

Original article

Tako-tsubo Syndrome in Men: Rare, but With Poor Prognosis

Alberto Pérez-Castellanos,^a Manuel Martínez-Sellés,^{b,c} Hernán Mejía-Rentería,^d Mireia Andrés,^e Alessandro Sionis,^f Manuel Almendro-Delia,^g Ana Martín-García,^h María Cruz Aguilera,ⁱ Eduardo Pereyra,^j José A. Linares Vicente,^k Bernardo García de la Villa,^a and Iván J. Núñez-Gil^{d,*}

^aServicio de Cardiología, Hospital de Manacor, Manacor, Balearic Islands, Spain

^bServicio de Cardiología, Hospital General Universitario Gregorio Marañón, CIBER de Enfermedades Cardiovasculares (CIBERCV), Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

^cUniversidad Complutense y Universidad Europea, Madrid, Spain

^dServicio de Cardiología, Instituto Cardiovascular, Hospital Clínico San Carlos, Madrid, Spain

^eServicio de Cardiología, Hospital Universitario Vall d'Hebron, Barcelona, Spain

^fUnidad de Cuidados Intensivos Cardiológicos, Servicio de Cardiología, Hospital de Sant Pau, Instituto de Investigación Biomédica Sant Pau (IIB Sant Pau), Barcelona, Spain

^gServicio de Cardiología, Hospital Virgen de la Macarena, Sevilla, Spain

^hServicio de Cardiología, Hospital Universitario de Salamanca, Instituto de Investigación Biomédica de Salamanca (IBSAL), CIBER de Enfermedades Cardiovasculares (CIBERCV), Salamanca, Spain

ⁱServicio de Cardiología, Hospital de La Princesa, Madrid, Spain

^jServicio de Cardiología, Hospital Universitario Arnau de Vilanova, Lérida, Spain

^kServicio de Cardiología, Hospital Clínico Lozano Blesa, Zaragoza, Spain

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ABSTRACT

Introduction and objectives: Tako-tsubo syndrome is a potentially serious disease during the acute phase. It mimics myocardial infarction, but with no potentially causative coronary lesions. The aim of this study was to analyze the clinical course and outcome of patients with tako-tsubo syndrome by sex.

Methods: We analyzed the characteristics of patients included in the RETAKO registry from 2003 to 2015, a multicenter registry with participation of 32 Spanish hospitals.

Results: Of 562 patients included, 493 (87.7%) were women. Chest pain was less frequent as an initial symptom in men than in women (43 [66.2%] vs 390 [82.8%]; $P < .01$). The prognosis was worse in men, with higher in-hospital mortality (3 [4.4%] vs 1 [0.2%]; $P < .01$), longer intensive care stay (4.2 ± 3.7 vs 3.2 ± 3.2 days; $P = .03$) and a higher frequency of severe heart failure (22 [33.3%] vs 95 [20.3%]; $P = .02$). However, dynamic obstruction at the left-ventricular outflow tract occurred exclusively in women (39 [7.9%] vs 0 [0.0%]; $P = .02$). The incidence of functional mitral regurgitation was also higher in women (52 [10.6%] vs 2 [2.9%]; $P = .04$).

Conclusions: Tako-tsubo syndrome shows wide differences by sex in terms of its incidence, presentation, and outcomes. Prognosis is worse in men.

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Síndrome de tako-tsubo en varones: infrecuente, pero con mal pronóstico

RESUMEN

Introducción y objetivos: El síndrome de tako-tsubo es un proceso patológico potencialmente grave durante la fase aguda. Simula un infarto de miocardio, sin que haya lesiones coronarias potencialmente responsables. El objetivo de este trabajo es analizar la evolución y el pronóstico de los pacientes con síndrome de tako-tsubo en función del sexo.

Métodos: Se analizaron las características de los pacientes incluidos en el registro RETAKO durante los años 2003 a 2015, un registro multicéntrico en el que participaron 32 hospitales españoles.

