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Clinical and echocardiographic course in tako-tsubo cardiomyopathy: Long-term follow-up from a multicenter study

Javier Matabuena-Gomez-Limon, MD [a,1,2], Sebastian Isaza-Arana, MD [a,1,2], Juan Robledo-Carmona, MD [b,2], Edgar Alania-Torres, MD [c,2], Javier Torres-Llergo, MD [c,2], Juan Ignacio Valle-Racero, BSN [a,2], Francisco Lopez-Pardo, MD [a,2], Angel Martinez-Martinez, MD, PhD [a,2], Manuel Jimenez-Navarro, MD, PhD [b,2], Jose Angel Urbano-Moral, MD, PhD [a,*,2]

[a] Cardiovascular Imaging Laboratory and Biomedicine Institute of Seville (IBiS), Virgen del Rocio University Hospital, Seville, Spain
[b] Unit of Clinical Management of Cardiology, Biomedicine Institute of Malaga (IBIMA), Cardiovascular Research Network (RIC) and University of Malaga, Virgen de la Victoria University Hospital, Malaga, Spain
[c] Non-invasive Cardiology Department, Cardiology Division, Jaen Medical Center, Jaen, Spain

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ABSTRACT

Objectives: To jointly describe clinical characteristics, ECG and echocardiographic findings, and adverse cardiovascular events in patients with tako-tsubo cardiomyopathy (TC) in the long-term.
Methods: Longitudinal multicenter study including retrospective analysis of clinical and ECG data, and follow-up evaluation with clinical interview, electrocardiogram and echocardiogram.
Results: Data from 66 cases of TC were available for analysis of clinical and adverse cardiovascular events, and 56 of them completed the follow-up visit including electrocardiogram and echocardiogram. Most patients (97%) were asymptomatic or oligosymptomatic (NYHA I [58%] or II [39%], respectively) at follow-up (median time: 3.7 [1.8–6.6] years). The vast majority of individual QRS complex and repolarization abnormalities had disappeared (87% with no ECG abnormalities at follow-up). On echocardiography, left ventricular ejection fraction was ≥50% in all patients (mean: 63 ± 6%). Wall motion abnormalities were observed in 4 patients (7%; 3 with apical wall motion abnormalities and 1 with mild global hypokinesia). Long-term outcomes were as follows: 4 deaths (6%), 2 cardiovascular and 2 non-cardiovascular; no atrial fibrillation development; no stroke events; 5 acute recurrence events of TC (8%). Globally, 57 patients (86%) had a clinical course free from adverse cardiovascular events.
Conclusions: After a long period following the admission event, patients discharged from TC remain asymptomatic or minimally symptomatic, and feature a low prevalence of both ECG and left ventricular wall motion abnormalities; moreover, the latter lead to a very mild impairment of ejection fraction. Among cardiovascular adverse events, recurrence of the TC event appears to play the most significant role.

1. Introduction

The suspicion, diagnosis and management of tako-tsubo cardiomyopathy (TC) have an evolving course. An acute phase with symptoms and ECG findings that, along with elevated biomarkers, generally lead to the examination of coronary arteries and ventriculography [1,2]. Secondly, a subacute phase where ECG and echocardiographic monitoring gain importance [2]. In most TC cases, left ventricular (LV) systolic function impairment involves, in a supposedly reversible manner, the LV mid-cavity and apical regions [1,3]. Furthermore, TC regional myocardial involvement is not circumscribed to ventricular segmentation determined by the distribution of coronary arteries [4]. These morphofunctional facets primarily detected by angiographic and echocardiographic examinations allow, together with a clinical presentation mimicking an acute coronary syndrome, for the suspicion and diagnosis of TC [1,5]. Lastly, a chronic or out-of-hospital phase, with a wide range of between-center possible approaches, from long-term clinical follow-up through stop of outpatient evaluation.

