Happy Heart Syndrome: Frequency, Characteristics and Outcome of Takotsubo Syndrome triggered by positive Life Events. Results from the multicenter international GEIST registry.

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ABSTRACT

Background The association with a preceding stressful event, either of physical or emotional nature, is a characteristic feature of Takotsubo syndrome (TTS). Negative emotions prior to an episode of TTS are common and led to the popular term 'broken heart syndrome'. In contrast, TTS triggered by pleasant emotions ('happy heart syndrome') is rare and scarcely investigated.

Objectives The aim of the present study was to analyze the frequency, clinical characteristics and prognostic implications of positive emotional stressors in the large, international, multicenter GErman, Italian and Spanish Takotsubo (GEIST) registry.

Methods Patients enrolled in the GEIST registry were categorized according to their preceding stressors. The present analysis compared TTS patients with pleasant events to those with negative emotional stressors.

Results Of 2,482 patients in the registry, 910 patients (36.7%) exhibited an emotional trigger consisting of 873 'broken hearts' (95.9%) and 37 'happy hearts' (4.1%). Consequently, the prevalence of pleasant emotional triggers was 1.5% of all TTS cases. Patients with 'happy heart syndrome' were more frequently male (18.9% versus 5.0%; $p<0.001$) and had a higher prevalence of atypical ballooning patterns (27.0% versus 12.5%; $p=0.010$) compared to TTS patients with negative preceding events. In-hospital complications including death, pulmonary edema, cardiogenic shock, or stroke (8.1% versus 12.3%; $p=0.449$) and long-term mortality rates (2.7% versus 8.8%; $p=0.196$) were similar in 'happy hearts' and 'broken hearts'.

Conclusions 'Happy heart syndrome' is a rare type of TTS characterized by a higher prevalence of male patients and atypical, non-apical ballooning compared to cases with negative emotional stressors. Despite similar short- and long-term outcome in

our study, additional data are needed to explore whether numerically lower events rates in ‘happy hearts’ turn statistically significant in a larger sample size.

Keywords Takotsubo syndrome; Broken heart syndrome; Happy heart syndrome; Outcome

CONDENSED ABSTRACT

‘Happy heart syndrome’ is a rare form of Takotsubo syndrome (TTS) triggered by positive life events. The incidence in the multicenter, international GEIST registry was 1.5% of all cases and 4.1% of emotionally triggered TTS. Compared to patients with negative emotional triggers, ‘happy hearts’ were more frequently male and had a higher prevalence of atypical, non-apical ballooning. In-hospital complications and long-term mortality rates were not significantly different in patients with positive and negative emotional stressors, despite numerically lower event rates in patients with ‘happy heart syndrome’.

ABBREVIATIONS

GEIST Registry	German-Italian-Spanish Takotsubo Registry
InterTAK Registry	International Takotsubo Registry
IQR	Interquartile range
LV	Left ventricular
TTS	Takotsubo syndrome

INTRODUCTION

Over the last decades, the awareness of Takotsubo syndrome (TTS) as an important cause of acute heart failure related to a typical pattern of transient left ventricular (LV) contraction abnormalities has increased significantly. A rising number of scientific publications focused on TTS and revealed several unique characteristics of this fascinating but complex clinical condition. Among these are episodes of physical or emotional stress which precede the occurrence of TTS in about two-thirds of patients [1-3]. Negative emotional triggers such as fear, grief, or interpersonal conflicts were associated with TTS soon after its first description leading to the popular term 'broken heart syndrome' [4]. However, more recent research revealed that TTS can also be provoked by pleasant emotional life events in some patients, which was named 'happy heart syndrome' [5]. Physical triggers are usually more common than emotional stress factors and include heavy physical activities and medical conditions or procedures [2]. Of note, the precipitating stress may also comprise a combination of physical and emotional issues (e.g. panic attack because of a medical procedure). On the other hand, spontaneous TTS in the absence of identifiable triggers can be observed in about one-third of cases [6].

