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ORIGINAL ARTICLE

Cumulative Impact of Stressful Life Events on the Development of Takotsubo Cardiomyopathy

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Abstract

Background The role of stressful life events in the onset of Takotsubo cardiomyopathy (TC) is unclear.

Purpose This study sought to examine associations between type, timing, and number of stressful life events and onset of TC.

Methods A case-control study conducted among consecutive incident female TC cases and myocardial infarction (MI) controls admitted to two emergency departments in New England. Healthy female controls (HC) were recruited from a volunteers' registry. Information about the timing, type, and number of triggers during the 6 months preceding hospitalization was systematically collected using the PERI Life Events Scale about 1 month post-discharge. Group differences were evaluated using ANOVA, chi-square, and Kruskal-Wallis statistics. Generalized linear models were used to adjust for confounding variables.

Results Between March 2013 and October 2015, 107 women were enrolled (45 TC, 32 MI, and 30 HC). Specific stressful events (death of a relative or close friend ($p = 0.006$); illness or injury to a relative or close friend ($p = 0.001$) were more prevalent in TC cases than MI and HC controls. The onset of TC was associated with exposure to multiple stressful life events during the 6 months preceding the index hospitalization ($p < 0.001$) but not with exposure to an acute, recent event ($p = 0.96$).

Conclusions TC onset was associated with specific life events (death or illness to close relative or friend) and with the number of stressful life events occurring in the 6 months preceding hospitalization. These findings suggest that grief and cumulative stress could play a major role in the onset of TC.

Keywords Cardiomyopathy · Stress · Heart failure · Women's health

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Introduction

Takotsubo cardiomyopathy (TC) is a syndrome primarily diagnosed in post-menopausal women characterized by transient left ventricular dysfunction and electrocardiographic abnormalities in the absence of significant coronary artery disease [1, 2]. Although the literature consistently reports that TC is often associated with an acute, emotionally intense event, up to one-third of TC cases have no identifiable precipitant [3], and the prevalence of documented emotional triggers varies considerably across studies (27.0 to 70.0%) [1, 4–6]. Moreover, methodologic differences in research design, timing of assessment, and the use of retrospectively collected data may contribute to the heterogeneity among studies, making conclusions difficult to interpret.

Collectively, current findings raise a number of questions about the role of acute emotional triggers in the onset of TC and suggest that other mechanisms are potentially involved in the development of this complex condition. For example, repeated exposure to stressful life events, and the accompanying

behavioral and psychological reactions associated with chronic stress have been implicated in the pathogenesis of cardiovascular disease in women [7]. Whether exposure to consecutive stressful life events confers increased risk for developing TC is unknown, but evidence of shared etiologic mechanisms involving exaggerated sympathetic activation and elevated catecholamine levels make such an association plausible [8]. It is also unclear whether the type and the nature of the emotional stressors are associated with onset of TC.

The purpose of this study was to examine whether the type, number, and timing of stressful life events are associated with the onset of TC.

Methods

This was a secondary analysis from a case-control study (i.e., enrolling incident cases and controls) of risk factors for the onset of TC among post-menopausal women. A detailed description of the study design and enrollment procedures has been published elsewhere [9]. In brief, to be enrolled, participants had to be female, aged 21 and older, proficient in English and to have access to a telephone. Cases were recruited among consecutive women presenting at emergency departments of three large medical centers in the New England region from March 2013 to October 2015 with a diagnosis of TC meeting Mayo Clinic criteria [10]. Controls were women newly admitted with a diagnosis of acute myocardial infarction (MI) at the same centers and a group of healthy female controls (HC) recruited from a registry of research volunteers at the University of Massachusetts Medical School. Eligibility criteria were confirmed by a trained physician abstractor blinded to the study outcomes. Interviewers and study participants were blinded to the study outcomes and to participants' case or control status. Informed consent and authorization to access medical records was obtained from all participants. Study protocols and procedures were approved by the institutional review board at each participating site.

Measures

Information about life events was systematically collected using the PERI Life Events Scale, [11] a 15-item scale adapted for use in the current study, administered during a telephone interview scheduled approximately 1 month after hospital discharge (TC and MI). Women were asked to indicate the type and approximate date of life events they had encountered in the 6 months prior to the index hospitalization. "Acute" stressful events were defined as any event occurring within the month preceding the index hospitalization. This definition is consistent with clinical criteria used to characterize acute emotional reactions in acute stress disorders. [12] Sociodemographic information was collected using standardized questionnaires. Medical history, including history of anxiety and depression, was obtained from the medical record by a trained physician abstractor.