Resultados: De los 562 pacientes incluidos, 493 (87,7%) eran mujeres. El dolor torácico fue menos frecuente como síntoma inicial en los varones que en las mujeres (43 [66,2%] frente a 390 [82,8%]; $p < 0,01$). El pronóstico fue peor en los varones, con mayor mortalidad intrahospitalaria (3 [4,4%] frente a 1 [0,2%]; $p < 0,01$), duración más prolongada de ingreso en cuidados intensivos ($4,2 \pm 3,7$ frente a $3,2 \pm 3,2$ días; $p = 0,03$) y mayor frecuencia de insuficiencia cardiaca grave (22 [33,3%] frente a 95 [20,3%]; $p = 0,02$). Sin embargo la aparición de obstrucción dinámica a nivel del tracto de salida del ventrículo izquierdo se observó exclusivamente en mujeres (39 [7,9%] frente a 0 [0,0%]; $p = 0,02$) y la incidencia de insuficiencia mitral funcional también fue mayor en ellas (52 [10,6%] frente a 2 [2,9%]; $p = 0,04$).

Palabras clave:

Síndrome de tako-tsubo

Sexo

Insuficiencia mitral

Obstrucción en tracto de salida del ventrículo izquierdo

* Corresponding author: Servicio de Cardiología, Hospital Clínico San Carlos, Avda. Profesor Martín Lagos s/n, 28040 Madrid, España.
E-mail address: ibnsky@yahoo.es (I.J. Núñez-Gil).

Conclusiones: El síndrome de *tako-tsubo* es una enfermedad que muestra grandes diferencias en función del sexo en cuanto a su incidencia, presentación y evolución, con un peor pronóstico en los varones. © 2017 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Abbreviations

LVOT: left ventricular outflow tract
TKS: tako-tsubo syndrome

INTRODUCTION

Tako-tsubo syndrome (TKS) is a generally reversible episode of acute left ventricular systolic dysfunction of variable severity. First described in 1990 in Japan, TKS has a similar clinical presentation to acute myocardial infarction, but occurs in the absence of coronary lesions that could account for the myocardial injury in affected individuals; moreover, the clinical symptoms of TKS resolve rapidly, with ventricular contraction normalizing in a matter of days or weeks.¹

The underlying mechanisms and pathophysiology of TKS are poorly understood; however, a mechanism has been proposed involving catecholamine-induced acute myocardial injury.² One characteristic noted since the first TKS studies is a marked difference in incidence between the sexes, with the condition being much more common in women, especially after the menopause.³ Most published studies have reported a female-to-male patient ratio of around 9:1.⁴⁻⁶

Tako-tsubo syndrome was historically considered a benign condition; however, over the years many complications have been reported in the acute phase of the syndrome,⁷⁻¹¹ especially in patients who develop heart failure.¹² Likewise, follow-up has revealed recurrent episodes in some patients.¹³ More recent studies have revealed morbidity and mortality rates similar to or higher than those observed in patients with acute coronary syndrome.⁶

The early view of TKS as a benign disorder has therefore been replaced by recognition that the patient's clinical course can be affected by potentially serious complications, especially those appearing in the first hours or days. Given the marked differences in TKS incidence by sex, we analyzed whether the type of complications and prognosis also differ between men and women. Knowledge of any such differences could facilitate their detection and help to improve patient prognosis.

