Rhode Island Takotsubo Cardiomyopathy Registry, in which 17% of the cases had no ECG abnormalities, our study reports only 3.3% of the cases with normal ECG. Troponin I level was positive in 96.7% of the patients with a mean peak troponin level of 2.7 ng/ml compared with 6.9 ng/ml reported by Regnante et al.,[6] and 13.9 ng/ml by Vidi et al.[10] Because of the clinical presentation and ECG abnormalities, most patients were initially treated for myocardial ischemia with loading doses of dual antiplatelet drugs and intravenous heparin. There is no clear consensus on the management of patients with TTC, but after cardiac catheterization most of our patients continued to receive ASA, β-blockers, and ACE inhibitors. In the majority of cases, this type of supportive therapy led to spontaneous left ventricular recovery. We observed several complications in our study group. In 3 cases, life-threatening arrhythmia occurred, and in 2 – cardiogenic shock; 2 patients required inotropic agents. One of the most frequent complications during the acute phase is an acute and reversible heart failure.[12-14] This may be supported by the fact that almost 50% of our patients received diuretics. Patients with TTC who survive acute phase are believed to have a good prognosis, and the recurrence rate is below 10%.[12,15]

Our study has several limitations. First, the case series presented here is based on retrospective analysis. Second, the cohort of patients was relatively small, but TTC syndrome is uncommon in the general population.

In conclusion, TTC was present in 0.5% of patients with ACS admitted to our department, mainly in postmenopausal women. Clinical presentation is indistinguishable from ACS, but the course is milder and the outcomes are better. The hypotheses about pathophysiology, in-hospital and long-term management of this reversible left ventricular dysfunction are still under evaluation.

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ARTYKUŁ ORYGINALNY

Przebieg kliniczny, leczenie i obserwacja odległa chorych z zespołem *takotsubo*

Doświadczenia jednego ośrodka

Grzegorz Opolski, Maciej M. Pawlak, Marek F. Roik, Janusz Kochanowski, Piotr Ścisło, Radosław Piątkowski, Janusz Kochman, Grzegorz Karpiński, Robert Kowalik, Marcin Grabowski, Paweł Balsam, Krzysztof J. Filipiak

I Katedra i Klinika Kardiologii, Warszawski Uniwersytet Medyczny, Samodzielny Publiczny Centralny Szpital Kliniczny, Warszawa

SŁOWA KLUCZOWE

zespół *takotsubo*, leczenie, obserwacja odległa, przebieg kliniczny

STRESZCZENIE

WPROWADZENIE Zespół *takotsubo* (ZT) jest rzadko spotykaną kardiomiopatią imitującą ostry zespół wieńcowy (OZW).

CELE Celem badania była retrospektywna analiza przebiegu klinicznego, sposobu leczenia oraz obserwacji odległej w grupie pacjentów z rozpoznanym ZT.

PACJENCI I METODY Spośród pacjentów hospitalizowanych w klinice od stycznia 2005 do stycznia 2010 r. wyodrębniono grupę chorych spełniających zmodyfikowane kryteria Mayo Clinic dotyczące rozpoznania ZT. Analizowano obraz kliniczny, przebieg leczenia oraz wyniki odległe grupy pacjentów z rozpoznanym ZT.

WYNIKI Do analizy włączono 31 pacjentów, a kobiety stanowiły 93,5%. Najczęstszymi objawami towarzyszącymi ZT były ból w klatce piersiowej i duszność wywołane stresem emocjonalnym lub fizycznym. U 2 pacjentów wystąpił wstrząs kardiogenny, u kolejnych 3 obserwowano ciężką arytmię komorową. W elektrokardiogramie uniesienie odcinka ST było obecne u 24 chorych. W fazie zaburzeń kurczliwości średnia frakcja wyrzutowa lewej komory wynosiła 42 ±8,6%, przy prawidłowej kurczliwości zwiększyła się do 58 ±7,9%. U 30 chorych stężenie troponiny I było dodatnie, ze średnią wartością 2,7 ±5,1 ng/ml. Średni czas trwania obserwacji odległej u 23 chorych wyniósł 955 ±502,8 dni. W tym okresie nie obserwowano nawrotu ZT.

WNIOSKI ZT najczęściej występowała u kobiet w okresie pomenopauzalnym. Obraz kliniczny ZT jest trudny do odróżnienia od OZW, jednak przebieg kliniczny i wyniki odległe są korzystniejsze.

Adres do korespondencji:
prof. dr hab. med. Grzegorz Opolski,
I Katedra i Klinika Kardiologii,
Warszawski Uniwersytet Medyczny,
Samodzielny Publiczny Centralny
Szpital Kliniczny, ul. Banacha 1a,
02-097 Warszawa,
tel.: 22-599-19-58,
fax: 22-599-19-57,
e-mail: grzegorz.opolski@wum.edu.pl

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