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Original article

Tako-tsubo Syndrome and Heart Failure: Long-term Follow-up

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ABSTRACT

Introduction and objectives: Tako-tsubo syndrome produces a variable degree of transient left ventricular dysfunction. Our objective was to determine the short- and long-term prognosis of this syndrome, the incidence of and risk factors for the development of heart failure, and the influence on heart failure on the long-term outcome in our patient population.
Methods: We prospectively recorded the clinical features and events during the hospital stay and follow-up of 100 patients with tako-tsubo syndrome. The risk factors for heart failure during hospital stay, considered as Killip class≥II, were assessed.
Results: Most of the patients were women (89%), with a mean age of 68 years. The distribution according to Killip class was: Killip I, 70 patients; Killip II, 15; Killip III, 5; and Killip IV, 10. Cardiovascular risk factors, including diabetes, were common in the overall group, but were more so in the heart failure cohort. The left ventricular ejection fraction was lower in the heart failure group (51% vs 42%; $P<.01$). There were no differences in preadmission medications or biomarkers of necrosis. Over a median follow-up of 1380 days, the incidence of events reported during the hospital stay and long-term follow-up, both for death and the combined endpoints, was higher in the heart failure cohort.
Conclusions: Although the prognosis in tako-tsubo syndrome is usually good, heart failure occurs quite frequently, mainly in patients with a greater number of comorbidities and poorer previous functional class. Moreover, heart failure is associated with a higher number of early and late adverse events. The overall long-term prognosis is good.

Síndrome de *tako-tsubo* e insuficiencia cardiaca: seguimiento a largo plazo

Palabras clave:
Síndrome de *tako-tsubo*
Apical ballooning
Pronóstico
Insuficiencia cardiaca

RESUMEN

Introducción y objetivos: El síndrome de *tako-tsubo* induce un grado variable de disfunción ventricular izquierda transitoria. Nuestro objetivo es determinar su pronóstico a corto y largo plazo y valorar la incidencia de insuficiencia cardiaca en este ámbito, los factores de riesgo relacionados con su desarrollo y su influencia en la evolución posterior en nuestro medio.
Métodos: Se recogieron prospectivamente las características clínicas y los eventos durante el ingreso hospitalario y durante el seguimiento de 100 pacientes con síndrome de *tako-tsubo*. Se llevó a cabo un análisis estratificado en relación con el desarrollo de insuficiencia cardiaca (Killip ≥ II) durante el ingreso índice.
Resultados: El 89% eran mujeres (media de edad, 68 años); 70 pacientes cursaban sin insuficiencia cardiaca; 15 estaban en Killip II; 5, en Killip III, y 10, en Killip IV. Los factores de riesgo cardiovascular —diabetes incluida— eran frecuentes, pero más en el grupo con insuficiencia cardiaca. La fracción de eyección del ventrículo izquierdo era inferior en aquellos con insuficiencia cardiaca al ingreso (el 51 frente al 42%; $p < 0,01$). No se detectaron diferencias en cuanto a los tratamientos previos al ingreso ni en los biomarcadores de necrosis. Durante una mediana de seguimiento de 1.380 días, se observaron más complicaciones intrahospitalarias y en la cohorte con insuficiencia cardiaca tanto para la variable combinada como para muerte.
Conclusiones: En el síndrome de *tako-tsubo*, la insuficiencia cardiaca es frecuente; se observa sobre todo en pacientes con más comorbilidades y peores clases funcionales previas y se asocia a más eventos

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adversos, tanto durante el ingreso como en el seguimiento a largo plazo. El pronóstico a largo plazo es generalmente bueno.