METHODS

Patient Inclusion

The data analyzed here are from the Spanish tako-tsubo registry (*REgistro español de síndrome de TAKO-tsubo*; RETAKO).⁵ RETAKO is a prospective study coordinated by the Ischemic Heart Disease and Acute Cardiovascular Care Section of the Spanish Society of Cardiology. Patient inclusion is voluntary. Diagnosis was confirmed by modified Mayo Clinic criteria.¹⁴

In this study, we analyzed data from TKS patients admitted consecutively to any of the 32 hospitals participating in RETAKO between January 2003 and December 2015. Records were compiled of clinical characteristics, in-hospital complications, analytical results, electrocardiograms, and the results of imaging analysis by echocardiography and other modalities available at each

center (magnetic resonance imaging was optional in the protocol). Initially, this information was recorded on a case report form and sent by e-mail to a data processing center; from 2014, information was directly recorded in an online case report form. Inclusion was conditional on the patient having undergone an invasive coronary angiography investigation that excluded significant obstructive lesions (> 50%) and any other potential cause of the clinical symptoms (eg, thrombus, dissection, or ulcer). Treatment and follow-up were always at the discretion of the attending physicians. Except for those patients who died before follow-up, inclusion in the analysis required at least 1 follow-up imaging examination by any modality (usually echocardiography) showing complete normalization of the segmental contraction abnormalities diagnosed in the acute phase.

The study was approved by the Ethics Committee of Hospital Clínico San Carlos, and patients gave informed consent to participate in the registry.

Triggering Factors

We recently proposed a classification of TKS according to its potential triggering factors.¹⁵ This classification distinguishes between primary forms, with no identifiable trigger or triggered by major psychological stress, and secondary forms, triggered by physical factors such as an asthma attack, surgery, trauma, or pheochromocytoma.¹⁶ The main interest of this classification is its prognostic implications; secondary TKS is associated with a worse short- and long-term prognosis.¹⁵ For the present analysis, possible triggering factors were noted during data collection, and patients were subsequently assigned to either the primary or the secondary TKS group.

Complications

We analyzed the appearance of the following complications during hospitalization:

- Severe heart failure, defined as acute pulmonary edema or cardiogenic shock. The incidence of shock was also analyzed independently.
- Moderate or severe acute functional mitral regurgitation, with no recorded clinical history or with recovery during follow-up.
- Dynamic left ventricular outflow tract (LVOT) obstruction. Obstructions were determined echocardiographically or from catheter pressure recordings, and obstructions > 25 mmHg were considered significant.³
- Major bleeding (anemia with a hemoglobin drop ≥ 2 g/dL or requiring transfusion).
- Others: intraventricular thrombus formation, systemic embolism and stroke, pulmonary thromboembolism, pericarditis, recurrent TKS during hospitalization, acute renal failure, in-hospital infection, catheterization complications, and in-hospital death.

Statistical Analysis

Data were analyzed with STATA, version 12.1 (StataCorp, United States). The study is descriptive. Continuous variables are

expressed as mean \pm standard deviation, and differences were analyzed by the Student *t* test or the Wilcoxon rank sum test for nonnormal distribution. Categorical variables are expressed as frequency and percentage and were compared by the chi-square test or by the Fisher exact test for nonnormal distribution. Differences were considered significant at $P < .05$.

RESULTS

Study Population

A total of 562 patients were included. The mean age was 69.5 ± 14.5 years, and 493 (87.7%) of the patients were women. No significant between-sex differences were observed for age, cardiovascular risk factors, or baseline functional class. A higher smoking prevalence was noted among men (Table 1).

Triggering Factors

A significantly higher proportion of women than men were classified as having primary TKS: 364 (78.5%) vs 42 (63.6%); $P < .01$.

Clinical Presentation

The most frequent symptom on presentation was chest pain; however, this symptom was significantly less frequent in men than in women (43 [66.2%] vs 390 [82.8%]; $P < .01$). In contrast, syncope was more frequent among men than women (13 [19.7%] vs 29 [6.2%]; $P < .01$). No major between-sex differences were observed for other symptoms recorded on admission: palpitations, shortness of breath, or autonomic symptoms (Table 2).

