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Clinical profile and in-hospital outcome of Caucasian patients with takotsubo syndrome and right ventricular involvement

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ABSTRACT

Aim: To determine the prevalence, clinical characteristics, in-hospital course and determinants of major adverse events in a cohort of Caucasian patients with Takotsubo syndrome (TTS) and right ventricular involvement (RVi), regardless of left ventricular variant forms.

Methods and results: The study population consisted of 424 patients (mean age 69.1 ± 11.5 years; female 92.2%) with a diagnosis of TTS divided into two groups according to the presence or absence of RVi. RVi patients (n = 57; 13.4%) showed a higher prevalence of comorbidities, especially respiratory diseases (p = 0.011), and a higher Charlson comorbidity index (CCI; p = 0.006) than non-RVi patients. In-hospital major adverse events (acute heart failure, cardiogenic shock and death) occurred more frequently in RVi patients (p < 0.001). Heart rate and CCI, along with the echocardiographic parameters of wall motion score index, E/e' ratio, tricuspid annular plane systolic excursion (TAPSE) and systolic pulmonary artery pressure (sPAP) were associated with adverse in-hospital outcome. At multivariate analysis, CCI (HR: 1.871; 95% CI: 1.202–2.912; p = 0.006), sPAP (HR: 1.059; 95% CI: 1.016–1.104; p = 0.007) and TAPSE (HR: 0.728; 95% CI: 0.619–0.855; p < 0.001) were independent correlates of the composite outcome in patients with RVi.

Conclusion: Patients with RVi are characterized by distinct clinical profile and should undergo closely clinical and echocardiographic monitoring. The presence of echocardiographic signs of right ventricular failure along with substantial comorbidities burden identify a cohort at higher risk of in-hospital major adverse cardiovascular events.

Abbreviations: BNP, brain natriuretic peptide; CCI, Charlson comorbidity index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FAC, fractional area change; HR, hazard ratio; iLVEDV, indexed LV end-diastolic volume; iLVESV, indexed LV end-systolic volume; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; RV, right ventricular; RVi, right ventricular involvement; sPAP, systolic pulmonary artery pressure; STE, ST-segment elevation; TAPSE, tricuspid annular plane systolic excursion; TIN, Tako-tsubo Italian Network; TR, tricuspid regurgitation; TTS, Takotsubo syndrome; WMSI, wall motion score index.

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1. Introduction

Takotsubo syndrome (TTS) is an intriguing pathology characterized by transient and reversible myocardial stunning involving the left ventricle in different variant forms [1–6]. However, besides the three different morphologic patterns of left ventricular (LV) myocardial dysfunction (i.e., apical – the most frequent –, midventricular and basal ballooning), also right ventricular involvement (RVi) has been described (i.e., biventricular ballooning) [7–11]. Although long-term prognosis of TTS is generally considered favorable [12], several threatening complications, particularly acute heart failure, can occur in the early phase in a consistent proportion of patients [2,13]. Advanced age, hypotension at hospital admission, severe LV systolic and diastolic dysfunction and significant mitral regurgitation (MR) are all conditions associated with an increased risk of early adverse events [13,14]. Recently, a Japanese study has reported a higher incidence of acute heart failure and in-hospital mortality in patients with biventricular ballooning [15]. In TTS patients with LV apical ballooning, a significant independent impact of RVi on in-hospital outcome was also demonstrated by our group [16]. The aim of this study was to describe the clinical profile and in-hospital course of a large Caucasian population of TTS patients with RVi and either LV apical ballooning or other variant forms. Determinants of major adverse events were also investigated.

2. Methods

2.1. Data collection

The data of 424 consecutive patients enrolled in the Takotsubo Italian Network (TIN) were reviewed. Patients were enrolled from twelve Italian referral cardiac centers in part retrospectively (from January 2002, to December 2004; n = 53, 27.8%) and partially prospectively (from January, 2005, to June 2014, n = 137, 72.2%). Eleven hospitals contributed by providing data from a minimum of 11 to a maximum of 32 patients for each center. The revised TIN diagnostic criteria subsequently incorporated by the Task force on TTS of the Heart Failure Association of the European Society of Cardiology were adopted as inclusion criteria [17,18]:

1. Typical transient LVwall motion abnormalities extending beyond a single epicardial, vascular distribution with complete functional normalization within 6 weeks,
2. Absence of potentially culprit coronary stenosis, or angiographic evidence of acute plaque rupture, dissection, thrombosis or spasm,
3. New and dynamic ST-segment abnormalities or T-wave inversion as well as new onset of transient or permanent left bundle branch block,
4. Mild increase in myocardial injury markers,
5. Clinical and/or instrumental exclusion of myocarditis.