A number of reasons might explain the physicians' variability in the approach to TC outpatient follow-up. Its etiology is not well defined [1]. Some cases have been reported in association with stress tests [6–7],

* Corresponding author at: Cardiovascular Imaging Laboratory and Biomedicine Institute of Seville (IBiS), Virgen del Rocio University Hospital, Ave. Manuel Siurot, Seville 41013, Spain.
E-mail address: jaurbanomoral@gmail.com (J.A. Urbano-Moral).
[1] Contributed equally to this paper.
[2] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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suggesting a sudden increase in catecholamine blood levels - induced by sympathetic nervous system overstimulation - as the underlying mechanism in TC cases with a stressful event as a trigger [2]. The fact that this catecholamine rise is limited in time may make some think that long-term follow-up is not necessary. Secondly, the concept of this condition's reversibility [2]. This general assumption, beyond myocardium detailed regional analysis or tissue characterization - i.e., by myocardial deformation techniques [8] or cardiovascular magnetic resonance [9] in acute and subacute phases -, does not help solve the issue of when and how these patients should be reevaluated after discharge.

Thus, it has largely been accepted that TC prognosis is generally benign. However, investigations on mortality and morbidity have regained interest in recent years as physicians have a broader knowledge of the disease. In-hospital mortality in TC has been reported to be lower (2.0–2.4%), as high (4.1%), or higher (8.6%) than that for acute coronary syndrome [10–13]. On the other hand, there is even more controversy on long-term prognosis of TC, which may currently be considered in debate. Recent publications indicate, by retrospective analysis, that there appears to be a complete recovery of ventricular function in less than two thirds of TC cases, but with analysis of only the first months after the event [14]. There is a lack of studies including together clinical aspects, cardiovascular imaging reevaluation (i.e., LV global or regional wall motion) and prognostic outcomes at a long follow-up period after the TC event. The aim of this study was to jointly describe clinical characteristics, ECG and echocardiographic findings, and adverse cardiovascular events in patients diagnosed with TC in the long-term.

2. Methods

2.1. Study population

This was a longitudinal multicenter study including retrospective analysis of clinical and ECG data by medical chart review, and follow-up evaluation with clinical interview, electrocardiogram and echocardiogram. A search in the admission electronic registry (since January 1st 2006 through December 31st 2014) of the Cardiology Department at three tertiary care hospitals was performed. The search terms “tako-tsubo syndrome”, “apical ballooning syndrome”, “stress cardiomyopathy”, “tako-tsubo cardiomyopathy” or “transient apical dyskinesia” were used as a condition to be included in the diagnosis of the hospital discharge report. The only inclusion criterion was an established diagnosis of TC according to previously reported diagnostic criteria [15] (which implies all patients underwent coronary angiography). This was accomplished by medical chart review of both clinical course and reports of the tests performed (i.e., coronary angiography, ventriculography, echocardiography, cardiovascular magnetic resonance, ECG, or biomarker data). Exclusion criteria were as follows: i) moderate or severe valve stenosis or regurgitation at the time of TC diagnosis; ii) moderate or severe coronary artery disease (lumen stenosis ≥50%) considered to be responsible for the clinical syndrome (angiographic evidence of coronary thrombosis and/or acute plaque rupture, plus regional wall motion abnormalities that could be explained by the vascular distribution of the compromised artery); iii) history of myocardial infarction. The study was approved by the corresponding institutions' human research committees; study participants who agreed to have a follow-up evaluation provided informed consent.

2.2. Index event

Demographic and clinical data (presence of a trigger stressful event and New York Heart Association [NYHA] functional class) related to the admission due to TC were collected by medical chart review. Besides, ECG abnormalities, both at admission and at discharge, were analyzed from the test reports.