Clinical Course and Complications During Hospitalization

Men had a worse prognosis, with higher incidences of severe heart failure (33.3% vs 20.3%; $P = .02$), cardiogenic shock (18.2% vs 6.4%; $P < .01$), and in-hospital mortality (4.4% vs 0.2%; $P < .01$). Men also had a higher rate of major bleeding (10.6% vs 2.8%; $P < .01$), a higher incidence of acute renal failure (22.7% vs 7.7%; $P < .01$), and a longer mean stay in intensive care (4.2 days vs 3.7 days; $P = .03$).

In contrast, dynamic LVOT obstruction was observed only in women (7.9%), and the incidence of moderate-to-severe acute mitral regurgitation was also lower in men (2.9% vs 10.6%; $P = .04$).

There was no between-sex difference in left ventricular ejection fraction ($42.7\% \pm 14.1\%$ in men vs $44.0\% \pm 11.9\%$ in women; $P = .45$) (Table 3).

DISCUSSION

This study confirms the existence of substantial differences in the manifestation of TKS in men and women, including a 9-fold higher incidence in women. More importantly, our results also reveal significant between-sex differences in the clinical course of TKS during hospitalization. There were no overall between-sex differences in left ventricular ejection fraction, a widely used parameter for determining the severity of a TKS episode. Despite this, men had a worse in-hospital prognosis, with higher mortality, longer periods in intensive care, a higher risk of severe hemodynamic instability, and higher rates of major bleeding and renal function impairment. Nonetheless, LVOT obstruction and mitral regurgitation were more frequent among women. This information will be useful to physicians attending TKS patients by facilitating early detection of these complications.

Some of the results presented here have been reported in previous studies. The approximately 9-fold higher TKS incidence in women has been widely reported.⁴⁻⁶ The more frequent diagnosis based on chest pain in women and the higher frequency of severe hemodynamic instability (cardiogenic shock) in men match the findings of a German-Austrian multicenter study with similar characteristics to ours, albeit with fewer patients.⁴ However, our study also identifies major between-sex differences not described in previous reports, including dynamic LVOT obstruction and mitral regurgitation during the acute phase, parameters not evaluated in the German-Austrian cohort.

Primary TKS was more common among women, although more than half of male patients also fell into this category. The higher frequency of primary TKS in women may help to explain, at least in part, the observed between-sex differences in complications and prognosis. Secondary TKS is triggered by physical factors, such as asthma attack, recent surgery, injury, and serious infection.¹⁵ In this patient group, it is therefore important to consider not only the specific properties of TKS, but also the underlying disease that triggers the condition; these patients are often hemodynamically unstable and are more likely to develop complications. However, the notably different prognosis of men and women with TKS likely also includes contributions from sex-determined factors. It is well established that male heart failure patients with left ventricular systolic dysfunction have a worse prognosis than women with the

Table 1
Baseline Patient Characteristics for the Total Cohort and Grouped by Sex

	Total Cohort (N = 562)	Women (n = 493)	Men (n = 69)	P
Age, y	69.5 \pm 14.5	69.7 \pm 14.2	67.3 \pm 16.7	.2
Hypertension	360 (66.7)	317 (66.9)	43 (65.2)	.78
Dyslipidemia	240 (44.7)	208 (44.0)	32 (50.0)	.36
Diabetes mellitus	116 (20.6)	103 (20.9)	13 (18.8)	.69
Smoking	73 (13.6)	59 (12.5)	14 (21.2)	.05
Obesity	90 (17.4)	83 (18.2)	7 (11.3)	.18
OSAS	12 (2.3)	10 (2.1)	2 (3.1)	.63
Baseline functional class				
I	419 (78.8)	362 (77.7)	57 (86.4)	.23
II	97 (18.2)	90 (19.3)	7 (10.6)	
III	16 (3.0)	14 (3.0)	2 (3.0)	

OSAS, obstructive sleep apnea syndrome.

Data are expressed as No. (%) or mean \pm standard deviation.

