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Impact of persistent ST elevation on outcome in patients with Takotsubo syndrome. Results from the GErman Italian STress Cardiomyopathy (GEIST) registry

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ABSTRACT

Background: Potential predictors of clinical complications of Takotsubo syndrome (TTS) are poorly known. Persistent ST-segment elevation (PSTE) may have an impact on outcome similar as previously reported in acute coronary syndrome. The aim of this study was to assess the prevalence and prognostic relevance of PSTE in patients with TTS.

Methods: Two-hundred-sixty-nine consecutive patients were enrolled in an international multicenter registry. PSTE was defined as the documentation of ST-elevation at least for the first 48 h of hospitalization. Long-term mortality was evaluated in median 1.9 years after the acute event.

Results: PSTE was found in 52 TTS patients (19%). Patients with PSTE were characterized by higher admission levels of troponin-I (23 ± 12 vs 8 ± 49 ng/L, $p < 0.001$), experienced a longer hospitalization (10 ± 5 vs 8 ± 3 days, $p = 0.02$) and a higher rate of in-hospital complications (31% vs 17% $p = 0.03$).

At multivariate analysis including PSTE, age, male sex, admission ejection fraction, PSTE (odds ratio [OR] 4.2; 95% confidence interval [CI] 1.4–13; $p = 0.01$), age (OR 1.05; 95%CI 1.00–1.10; $p = 0.03$) and admission ejection fraction (OR 0.93; 95%CI 0.87–0.99; $p = 0.02$) were independent predictors of in-hospital complications. At long-term follow-up no significant differences in terms of mortality were observed between patients with and without PSTE (19% vs 15%; $p = 0.5$). However, PSTE was a predictor of major cardiac adverse events (MACE) at follow-up (HR 2.32, 95% CI 1.02–5.31, p 0.045).

Conclusions: In TTS patients, PSTE is a common finding, represents an independent predictor of in-hospital complications and could be associated with MACE at follow-up.

1. Introduction

Takotsubo syndrome (TTS) is a form of acute heart failure with transient ventricular dysfunction affecting mostly postmenopausal women after either a physical or an emotional stressor. Several pathogenetic mechanisms have been hypothesized (e.g. coronary spasm, catecholamine induced myocardial stunning and/or toxicity or microcirculatory dysfunction) [1,2]. Rule out electrocardiography (ECG) algorithms have been proposed to distinguish TTS from acute coronary syndrome (ACS) on the basis of ST-segment elevation (STE), however with a very low sensitivity and negative predictive value [3]. Therefore, coronary angiography is still essential for a final diagnosis of TTS. Several recently published studies clearly demonstrate that TTS is associated with a substantial risk of in-hospital complications and considerable short- and long-term mortality rates [4,5].

During acute myocardial infarction, the presence of persistent ST-segment elevation (PSTE) after both percutaneous and pharmacological revascularization is strongly associated with complications and a poor prognosis [6]. Less is known on the prognostic role of PSTE in patients with TTS. The aim of the present study was therefore to evaluate

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the prognostic value of PSTE at short- and long-term follow-up among patients with TTS.

2. Methods

2.1. Study design and population

The study group included 269 consecutive patients with TTS who were enrolled in a multicenter-international registry (GErman and Italian STress Cardiomyopathy [GEIST] registry) involving four institutions (Ospedali Riuniti, University of Foggia – Cardiology Department, Apulia, Italy; "Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo, Apulia, Italy; Santa Maria degli Angeli Hospital, Putignano, Apulia, Italy; University of Leipzig – Heart Center, Leipzig, Germany). The entire study population fulfilled the TTS diagnostic criteria: (a) transient hypokinesis, akinesis, or dyskinesis of the left ventricular (LV) apical and/or midventricular or basal segments extending beyond a single epicardial vessel distribution territory; (b) absence of significant obstructive coronary artery disease explaining the extent of wall motion abnormalities and absence of acute plaque rupture on coronary angiography; (c) new ECG abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin levels; and (d) absence of pheochromocytoma and myocarditis [7,8]. Furthermore, cardiac magnetic resonance imaging was performed at one institution (University of Leipzig – Heart Center, Germany) in patients without contraindications to confirm the diagnosis [9]. All patients underwent clinical examination and baseline characteristics were recorded. Complete recovery of systolic LV function within 6 months after the acute event was documented in all patients.

2.2. Electrocardiogram analysis

Twelve lead ECGs were routinely recorded at admission and after 48 h (recording speed of 25 mm/s and amplification of 10 mm/mV). Patients with time lags between hospitalization and ECG recording >3 h and/or time between with symptoms onset and ECG recording >6 h were excluded from the study.

