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Prevalence and prognostic relevance of atrial fibrillation in patients with Takotsubo syndrome

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ABSTRACT

Background: Takotsubo syndrome (TTS) is associated with a considerable risk of complications during the acute phase and substantial long-term mortality rates. Concomitant atrial fibrillation may have an impact on outcome in these patients. Aim of this study was to assess the prevalence and prognostic relevance of atrial fibrillation in TTS.
Methods: We performed an international, multicenter study including 387 TTS patients consecutively enrolled at 3 centers. Atrial fibrillation was defined as known history before admission or documented episodes during hospital stay. Long-term mortality was evaluated in median 2.9 years after the acute event.
Results: Atrial fibrillation was found in 97 TTS patients (25.1%) and was associated with older age ($p < 0.01$), less emotional triggers ($p = 0.03$), higher incidence of cardiogenic shock ($p < 0.01$), lower left ventricular ejection fraction ($p < 0.01$), and a prolonged hospital stay ($p < 0.01$). Determinants of atrial fibrillation at admission ($n = 34$ patients; 9.0%) in multivariate logistic regression analysis were age ($p = 0.001$) and cardiogenic shock ($p = 0.013$). Long-term mortality was significantly higher in TTS patients with as compared to patients without atrial fibrillation (35.2% versus 15.3%; hazard ratio 3.02, 95% confidence interval 1.90–4.78; $p < 0.001$). In multivariate Cox regression analysis atrial fibrillation was identified as an independent determinant of outcome even after adjustment for clinical variables, left ventricular functional parameters (ballooning pattern, ejection fraction), and cardiogenic shock.
Conclusions: In TTS patients, atrial fibrillation is frequent and associated with increased long-term mortality rates. Furthermore, our study identifies atrial fibrillation as an independent predictor of outcome and a potential tool for risk stratification in TTS.

1. Introduction

During the last decades, Takotsubo syndrome (TTS) emerged as an increasingly recognized form of acute heart failure and an important differential diagnosis in patients with suspected acute coronary syndrome [1–3]. The transient character of the circumscribed left ventricular (LV) contraction abnormalities and the absence of irreversible myocardial damage initially led to the assumption of a favorable prognosis of TTS patients [4]. However, meanwhile several studies demonstrated a substantial risk of complications and considerable mortality rates during and after acute TTS presentation [5–7]. Consequently, efforts were directed to identify determinants of outcome and develop risk stratification models in order to optimize management strategies and potentially avoid complications and improve prognosis. Factors associated with adverse outcome include age, male sex, diabetes mellitus, physical stressful triggers, cardiogenic shock, lower LV ejection fraction, and arrhythmias [7–14]. In addition, recently published data suggest atrial fibrillation as a prognostic factor for short- and long-term mortality [15]. However, the retrospective, single-center design and the small study population are obvious limitations of this investigation. Therefore, the aim of the present study was to assess the prevalence and prognostic relevance of atrial fibrillation in a large, multicenter, international cohort of patients with TTS.

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Table 1
Baseline clinical characteristics.

Variable	All patients (n = 387)	Atrial fibrillation (n = 97)	No atrial fibrillation (n = 290)	p
Age (years)	74 (66, 79)	78 (73, 83)	72 (63, 78)	<**0.01**
Male sex	40 (10.3)	12 (12.4)	28 (9.7)	0.45
Cardiovascular risk factors				
Current smoking	76 (19.6)	16 (16.5)	60 (20.7)	0.37
Hypertension	309 (79.8)	82 (84.5)	227 (78.3)	0.18
Hypercholesterolemia	130 (33.6)	29 (29.9)	101 (34.8)	0.37
Diabetes mellitus	89 (23.0)	28 (28.9)	61 (21.0)	0.11
Days of hospitalization	6 (4, 9)	8 (4, 13)	6 (4, 8)	<**0.01**
Stressful event*	256 (66.1)	57 (58.8)	199 (68.6)	0.08
Emotional	95 (24.5)	16 (16.5)	79 (27.2)	**0.03**
Physical	164 (42.4)	41 (42.3)	123 (42.4)	0.98
Ballooning pattern†				
Apical	298 (77.0)	84 (86.6)	214 (73.8)	<**0.01**
Midventricular	84 (21.7)	13 (13.4)	71 (24.5)	**0.02**
Basal	4 (1.0)	–	4 (1.4)	0.25
Cardiogenic shock	42 (10.9)	22 (22.7)	20 (6.9)	<**0.01**
LV ejection fraction (%)	40 (35, 48)	36 (31, 45)	42 (35, 49)	<**0.01**

Data are presented as number (percentage) of patients and median (interquartile range). p-Values were calculated for the comparison between TTS patients with and without atrial fibrillation. Numbers in bold type indicate a significant difference.
CK = creatine kinase; LV = left ventricular.
* 3 patients exhibited both a physical and an emotional trigger.
† One patient exhibited isolated right ventricular ballooning.