Patient with aborted infarction, lised thrombus, Prinzmetal angina or type II-IV myocardial injury (according to the third universal definition of myocardial infarction) as well as those presenting more than 24 h after symptom onset were excluded. [19] Clinical variables were recorded on a standardized form that included information on patient demographics, signs and symptoms at presentation, medical history, trigger events (emotional or physical), ST-segment changes on admission, and clinical observations during hospitalization (including major and minor cardiac events) identified as previously described [15]. Preexisting comorbidities were recorded and Charlson comorbidity index (CCI) was calculated [20]. Blood samples were collected every 6 h to measure troponin I concentrations in the acute phase (24–48 h from admission), and collection continued until a peak value was observed. Daily brain natriuretic peptide (BNP) levels were also recorded during the acute phase. All patients underwent coronary angiography and left ventriculography within 24 h of symptom onset to confirm TTS diagnosis. Major adverse events were a composite of acute heart failure (pulmonary edema), cardiogenic shock and in-hospital mortality defined as previously described [14]. The study was approved by the local ethics committee. All patients gave consent for the use of their medical records for research purposes.

2.2. Echocardiography and right ventricular assessment

Standard transthoracic two-dimensional echocardiography was performed within 6 h of hospital admission, before coronary angiography. A commercially available cardiac ultrasonography system with a 2.5 to 4.5-MHz phased-array transducer with second harmonic capability was used for complete two-dimensional Doppler echocardiography. All examinations were performed by observers blinded to clinical data. All echocardiographic images were digitally recorded and reviewed by 2 expert readers (R.C. and F.R.). Three cardiac cycles from the apical 4- and 2-chamber views and the parasternal short-axis view at the level of the mitral valve and papillary muscles were stored in cine-loop format for off-line analysis. LV ejection fraction (LVEF), wall motion score index (WMSI), E/e' ratio, MR and LV outflow tract obstruction (LVOTO) were evaluated as previously described [13]. According to the localization of regional wall motion abnormalities in the apex, mid or basal segments, the morphological pattern of the left ventricle was defined as typical apical, mid-ventricular or basal ballooning, respectively. RVi has been defined as firstly described by Elesber et al. [9], RV wall motion was evaluated qualitatively by visual assessment, in parasternal long-axis, apical and subcostal 4-chamber views [9]. The echo transducer was adjusted to the level of the RV chamber to achieve optimal visualization of RV size and endocardial borders. RVi was identified by the detection of severe akinesia or dyskinesia, localized exclusively at the apical and/or mid RV segments (biventricular ballooning), with sparing of the basal segments ("reverse McConnell's sign") (Fig. 1) [9,21]. Patients with only RV segmental hypokinesia were excluded. As indices of RV systolic function, tricuspid annular plane systolic excursion (TAPSE) and fractional area change (FAC) were measured as previously described [13]. Tricuspid regurgitation (TR) severity was assessed semiquantitatively by color flow and spectral Doppler. A regurgitant jet area ≤ 5 cm, between 6–10 cm and >10 cm was considered to estimate mild, moderate and severe TR, respectively [22]. By using continuous wave Doppler, TR peak velocity recorded from any view was used to determine systolic pulmonary artery pressure (sPAP) with the simplified Bernoulli equation [23]. Mean right atrial pressure was estimated by evaluating inferior vena cava dilation and respiratory excursion according to standard method [24]. The study population was then divided into two groups with and without RVi. To evaluate the predictors of major adverse events in RVi patients, the RVi group was further divided into two subgroups, based on the presence or absence of major adverse events during hospitalization.

2.3. Statistical analysis

Normally distributed continuous variables were reported as mean ± standard deviation, whereas non-normally distributed continuous variables were presented as median and interquartile range. Categorical variables were reported as number of patients (%). Continuous variables were then compared with independent sample Student's t-test or Wilcoxon-Mann–Whitney test, and categorical variables were compared with chi-square statistic or Fisher's exact test, when appropriate. The associations of selected variables with major adverse events were assessed with the Cox proportional hazards model using univariate and stepwise multivariate procedures. A significance of 0.05 was required for a variable to be included in the multivariate model, whereas 0.1 was the cut-off value for exclusion. Hazard ratios (HR) with 95% confidence intervals (CIs) were estimated. Selected variables identified during univariate analysis (heart rate, CCI, WMSI, E/e' ratio, TAPSE and sPAP) were then entered in the multivariate analysis logistic regression model to determine independent predictors of major adverse events. The Hosmer-Lemeshow statistic was used to assess the goodness-of-fit of the logistic regression model. A p-value <0.05 was considered