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Original article

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

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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.

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

Palabras clave:
Síndrome de *tako-tsubo*
Sexo
Insuficiencia mitral
Obstrucción en tracto de salida del ventrículo izquierdo

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 ± 3,7 frente a 3,2 ± 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%]; $p = 0,04$).

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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.

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 echocardiograpy and other modalities available at each center (magnetic resonance imaging was optional in the protocal). 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 were considered significant.[3]
- Major bleeding (anemia with a hemoglobin drop $\geq$ 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

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