Previously published registry data provide detailed summaries of the specific triggering events in populations with TTS and their association with demographic and clinical features (e.g. higher prevalence of physical triggers in male patients) [2-5]. Outcome data consistently show increased rates of adverse events in secondary TTS triggered by physical events compared to emotionally triggered TTS or cases without evident triggering factors [6, 7]. Among patients with emotional stressors, a similar prognosis was reported in patients with 'broken' and 'happy heart syndrome' [5]. However, evidence regarding TTS following positive life events is derived from only

one cohort (n=20 patients) [5] and particularly the clinical course and prognostic implications are not sufficiently covered by current literature. Therefore, the aim of this study was to comprehensively investigate patients with ‘happy heart syndrome’ in the large, international German-Italian-Spanish Takotsubo (GEIST) Registry.

MATERIAL AND METHODS

Study population, design and definitions

The international, multicenter GEIST Registry (ClinicalTrials.gov Identifier: NCT04361994) currently contains 2,492 data sets from 49 participating study centers in Germany (3 institutions, 488 patients), Italy (10 ~~8~~ institutions, 971 patients) and Spain (38 institutions, 1,033 patients). Patient enrollment is performed partially retrospective and prospective (from 2017 onwards). Inclusion in the registry requires a definite diagnosis of TTS according to current consensus criteria, which were the Mayo Clinic diagnostic criteria [8] until 2016 and the European consensus criteria [9] thereafter. The registry collects demographic data, cardiovascular risk factors, comorbidities, preceding stressful triggers, clinical presentation, electrocardiographic findings, echocardiographic parameters, medications, in-hospital complications and long-term outcome. The ballooning patterns were defined as apical, midventricular, basal, or focal, as previously described in detail [2].

For the present analysis, the study population was stratified by the preceding stressors, which were classified as “physical”, “emotional” or “no identifiable trigger” according to the nature of the episodes. Emotional triggers were further categorized as ‘broken hearts’ in case of negative and ‘happy hearts’ in case of positive emotional events, which was the main focus of this study. Differentiation of the respective triggers was performed as previously suggested [3, 5]. Patients with a potential combination of physical and emotional events, which could not be clearly separated (e.g. based on the temporal proximity to the occurrence of TTS), and patients with unavailable information regarding triggering events were excluded from the analysis (n=10).

In-hospital complications were defined as death, pulmonary edema, cardiogenic shock, and stroke. Pulmonary edema was considered to be present in cases of respiratory distress and pulmonary rales due to pulmonary congestion, as confirmed by chest radiography, a respiratory rate of more than 20 breaths per minute, and an arterial pH <7.35 (arterial hydrogen ion concentration greater than 45 nmol/L) [10]. Cardiogenic shock required a systolic blood pressure lower than 90 mmHg for more than 30 minutes and clinical signs of pulmonary congestion and impaired organ perfusion, defined as at least 1 of the following: (a) altered mental status; (b) cold, clammy skin and extremities; (c) oliguria (urine output ≤30 mL per hour); or (d) arterial lactate level of 2 mmol/L or more [11]. Stroke was confirmed by a neurologist and defined as ischemic or hemorrhagic stroke with an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction according to the updated stroke criteria [12]. In addition, all-cause mortality was assessed during long-term follow-up (mean 3.4 years). These data were acquired thorough regular outpatient visits, medical records and telephone interviews with the patients, relatives and treating physicians.

The study was conducted according to Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent before inclusion in the registry, which meets the requirements of the respective local ethics committees.

Statistical analysis

Categorical variables are presented as number and percentage of patients and were compared with the Chi-square test. Continuous variables were non-normally distributed in Shapiro-Wilk testing and are therefore expressed as median with interquartile range (IQR). Between-group differences were assessed with the non-parametric Mann-Whitney U test. Kaplan-Meier plots and log-rank testing were used to compare long-term mortality rates between groups. Independent predictors for in-

hospital complications were assessed in univariate and stepwise multivariable logistic regression analysis including all baseline clinical characteristics. Only significant variables in univariate analysis were included in multivariable testing. Results are presented as odds ratios with 95% confidence intervals. Likewise, univariate and stepwise multivariable Cox regression models were used to determine independent predictors of long-term mortality, which are presented as hazard ratios with 95% confidence intervals.

This study focused on patients with emotionally triggered TTS, which were dichotomized in those with negative events ('broken heart') and those with pleasant events ('happy heart').