Statistical Analysis

Group differences were evaluated using ANOVA for continuous data and chi-square statistics for categorical outcomes. Kruskal-Wallis test was used to compare the mean total number of stressful life events during the 6 months across groups. Generalized multivariate linear models were used to adjust for variables associated with the outcomes of interest (i.e., anxiety) [13]. Since TC and MI occur more frequently among post-menopausal women, and HC women had a similar age distribution, we did not anticipate substantial confounding by age, and in fact, age was not associated with the outcomes. For all estimates, p values or 95% confidence intervals were calculated. All analyses were performed with SPSS version 22.0 (SPSS Inc., Chicago, Illinois).

Results

Between March 2013 and October 2015, 107 women were enrolled (45 TC, 32 MI, and 30 HC). Demographic characteristics were similar across groups with the exception of income and education, which were higher in the HC group. A history of anxiety disorders was also more prevalent among TC cases than MI and HC controls. Clinical characteristics at admission were similar except for expected differences in peak troponin levels and systolic blood pressure (Table 1).

In regard to the type of event (Table 2), TC women were significantly more likely to report the recent death of a spouse, close friend, or relative compared to MI or HC during the previous 6 months ($p = 0.006$). Recent illness or injury to a close friend or relative was also significantly more prevalent in TC cases compared to both MI and HC ($p = 0.001$), while the prevalence of injury or illness to self did not differ between TC and MI. Financial, legal, employment difficulties, or relationship problems were similar across groups.

The mean total number of stressful life events significantly differed between groups ($p < 0.001$) with TC women reporting a greater number of prior stressful life events than MI or HC women (Table 2). TC women were more likely to endorse experiencing multiple (3 or more) stressful life events compared to MI or HC controls, whereas MI controls were more likely to report a single stressful event prior to their cardiovascular event, and HC women were more likely to report none (Fig. 1). Adjusted analyses suggested a significant association between group and mean number of events, after controlling for pre-morbid anxiety. Specifically, TC participants reported significantly more stressful life events compared to MI (TC vs. MI: beta = 0.69, SE = 0.31, $p = 0.03$) and HC controls (TC vs. HC: beta = 1.21, SE = 0.30; $p < 0.001$).

Table 1 Baseline characteristics of cases and controls*

	TC = 45	MI = 32	HC = 30	*p*†
Age (years) (mean (SD))	62.4 (10.8)	64.6 (15.3)	55.9 (12.4)	0.08
American Indian or Alaskan	1 (2%)	0	0	0.49
Asian or Pacific islander	0	0	1 (3%)	0.28
Black or African-American	0	1 (3%)	0 (0%)	0.31
Hispanic/Latino	3 (7%)	6 (19%)	3 (10%)	0.26
White (not Hispanic)	40 (91%)	25 (78%)	26 (87%)	0.28
Education				
≤High school diploma	20 (46%)	19 (59%)	3 (10%)	<.001
College or some college	23 (52%)	13 (41%)	24 (80%)	0.006
Post-graduate	1 (2%)	0	3 (10%)	0.09
Income				
Less than $35,000	23 (52%)	17 (53%)	4 (13%)	0.001
$35,000 to $74,999	9 (20%)	6 (19%)	12 (40%)	0.10
$75,000 or more	9 (21%)	6 (19%)	14 (47%)	0.02
Do not know	3 (7%)	3 (9%)	0 (0%)	0.25
Coronary risk factors				
Family history of coronary heart disease	18 (40%)	16 (50%)	0	<.001
Diabetes mellitus	8 (18%)	14 (44%)	3 (10%)	0.004
Hyperlipidemia	17 (38%)	19 (59%)	8 (27%)	0.03
Hypertension	26 (58%)	22 (69%)	5 (17%)	<.001
Body mass index (kg/m^2)	22.3 (9.7)	29.2 (7.8)	–	0.009
Ever a smoker	31 (71%)	22 (69%)	13 (45%)	0.06
Physically active‡	21 (48%)	17 (53%)	20 (69%)	0.20
Medical history				
Coronary bypass	0	2 (6%)	0	0.09
Percutaneous coronary intervention	0	3 (9%)	0	0.03
Stroke	0	2 (6%)	0	0.09
Anxiety disorder	11 (24%)	3 (9%)	0	0.007
Mood disorder	9 (20%)	7 (22%)	5 (17%)	0.87
Clinical characteristics at admission				
Systolic blood pressure (mmHg) (mean (SD))	119 (23)	130 (23)	N/A	0.04
Diastolic blood pressure (mmHg) (mean (SD))	70 (17)	75 (19)	N/A	0.24
Ejection fraction (%)	40 (10)	48 (12)	N/A	0.02
Peak CPK (IU/L) (mean (SD))	398.0 (515.8)	566.0 (367.5)	N/A	0.63
Peak troponin (ng/ml) (mean (SD))	2.9 (3.2)	6.8 (7.8)	N/A	0.01
Heart rate (bpm) (mean (SD))	91 (26)	86 (18)	N/A	0.37