Table 2
Clinical Presentation of Tako-tsubo Syndrome

	Total cohort (N=562)	Women (n=493)	Men (n=69)	P
Primary TKS	406 (76.6)	364 (78.5)	42 (63.6)	<.01
Chest pain	433 (80.8)	390 (82.8)	43 (66.2)	<.01
Autonomic symptoms	250 (46.7)	224 (47.8)	26 (39.4)	.20
Dyspnea	216 (40.5)	188 (40.3)	28 (42.4)	.74
Palpitations	43 (8.1)	41 (8.8)	2 (3.0)	.11
Syncope	42 (7.9)	29 (6.2)	13 (19.7)	<.01
<i>Initial ECG characteristics</i>				
ST segment elevation	324 (62.1)	279 (60.7)	45 (72.6)	.07
ST segment depression	79 (15.2)	73 (16.0)	6 (9.7)	.20
Negative T waves	190 (36.7)	168 (36.8)	22 (35.5)	.84
Admission LVEF	43.8 ± 12.2	44.0 ± 11.9	42.7 ± 14.1	.45
Right dominance	448 (88.9)	395 (88.6)	53 (91.4)	.52
Myocardial bridging with systolic compression of the LAD	17 (3.0)	14 (2.8)	3 (4.4)	.49

ECG, electrocardiogram; LAD, left anterior descending coronary artery; LVEF, left ventricular ejection fraction; TKS, tako-tsubo syndrome. Data are expressed as No. (%) or mean ± standard deviation.

Table 3
Clinical Course and Complications

	Total Cohort (N=562)	Women (n=493)	Men (n=69)	P
Length of ICU stay, d	3.3 ± 3.3	3.2 ± 3.2	4.2 ± 3.7	.03
Length of hospital stay, d	8.6 ± 6.9	8.5 ± 6.7	9.4 ± 8.2	.29
<i>In-hospital complications</i>				
Severe heart failure	117 (21.9)	95 (20.3)	22 (33.3)	.02
Cardiogenic shock	42 (7.9)	30 (6.4)	12 (18.2)	<.01
Mitral regurgitation (moderate-severe)	54 (9.6)	52 (10.6)	2 (2.9)	.04
LVOT obstruction	39 (7.0)	39 (7.9)	0 (0.0)	.02
IV thrombus	16 (3.0)	15 (3.2)	1 (1.6)	.46
Systemic embolism	7 (1.3)	7 (1.5)	0 (0.0)	.32
PTE	2 (0.4)	1 (0.2)	1 (1.5)	.11
Stroke	15 (2.8)	11 (2.4)	4 (6.1)	.09
Pericarditis	6 (1.1)	5 (1.1)	1 (1.5)	.75
Major bleeding	20 (3.8)	13 (2.8)	7 (10.6)	<.01
Recurrent TKS during hospitalization	36 (6.9)	31 (6.7)	5 (7.9)	.73
Acute renal failure	50 (9.6)	35 (7.7)	15 (22.7)	<.01
In-hospital infection	113 (21.5)	94 (20.5)	19 (28.8)	.13
Catheterization complication	28 (5.3)	22 (4.8)	6 (9.2)	.13
In-hospital death	4 (0.7)	1 (0.2)	3 (4.4)	<.01

ICU, intensive care unit; IV, intraventricular; LVOT, left ventricular outflow tract; PTE, pulmonary thromboembolism. Data are expressed as No. (%) or mean ± standard deviation.

same condition; moreover, this difference is independent of left ventricular ejection fraction^{17,18} and is more pronounced in patients with nonischemic dilated cardiomyopathy than in ischemic patients.¹⁹