All analyses were performed with MedCalc version 19.6.4. (MedCalc Software, Ostend, Belgium) and SPSS version 27.0 (IBM, Armonk, New York, USA). A 2-tailed *p*-value <0.05 was considered statistically significant.

RESULTS

A total of 2,482 patients with confirmed TTS were considered for this study. Of these, 855 patients (34.4%) had a physical, 910 patients (36.7%) an emotional, and 717 patients (28.9%) no identifiable trigger before the episode of TTS. Emotionally triggered TTS was mainly related to negative events (n=873, 95.9%) whereas 37 patients (4.1%) experienced 'happy heart syndrome'. The exact pleasant triggers are provided in Table 1.

The baseline clinical characteristics of TTS patients with negative and pleasant emotional triggers are presented in Table 2. Both groups consisted predominantly of postmenopausal women. However, the number of male patients was significantly higher in 'happy' compared to 'broken heart syndrome' (18.9% versus 5.0%; p<0.001). Cardiovascular risk factors and comorbidities did not show relevant

differences. Diabetes mellitus was numerically more prevalent among patients with negative triggers without reaching statistical significance. Clinical presentation, ECG changes and LV ejection fraction were also similar between the groups. The LV contraction patterns, however, showed a significantly higher number of patients with atypical, non-apical LV ballooning, particularly midventricular ballooning, in patients with 'happy heart syndrome' (p=0.046; Table 2).

In-hospital complications and long-term outcome did not show statistically significant differences in patients with 'happy' and 'broken heart syndrome' despite numerically lower event rates among TTS patients with pleasant triggers (Table 3, Figure 1). In regression analysis, positive preceding events were not identified as predictors for the in-hospital clinical course (p=0.452) or long-term outcome (p=0.270) among patients with emotionally triggered TTS.

DISCUSSION

The data presented here are derived from one of largest TTS registries worldwide including the largest cohort of patients with 'happy heart syndrome' in current literature. The main results of our study are that (a) joyful triggers are rare and account for <5% of emotionally triggered TTS and <2% of all cases; (b) patients with 'happy heart syndrome' are more frequently male and exhibit a higher prevalence of atypical, non-apical ballooning compared to patients with 'broken heart syndrome'; and (c) in-hospital complications and long-term mortality are similar in cases with positive and negative emotional events, despite numerically lower event rates in patients with 'happy heart syndrome'.

Increasing research efforts during the last decade yielded a solid knowledge of the nature of TTS including the variety and clinical implications of triggering events. The initial assumption that TTS is primarily triggered by negative emotional stress was

corrected by multiple subsequent studies showing that the syndrome can also be triggered by physical events or occur without an evident stressor[1-7]. Although physical triggers are generally considered to be more frequent, the ratio of physically triggered, emotionally triggered and unprovoked TTS in large registries including GEIST is approximately 1:1:1 [2]. More recently, TTS has also been linked to pleasant emotional events ('happy heart syndrome') in an analysis from the International Takotsubo (InterTAK) Registry [5]. Our study expands the knowledge regarding this subgroup of TTS patients by adding almost twice as much cases as previously reported. The prevalence of 'happy heart syndrome' in the InterTAK registry was 4.1% of patients with emotionally triggered TTS and 1.1% of all cases and, therefore, almost identical to the here reported numbers from the GEIST registry (4.1% and 1.5%, respectively) [5]. Consequently, the occurrence of TTS seems much more likely after negative compared to positive emotional events. Although still incompletely understood, a brain-heart interaction with sympathetic overdrive and catecholamine excess are most likely key factors in the pathophysiology of TTS [1, 13]. Nevertheless, everybody is exposed to stressors in daily life, but only a few people develop TTS, and most of these individuals were exposed to stressful events before without an episode of TTS. This fact points to an individual susceptibility/vulnerability and further implies that a certain stress level is required to trigger the occurrence of TTS. The markedly divergent incidences of 'broken' and 'happy heart syndrome' suggest that negative stressors excess this threshold more easily while positive emotions require more potent stimuli to provoke a sufficiently high release of catecholamines. The role of the central nervous system in the pathogenesis of various cardiovascular diseases is generally accepted [14] and different effects following positive and negative emotions have also been reported in several studies. However, the exact molecular pathways are insufficiently understood and consequently pathophysiological considerations