*Values are *n* (%) unless otherwise indicated

† *ANOVA* or chi-square

‡Walking outdoors for at least 10 min once a week

N/A not applicable

Finally, as shown in Table 2, TC cases were not significantly more likely than MI to experience a stressful life event within 1 month prior to their index hospitalization ($p = 0.96$).

Discussion

The principal findings from this study are (1) the occurrence of TC was associated with certain life events (death, medical illness, or injury to a close friend or relative) but not with others; (2) TC was associated with the number of stressful life events during the 6 months preceding hospitalization; (3) we found that TC onset was not associated with exposure to stressful life events occurring close (1 month) to hospitalization.

The finding that certain stressful life events (e.g., bereavement, severe medical illness, or injury) were associated with TC is consistent with results of other studies [1, 5, 14]. A retrospective study by Yerasi et al. found an emotional trigger in approximately 10% of TC cases, which ranged from minor (e.g., "upset reading email") to major life events (e.g., death of a family member). A large prospective study of men and women from the International Takotsubo Registry reported the presence of an emotional trigger in 28% of TC cases, of which grief was the most frequently reported event (22%) [1]. Data from the registry were also compared to age- and sex-matched MI controls, however, differences in the prevalence of emotional triggers were not evaluated. Another study using data from the International Takotsubo Registry data examined the prevalence of pleasant and unpleasant emotional events

Table 2 Prevalence of stressful life events during the 6 months preceding the index hospitalization

Type of event†	TC (n = 44) N (%)	MI (n = 32) N (%)	HC (n = 30) N (%)	p
Death of a family member, close friend, or relative	15 (34.1%)	2 (6.3%)	4 (13.3%)	0.006
Serious illness or injury to close friend or relative	12 (27.3%)	0 (0.0%)	2 (6.7%)	0.001
Serious illness or injury to self	34 (79.1%)	25 (78.1%)	3 (10.0%)	<0.001
Financial, legal, occupational problems	8 (19.0%)	8 (25.8%)	4 (13.3%)	0.47
Relationship problems	7 (15.9%)	4 (12.5%)	3 (10.0%)	0.76
Stressful event within 1 month of admission	29 (56.9%)	22 (43.1%)	N/A	0.96
Total number of events*	2.03 (1.39)	1.25 (1.08)	0.63 (0.85)	<0.001

†Multiple stressful life events were reported by some women and were individually categorized by type of event

*Means (SD)

N/A not applicable

among 485 TC patients with an identified emotional trigger [14]. Of these, 4.0% reported a pleasant precipitating event, and 96.0% reported a negative emotional event. Though this study is the first to examine both pleasant and unpleasant emotional precipitants of TC, conclusions should be interpreted with caution as pre-conceived categories (e.g., pleasant vs. unpleasant events) may not fit individuals' emotional experiences which are often complex and potentially conflicted (e.g., death of a spouse can lead to intense sadness but also significant emotional relief if they had been suffering from prolonged illness). A possible explanation for the association between TC onset and grief or illness to close relatives is that intense grief and caregiver responsibilites may lead to decreased self-care, anxiety, and alterations in health behaviors (e.g. poor dietary and sleep habits, substance use, and poor medication adherence), which, in turn, have been implicated in the pathogenesis of cardiovascular disease in women [15, 16] and may increase risk for TC [8, 9].

Our study also found that the exposure to repeated stressful life events was associated with the onset of TC. The role of chronic stress in the onset of TC has been examined in two prior studies [6, 7]. A qualitative study conducted among postmenopausal TC women found that most women reported "feeling worn down to the bone" after exposure to chronic low-intensity stress preceding their index cardiovascular event [7]. Further, women with an identifiable trigger reported that exposure to a prolonged stressor was more psychologically "burdensome" than the acute event they experienced prior to the onset of TC. Similarly, a prospective case-control study by Delmas et al. found a significant association between chronic stress (e.g., "taking care of a dependent child or husband") and the onset of TC [6]. However, the impact of exposure to multiple stressful life events over time was not a focus of this investigation.