Abbreviations

HF: heart failure
TKS: tako-tsubo syndrome

INTRODUCTION

Tako-tsubo syndrome (TKS), also known as "broken heart syndrome", transient apical dyskinesia, or apical ballooning, is an apparently temporary cardiomyopathy that produces a variable degree of ventricular dysfunction, predominantly in the left ventricle, and is, by definition, reversible. Occasionally related to stressful situations, in approximately half of all cases, this entity is also included in the broader group of stress cardiomyopathy.[1,2]

The most striking feature of TKS is the absence of significant stenosis on coronary angiogram, although, clinically and electrocardiographically, its characteristics resemble those of acute coronary syndrome, including elevation of biomarkers of necrosis.[3,4]

This syndrome was described in the early 1990s in a brief series of Japanese cases,[5,6] and was initially considered to be a rare disease; some years later, probably due to dissemination of knowledge on this entity, the existence of TKS has been confirmed with increasing frequency on every continent and in every race.[7,8] In our environment, both typical and atypical forms have been reported,[9,10] and TSK has even been diagnosed in patients with previous ischemic heart disease.[11]

Although benign and transient, paradoxically, TSK is not free of serious complications, mostly occurring during the hospital stay, in the acute phase; the most common adverse event is the development of variable degrees of heart failure (HF).[4,12]

The purpose of this study was to determine the incidence of and risk factors for the development of HF in a case series with a final diagnosis of TKS in our environment, as well as to carry out a long-term follow-up. In addition, we analyzed the possible influence of this in-hospital complication on the disease course during the follow-up of these patients.

METHODS

Patient Inclusion, Study, and Follow-up

In the present study, the clinical, electrocardiographic, analytical, and characteristics were carefully and prospectively recorded, as were the events occurring during the hospital stay and follow-up of 100 consecutive patients with a diagnosis of TKS, according to the Mayo criteria[1] (modified in 2008). All patients had to meet all of the following inclusion criteria and none of the exclusion criteria:

- Clinical presentation resembling that of acute coronary syndrome.
- Transient segmental left ventricular dysfunction, without significant stenosis (≥50%) or plaque rupture as the potential cause of the findings of coronary angiography performed during the hospital stay. Echocardiography and coronary angiography were carried out in all patients during the acute phase, with median delays of 0 and 1 day, respectively. Subsequent complete ventricular recovery had to be be verified by means of imaging studies (with at least a complete echocardiogram).
- New electrocardiographic abnormalities (either ST segment elevation or depression, or repolarization abnormalities expressed by deeply inverted T waves) and elevated biomarkers (especially troponin in all patients).
- Exclusion of: pheochromocytoma, intracranial involvement, previously known ischemic heart disease, severe organic valve disease, or prosthetic heart valves.

The participants were recruited from 2002 to 2010 inclusive. A *post hoc* (retrospective) analysis was carried out to assess the development of HF based on a dichotomous approach considering a Killip class of II or higher during the initial hospital stay to indicate the presence of HF. The degree of HF was evaluated according to the well-known Killip-Kimball classification, which establishes 4 groups: class I, no clinical or radiological signs of HF; class II, evident dyspnea, pulmonary crackles, elevated central venous pressure, and third heart sound; class III, pulmonary edema demonstrated by chest X-ray; and class IV, evidence of cardiogenic shock, according to the criteria of the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial.[13]

All patients were treated according to the criteria of their attending physician, which was adjusted to the norms indicated by the clinical practice guidelines in force at each time point. The imaging study employed to verify full recovery was a complete echocardiogram. In some cases, the patient underwent additional noninvasive imaging studies (for example, cardiac magnetic resonance).

Since hospital discharge, follow-up contact has been made with all of the patients at least once a year, either in the cardiology unit or by telephone interview. During this period, the following situations were considered adverse events: all-cause readmission to the cardiology unit, recurrence of pain, and all-cause mortality, and, as the combined endpoint (a major adverse cardiac event), the development of any of these events.

Statistical Analysis

The variables are expressed as mean (standard deviation), percentages, or median [interquartile range], depending on the quality and distribution of the variable. The tests employed to compare the variables (χ^2, Student's t, ANOVA, etc.) were selected in accordance with these characteristics. The independent predictors of HF were estimated using a binary logistic regression model (multivariate analysis). The variables included in these multivariate models were selected on the basis of the results obtained in the univariate analyses, and are described in the text. The goodness of fit of the models was estimated by the Hosmer-Lemeshow test. The occurrence of events during follow-up was studied using the Kaplan-Meier technique, and the differences in