regarding the effects of positive/negative triggers in TTS remain hypothetical [5, 15]. Likewise, the observed differences in clinical characteristics are difficult to explain. While the increased proportion of male patients with 'happy heart syndrome' is a novel observation, the higher number of patients with midventricular ballooning has been consistently reported in the analysis from the InterTAK registry [5]. Differences in the sympathetic innervation of the heart with an apical-basal gradient of sympathetic nerve endings and ß1/ß2-adrenoceptor density in combination with a switch from the positive inotropic G_S to the negative inotropic G_I pathway in case of supraphysiological levels of epinephrine could explain the characteristic apical ballooning in patients with TTS [1, 16, 17]. The variability of regional ß-adrenoceptor distribution, e.g. with a downregulated expression after sympathetic stimulation, might explain atypical variants of TTS and alternating ballooning patterns in patients with recurrent TTS episodes [16, 18]. Therefore, a variable extent and/or time course of the catecholamine release as well as a differential myocardial response according to pleasant/negative emotions could explain the divergent ballooning patterns and incidences, which again remains speculative and has to be proven in experimental studies.

The prognosis following TTS is meanwhile well studied. Patients show a substantial risk of acute cardiovascular complications and considerable long-term mortality rates mostly attributable to non-cardiovascular comorbidities [19, 20]. Moreover, several studies investigated the clinical course according to the triggering events and emphasize the usefulness of the preceding stressors as potent markers for risk stratification [6, 7, 21]. Our study is the first to provide systemic data regarding acute complications and long-term prognosis in patients with 'happy heart syndrome'. The observed event rates were even lower than in the 'broken heart' group albeit the statistical significance level was not reached. Lower short-term adverse events in

patients with atypical TTS variants, as previously suggested [22], or an impact of the dynamics of catecholamine release are among potential explanations for these findings. Nevertheless, although being the largest cohort of patients with 'happy heart syndrome', the sample size is probably still too small to derive valid outcome data, which leads to the limitations of the presented registry trial.

The observational nature of the study has some inherent limitations, such as missing values in single patients or unmeasured confounders that could impact the results. Furthermore, the length of clinical follow-up varied considerably between patients and participating centers. The sample size of patients with pleasant triggers is still small, which might have prevented statistical significance in clinically relevant findings. Although our study emphasizes some interesting aspects in patients with happy heart syndrome, it cannot provide insights into the exact pathophysiological mechanisms involved. These aspects have to be addressed in future, experimental studies.

CONCLUSIONS

This international, multicenter registry study reports the largest cohort of patients with 'happy heart syndrome' in current literature and expands our knowledge concerning this rare disease. Compared to cases with negative preceding stressor, patients with pleasant triggers were more frequently male and had a higher prevalence of atypical, non-apical ballooning. In-hospital complications and long-term mortality rates were similar among 'broken hearts' and 'happy hearts'. However, additional data are required to evaluate whether the numerically lower event rates in TTS triggered by positive life events turn significant in larger patient cohorts.

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CONFLICTS OF INTEREST

None

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Table 1 Happy Heart triggers

Birthday party / family celebration (n=7)
Meeting friends / Date (n=4)
Wedding (n=3)
Receiving good news (n=2)
Artistic performance in public (joyful, n=2)
Emotional family reunion (n=2)
During/after relaxing spa visit (n=2)
Favorite soccer team won game
Emotional speech at a friend's birthday party
Vacation in Paris (pleasant anticipation)
New Year's Eve
Taking care of grandson for the first time (joyful)
Family member recovered from lymphoma
During holidays (sitting on a boat, watching fireworks)
Baptism of the grandson
During a music concert with pleasant emotional memories
After winning Bingo
Watching son on television (inauguration ceremony of Olympic games)
Preparing Christmas dinner (pleasant anticipation)
Resolution of family problems
During gardening (joyful)
After birth of grandchild