Our study provides further clarification on the role of cumulative stress in the onset of TC by showing a clear relationship between the number of stressful life events and TC diagnosis. This pattern was markedly different than that observed in MI and HC controls, suggesting the unique contribution of cumulative stress in the pathogenesis of TC.

Strengths

This is the first systematic study of the association between repeated stressful life events and newly diagnosed TC. If confirmed in larger and more diverse populations, the role of

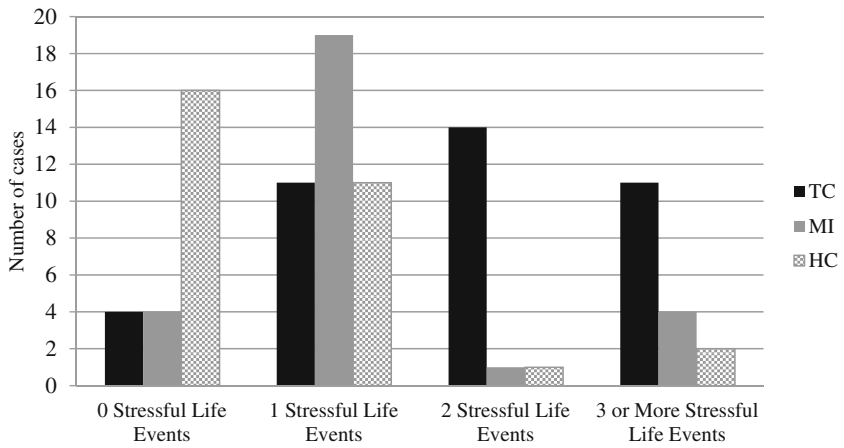

Fig. 1 Distribution of cases and controls by number of stressful life events during the 6 months preceding hospitalization

cumulative stress as a potential risk factor for TC has considerable implications for future research and clinical practice. In terms of research, whether there is a dose-response relationship between cumulative stress and the onset of TC is unknown and may provide critical insight into the pathogenesis of TC. Perceived social support, coping style, and other patient characteristics may moderate this association and should also be considered in future studies. Clinically, a chronic stress paradigm for TC provides a potential framework for intervention. Whereas recommendations to avoid stressful life events are not realistic, efforts to increase clinician attention to symptoms of chronic stress in at risk populations (e.g., postmenopausal women) may provide opportunities for early intervention and prevention.

Limitations

A number of limitations should be noted with regard to the current study. First, the small sample size and exclusive enrollment of women may limit the generalizability of study findings. However, more than 90% of TC cases are diagnosed in women so findings from the current study are likely applicable to the majority of TC cases. A second limitation is recall bias, which is common in case-control studies. Notably, interviews were conducted at least 1 month after discharge to minimize the potential effect of hospitalization-related distress on patient's recall of stressful life events, and we included a control group of women newly admitted with a diagnosis of MI. We also statistically controlled for baseline levels of anxiety, as anxious individuals have heightened perceptions of stress and are more likely to recall stressful events than individuals without a history of anxiety [17]. Third, the present study did not measure women's subjective responses (e.g., perceived stress, coping self-efficacy, and coping style) to stressful life events; these factors could play an important role in the onset of TC and should be measured in future studies. Finally, recruitment of healthy controls from a volunteer research registry may have introduced selection bias; we note, however, that most demographic and other characteristics were similar across groups.

Conclusions

In sum, our results suggest that type of stressful event and exposure to repeated stressful events, rather than temporal proximity to the event, may play a role in the onset of TC.

Further research is necessary to confirm these associations in larger and more diverse samples.

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Compliance with Ethical Standards

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Authors' Statement of Conflict of Interest and Adherence to Ethical Standards Authors Lindsey Rosman and Shira Dunsiger declare that they have no conflict of interest. Elena Salmoirago-Blotcher, Md, PhD: this work was supported by American Heart Association (Dallas, TX) award 13CRP1334001 to Dr. Elena Salmoirago-Blotcher. The AHA did not have any role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript. All procedures, including the informed consent process, were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Research Involving Human Participants and/or Animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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