ST-segment elevation (STE) was defined as shift from the J point in at least two contiguous leads ≥0.1 mV in all leads, except in V2–V3 where ≥0.15 mV was used both in males and in females [10]. If the J point was not easily identifiable, as in most cases, the subsequent TP segment (indicating the isoelectric line) was conventionally employed as reference marker [11]. The ECG data were analyzed independently by two operators in a blinded manner.

2.3. Definition of persistent ST-elevation

PSTE was defined as inadequate resolution of STE within 48 h from admission. The peak ST-segment level was measured on the admission ECG and follow-up ECG 48 h after admission. Inadequate resolution of STE after 48 h and consequently PSTE was defined as ≤50% resolution of peak STE.

2.4. Clinical examination and echocardiography

All patients underwent clinical examination. Age, gender, medical history and kind of stressors were recorded. A two-dimensional Doppler echocardiographic examination was performed on admission and serially according to clinical condition for assessment of LV wall motion abnormalities and LV thrombi. The left ventricular ejection fraction (LVEF) was calculated biplane using the Simpson method from the apical four-chamber and two-chamber view [12].

2.5. Blood tests

Blood tests were obtained by venipuncture in order to measure circulating levels of cardiac troponin-I and NT-pro-BNP at admission and serially according to clinical condition. The upper limit of normal for apparently healthy persons (95th percentile) was 150 pg/ml for NT-pro-BNP and <0.5 ng/ml for troponin I.

2.6. Follow-up and definition of outcome

In-hospital complications included death, cardiogenic shock, pulmonary edema and LV thrombus. Pulmonary edema was considered in case of respiratory distress and pulmonary rales due to pulmonary congestion, as confirmed by chest radiography, a respiratory rate of >20 breaths per minute, and an arterial hydrogenion concentration of >45 nmol/l (pH <7.35) [13].

Cardiogenic shock was considered present if a patient had a systolic blood pressure of <90 mm Hg for >30 min. Moreover, the patient had to exhibit clinical signs of pulmonary congestion and impaired organ perfusion, defined as at least one of the following: (a) altered mental status; (b) cold, clammy skin and extremities; (c) oliguria (≤30 ml per hour); or (d) arterial lactate level >2 mmol/l [14].

Major cardiac adverse events (MACE) considered at follow-up were total mortality (cardiovascular and non), TTS recurrence and re-hospitalization for heart failure or cardiac arrhythmia. Long-term outcome was assessed during regular outpatient visits or via telephone contact with patients, relatives and treating physicians. All events were verified via medical records and evaluated by a clinical event committee.

2.7. Statistical analysis

Continuous variables were reported as mean ± standard deviation, and categorical variables were expressed as proportions; groups were compared with paired, unpaired *t*-test or χ^2 test.

Logistic regression analysis was used to calculate odds ratios (OR) with 95% confidence intervals (CI) for the incidence of adverse events during hospitalization. Kaplan–Meier plots and Log-rank test were used to analyze event-free survival at short- and long-term follow-up.

Multivariate analysis was used to correct results for principal confounders. Cox regression analysis was used to calculate hazard ratio with 95% CI. Variables significant at univariate analysis or significant predictors of complications in other studies were included in multivariate analysis.

A *p*-value <0.05 was considered as statistically significant.

Table 1
Baseline clinical, echocardiographic and laboratory features of the study population. LVEF = left ventricular ejection fraction; adm. = admission; Std.Dev. = standard deviation; TNi=troponin I; STE = ST segment elevation.

	Population	*N* = 269	Persistent STE	*N* = 52	No persistent STE	*N* = 217	
	Mean	Std. dev.	Mean	Std. dev.	Mean	Std. dev.	p
Age, years	72	12	73	±13	72	±12	0.78
Male sex	13%		13%		13%		0.91
Hypertension	77%		77%		78%		0.89
Diabetes	26%		25%		27%		0.78
Dyslipidemia	31%		37%		31%		0.40
Smoker	17%		23%		15%		0.17
COPD	16%		16%		16%		0.98
Neurological disorders	16%		24%		14%		0.24
Emotional stress	26%		25%		27%		0.80
Physical stress	44%		44%		44%		0.99
Hospital stay, days	8	3.5	10	±5	8	± 3	**0.01**
Admission LVEF, %	39	9	39	7	39	10	0.83
Discharge LVEF %	50	8	48	7	50	7	0.09
Apical ballooning	82%		87%		82%		0.39
Mid ballooning	17%		13%		17%		0.58
Basal ballooning	1%		0		1%		0.62
ECG features at admission							
ST elevation	45%		100%		35%		**0.01**
Long QT	34%		8%		39%		**0.01**
Negative T waves	53%		44%		55%		0.31
NTproBNP adm. pg/ml	12,627	12,849	13,964	8721	12,055	13,886	0.58
TNi adm. ng/ml	4,8	18.1	23.5	12	8	49	**0.01**

Bold entries statistically significant p values.

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