Table 2 Baseline clinical characteristics

Variable	Broken Heart (n=873)	Happy Heart (n=37)	p
Age, years	70 (61, 77)	69 (62, 78)	0.661
Male sex	44/873 (5.0)	7/37 (18.9)	**<0.001**
Cardiovascular risk factors			
Hypertension	574/869 (66.1)	25/37 (67.6)	0.849
Diabetes mellitus	147/868 (16.9)	2/37 (5.4)	0.064
Hypercholesterolemia	364/826 (44.1)	16/34 (47.1)	0.731
Current Smoking	142/868 (16.4)	5/37 (13.5)	0.646
Obesity *	99/748 (13.2)	4/36 (11.1)	0.713
Comorbidity			
Coronary artery disease	90/762 (11.8)	3/36 (8.3)	0.525
Atrial fibrillation	89/775 (11.5)	5/36 (13.9)	0.660
Malignancy	79/761 (10.4)	5/28 (17.9)	0.208
Pulmonary disease	83/777 (10.7)	3/31 (9.7)	0.859
Neurologic disorder	89/689 (12.9)	5/28 (17.9)	0.448
Psychiatric disorder	109/717 (15.2)	2/27 (7.4)	0.265
Clinical presentation			
Chest pain	604/786 (76.8)	26/32 (81.2)	0.562
Dyspnea	214/786 (27.2)	11/32 (34.4)	0.375
Killip class at admission			0.576
1	708/873 (81.1)	33/37 (89.2)	
2	67/873 (7.7)	1/37 (2.7)	
3	50/873 (5.7)	2/37 (5.4)	
4	48/873 (5.5)	1/37 (2.7)	
ST-segment change	633/774 (81.8)	25/37 (67.6)	0.872
Ballooning pattern†			**0.046**
Apical	763/872 (87.5)	27/37 (73.0)	
Midventricular	91/872 (10.4)	8/37 (21.6)	
Basal	14/872 (1.6)	2/37 (5.4)	
Focal	4/872 (0.5)	-	
Initial LV-EF (%)	40 (35, 45)	43 (31, 45)	0.277
Follow-up LV-EF (%)	60 (55, 65)	60 (56, 64)	0.670
Discharge medication			
Aspirin	467/754 (61.9)	18/37 (48.6)	0.105
Dual antiplatelet therapy	49/516 (9.5)	4/35 (11.4)	0.708
Oral anticoagulation	95/661 (14.4)	9/37 (24.3)	0.098
Beta blocker	561/722 (77.7)	28/37 (75.7)	0.773
ACE inhibitor / AT-R blocker	562/765 (73.5)	28/37 (75.7)	0.766
Aldosterone antagonist	33/517 (6.4)	2/35 (5.7)	0.875
Diuretic	153/504 (30.4)	5/32 (15.6)	0.077
Statin	429/753 (57.0)	23/37 (62.2)	0.534

Data are presented as number (percentage) of patients and median (interquartile range).

P-values were calculated for the comparison between 'happy' and 'broken heart syndrome'. Numbers in bold type indicate a significant difference.

* defined as body mass index ≥30 kg/m²

† One patient exhibited isolated right ventricular ballooning.

ACE = Angiotensin converting enzyme; AT-R = Angiotensin receptor; LV-EF = left ventricular ejection fraction.

Table 3 In-hospital complications and long-term outcome

Variable	Broken Heart (n=873)	Happy Heart (n=37)	p
In-hospital complication*	107/873 (12.3)	3/37 (8.1)	0.449
In-Hospital death	11/798 (1.4)	0/37 (0)	0.473
Pulmonary edema	53/873 (6.3)	2/37 (5.4)	0.868
Cardiogenic shock	48/873 (5.5)	1/37 (2.7)	0.461
Catecholamine therapy	42/763 (5.5)	1/37 (2.7)	0.461
Mechanical circulatory support	13/821 (1.6)	1/37 (2.7)	0.599
Stroke	7/758 (0.9)	-	0.563
Length of stay in hospital (days)	6 (4, 8)	6 (5, 9)	0.755
Long-term mortality	70/798 (8.8)	1/37 (2.7)	0.196

Data are presented as number (percentage) of patients and median (interquartile range).
P-values were calculated for the comparison between 'happy' and 'broken heart syndrome'.
*Death, cardiogenic shock, pulmonary edema, or stroke

Figure 1 Kaplan-Meier plot