2. Methods

2.1. Study design and population

This international, multicenter study included 387 TTS patients consecutively enrolled at 3 centers: University Heart Center Lübeck, Germany (n = 108), University of Leipzig – Heart Center, Germany (n = 178), and University of Foggia – Cardiology Department, Italy (n = 101). All patients fulfilled the TTS diagnostic criteria: (a) transient hypokinesis, akinesis, or dyskinesis of the 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 electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin levels; and (d) absence of pheochromocytoma and myocarditis [1,3]. Furthermore, cardiac magnetic resonance imaging was performed at 1 institution (University of Leipzig – Heart Center) in patients without contraindications to confirm the diagnosis [4]. Complete recovery of systolic LV function within 6 months after the acute event was documented in all patients.

Atrial fibrillation was defined as known history of atrial fibrillation before admission for TTS or documented episodes of atrial fibrillation during the hospital stay. All TTS patients were monitored at coronary care units for at least 24 h and underwent serial 12-lead electrocardiography (ECG). Additional Holter monitoring was performed according to the treating physicians' discretion. All available documents were analyzed by 2 independent, blinded investigators. Any disagreements were resolved by consensus. Long-term outcome was assessed during regular outpatient visits or via telephone contact with the patients, relatives, and treating physicians. Deaths were classified cardiovascular, non-cardiovascular, or unknown if further information regarding the circumstances of death were not available. All events were verified via medical records and evaluated by a clinical events committee.

The study was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki. Patients provided written informed consent.

2.2. Statistical analysis

Categorical variables are presented as number (percentage) of patients and were compared with the Chi-square test. Continuous variables were assessed for normal distribution with the Shapiro-Wilk test. Since all continuous data were non-normally distributed, they are reported as median (interquartile range) and were compared with the Mann-Whitney *U* test.

Baseline characteristics were compared between TTS patients with and without atrial fibrillation. Determinants of atrial fibrillation at admission were assessed by univariate and stepwise multivariate logistic regression analysis. Variables with a significant p-value in univariate analysis were included in multivariate testing. Long-term mortality was determined according to the presence of atrial fibrillation using Chi-square test, Kaplan-Meier method, and log-rank testing. Univariate and stepwise multivariate Cox regression analysis was performed to obtain hazard ratios (HR) and 95% confidence intervals (CI). Multivariate testing included only variables with a significant p-value in univariate analysis and comprised 3 models: model 1 included atrial fibrillation and clinical variables, LV functional parameters (ballooning pattern, ejection fraction) were added in model 2, and model 3 additionally contained the presence of cardiogenic shock.

Statistical analyses were performed with SPSS (version 17.0; SPSS Inc., Chicago, IL). A 2-sided p-value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Study population

The present analysis is based on 387 patients with confirmed TTS. The clinical characteristics reflect a typical TTS population of primarily postmenopausal women (Table 1). A stressful trigger was identified in about two thirds of patients and apical ballooning was the predominant contraction pattern. LV function recovered completely in all patients. Long-term follow-up data were available in 372 patients (96.1%) after a median 2.9 years (interquartile range 1.3, 4.9) and revealed an all-cause mortality of 20.2%.

3.2. Incidence, clinical characteristics and determinants of atrial fibrillation in TTS

A history of atrial fibrillation (n = 69, 17.8%) or new episodes of atrial fibrillation during the hospital stay (n = 28, 7.2%) were observed in 97 patients (25.1%). These patients were significantly older (p < 0.01) and had less emotional triggers (p = 0.03) compared to patients without atrial fibrillation (Table 1). Moreover, atrial fibrillation was associated with a higher incidence of cardiogenic

Table 2
Predictors of atrial fibrillation at admission in univariate and multivariate logistic regression analysis.

Variable	Univariate		Multivariate	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Age (years)	1.08 (1.03–1.12)	<**0.001**	1.08 (1.03–1.13)	**0.001**
Male sex	0.47 (0.11–2.03)	0.311		
Current smoking	0.77 (0.31–1.93)	0.583		
Hypertension	1.34 (0.54–3.33)	0.531		
Hypercholesterolemia	0.94 (0.46–1.95)	0.875		
Diabetes mellitus	2.23 (1.10–4.55)	**0.027**	–	n.s.
Stressful trigger	0.64 (0.32–1.28)	0.207		
Physical trigger	0.71 (0.35–1.45)	0.350		
Emotional trigger	0.83 (0.37–1.89)	0.664		
Apical ballooning	1.61 (0.65–3.98)	0.307		
Initial LV ejection fraction (%)	0.96 (0.93–1.00)	**0.028**	–	n.s.
Cardiogenic shock	3.09 (1.34–7.10)	**0.008**	3.01 (1.26–7.23)	**0.013**

Numbers in bold type indicate a predictor of atrial fibrillation at admission.
CI = confidence interval; CK = creatine kinase; LV = left ventricular; n.s. = not significant.

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