2.3. Follow-up

New York Heart Association functional class was reevaluated either at a follow-up visit to a cardiology outpatient clinic or by contacting patients or relatives by phone calls. Patients attending the follow-up clinic also had a 12-lead electrocardiogram and a transthoracic echocardiogram. Electrocardiographic abnormalities, mainly bradyarrhythmias, and depolarization/repolarization findings, were described - i.e., ST-segment deviation was defined as an elevation or depression of at least 1 mm in amplitude in more than two contiguous leads, and T wave inversion was defined as inversions in at least three contiguous leads [16]. All ECG data were transferred to the study core-lab (one of the three participating centers) for analysis by one single, blinded reader for results purposes. Echocardiographic studies were performed with the commercially available scanner Philips iE33 Ultrasound (Philips; Best, The Netherlands); standard 2-dimensional and Doppler echocardiography was performed with the S5-1 transducer (Philips; Best, The Netherlands), according to the recommendations of the American Society of Echocardiography [17] and stored in the Xcelera database system (Philips; Best, The Netherlands). All echocardiographic data were transferred to the study core-lab for analysis by one single, blinded reader for results purposes.

2.4. Adverse cardiovascular events

Incidence of adverse cardiovascular events - atrial fibrillation, stroke, TC recurrence and death - occurring from one month following the date of the index event were investigated by medical chart review, patient interview at the follow-up visit, and by phone calls when necessary. Diagnosis of recurrence required a similar clinical event fulfilling the diagnostic criteria, including repeat coronary angiography.

2.5. Statistical analysis

Categorical variables are expressed as frequencies (percentages). Continuous variables were tested for normality (by using Kolmogorov-Smirnov test) and are shown as mean ± standard deviation or median [quartile 1-quartile 3], as appropriate. The Kappa statistic was used to describe the level of agreement between echocardiographic readings from two independent readers regarding the presence versus absence of LV wall motion abnormalities in the follow-up echocardiogram of all patients. The statistical analysis was performed using IBM SPSS Statistics 20.0 (IBM Corp.; Armonk, New York, United States).

3. Results

By the search in the admission electronic registry from the three participating centers 90 patients previously admitted with diagnosis of TC were identified (Fig. 1). All 90 patients met the diagnostic criteria for TC. None had significant valve disease or coronary artery disease at the time of the TC event. Hospital admission of all patients was due to TC with no other causes as concurrent comorbidities. Ten patients declined participation in the prospective electrocardiographic and echocardiographic evaluation (retrospective data - i.e., by medical chart review and phone calls - were available from five of them) and 20 could not be located (retrospective data - i.e., by medical chart review - were available from one of them). Eventually, data from 66 cases of TC were available for analysis of clinical and adverse cardiovascular events, and 56 of those (4 patients had died at the time of follow-up) completed the follow-up visit including electrocardiogram and echocardiogram.

Table 1 shows clinical characteristics of the study population related to the TC index event. Information about the presence or absence of a stressful trigger was available from 51 patients (Fig. 2). Electrocardiographic findings at different time points are depicted in Fig. 3. At discharge, over half of the patients (55%) were in NYHA functional class I, and almost all the remaining (44%) were in class II; only one patient had minimal exertion dyspnea (class III).

3.1. Clinical, electrocardiographic and echocardiographic follow-up

Median follow-up time was 3.7 [1.8–6.6] years. Most patients (97%) were asymptomatic or oligosymptomatic (NYHA functional class I or II, respectively) at the time of follow-up (Fig. 4). One patient worsened from NYHA functional class II to III, and together with another patient, who maintained his functional status since discharge, were the only ones in functional class III. In these two patients signs and symptoms consistent with heart failure were verified (among them congestion); neither of them complained about symptoms suggesting paroxysmal atrial fibrillation nor had any other system comorbidity; NT-proBNP levels (not included in the study design) showed levels >200 pg/mL, and their echocardiogram showed no wall motion abnormalities (ejection fraction 65% and 67%, respectively) but dilated left atrium, and E/e′ ratio > 15. There were no patients in NYHA functional class IV. At follow-up, the vast majority of individual QRS complex and repolarization abnormalities had disappeared (87% with no ECG abnormalities) (Fig. 3.C). Bradyarrhythmias or bundle branch blocks were not detected on electrocardiogram, although one patient had had a permanent pacemaker implantation. On echocardiography, ejection fraction was ≥50% in all patients (mean ejection fraction: 63 ± 6%). Globally, LV wall motion abnormalities were observed in 4 of 56 patients (7%). Three of them