One of the possible complications during the acute phase is dynamic LVOT obstruction, although this is normally reversible, correcting as left ventricular systolic function improves.²⁰ To our knowledge, the clear between-sex differences in the appearance of this complication have not been reported in previous studies. Few published series have reported the incidence of dynamic LVOT obstruction in TKS patients, and even fewer have identified the sex of patients with this condition. In line with our registry, a systematic analysis in a series of just 32 patients (31 women and 1 man) identified LVOT obstruction in 8 patients, all of them women.²¹ In addition to being women, the patients with LVOT were more elderly than other TKS patients, and all of them had a

septal bulge (sigmoid septum).²¹ However, demographic studies have revealed no differences by sex in the prevalence of sigmoid septum in the general population,²²⁻²⁴ and therefore sigmoid septum cannot explain the higher incidence of dynamic LVOT obstruction among female TKS patients. Analysis of other conditions has revealed an association between female sex and a higher incidence of LVOT obstruction among patients diagnosed with hypertrophic cardiomyopathy.^{25,26} In TKS, the underlying cause of the sex-association may be a different spatial distribution of catecholaminergic receptors in the left ventricle myocardium, with a steeper base-to-apex gradient in women. The resulting excessive release of catecholamines² could produce the observed difference in the classic pattern between strictly basal hypercontractility and akinesia in the middistal segments, thereby favoring the more frequent dynamic LVOT obstruction seen in women.

Another complication that was more frequent in women was mitral regurgitation, classified as moderate or severe. Two characteristic underlying mechanisms of functional mitral regurgitation could account for its appearance during the acute phase of TKS^{7,27}: a) the most common mechanism is apical displacement of the mitral leaflet coaptation point (tethering), produced by the dilatation and altered contraction of the medioventricular segments, and b) the second mechanism is systolic movement of the anterior mitral leaflet in patients with dynamic LVOT obstruction; this mechanism is less frequent but has been described in several reports and can sometimes coexist with tethering. Our finding that one of these causative mechanisms (LVOT obstruction) occurred only in women in our cohort could help to explain, at least in part, the higher frequency of acute functional mitral regurgitation in TKS among women.

Limitations

The characteristics of the registry impose some limitations on the study. The voluntary nature of study participation may have introduced an inclusion bias, resulting in some types of patients not being represented in the cohort. Inclusion in the registry required a coronary angiography examination to confirm the absence of coronary lesions that could explain the symptoms. However, not all patients underwent this test, potentially resulting in the exclusion of patients with TKS. This will mostly have affected very elderly patients or those with a history of severe comorbidities; in these situations, a physician may prefer to avoid the use of an invasive technique and opt for a more conservative approach even when the initial suspected diagnosis is acute coronary syndrome. In other instances, angiography may not have been possible due to the severity of the initial symptoms; this would have been the case, for example, of a patient in whom TKS caused sudden death. The requirement of a coronary angiography investigation may therefore have led to underestimation of the severity and frequency of complications. Although the study recorded a higher frequency of functional mitral regurgitation in women, no systematic record was compiled of the underlying mechanism. Finally, angiographic and other data were analyzed by the investigators in each center, without the intervention of a central laboratory.

CONCLUSIONS

Tako-tsubo syndrome is a disease process showing pronounced differences between the sexes. Not only was TKS 9 times more common in women, its clinical course also showed a major divergence between men and women, with an overall worse prognosis in men, who showed worse hemodynamic deterioration and a higher rate of in-hospital mortality. Despite this trend, dynamic LVOT obstruction was observed only in female TKS patients, who also had a higher incidence of functional mitral regurgitation.

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CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

- Tako-tsubo syndrome is a potentially serious disease during its acute phase, associated with a relatively high rate of possible complications that result in notable in-hospital morbidity and mortality.
- There is a well established difference by sex in the appearance of TKS, with a female-to-male patient ratio of 9:1.

WHAT DOES THIS STUDY ADD?

- The pattern of complications differed greatly between women and men with TKS. The overall prognosis was worse in men, who showed worse hemodynamic deterioration and had a higher rate of in-hospital mortality. Nevertheless, dynamic LVOT obstruction was a TKS complication found only in women, and female TKS patients also had a higher incidence of functional mitral regurgitation.

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