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Review

Left Ventricular Ballooning Patterns in Recurrent Takotsubo Cardiomyopathy: A Systematic Review and Meta-analysis of Reported Cases

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Recurrent takotsubo cardiomyopathy (TTC) and the clinical profiles and outcomes of patients have not been fully evaluated, nor has the effect of left ventricular ballooning pattern. After searching the medical literature for reports of patients with recurrent TTC, we identified 84 articles with 101 case descriptions. We divided the cases into those with only apical left ventricular ballooning patterns at recurrence (typical, n=60), and those with at least one midventricular or basal ballooning pattern (atypical, n=41). We then compared their clinical profiles and outcomes.

The groups were similar in terms of baseline demographic characteristics, presence and types of triggers, use of heart failure medications at TTC recurrence, electrocardiographic changes at presentation, initial left ventricular ejection fractions, timespans between recurrent TTC episodes, and recovery times after each event. However, patients in the atypical group had significantly fewer severe adverse events (cardiogenic shock and cardiac arrest) than did those in the typical group, with an estimated 63% lower odds (adjusted odds ratio=0.37; 95% CI, 0.14–0.97; P=0.039). Survival to hospital discharge was statistically similar but lower in the typical group (n=53; 88.3%) than in the atypical group (n=24; 96%).

Our results suggest that left ventricular ballooning patterns influence clinical outcomes, and that outcomes are more favorable in patients with recurrent TTC who have atypical left ventricular ballooning patterns. ***(Tex Heart Inst J 2021;48(5):e207223)***

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Takotsubo cardiomyopathy (TTC) presents with various left ventricular (LV) ballooning patterns, typically in the absence of obstructive coronary artery disease, and is usually followed within days by the universal recovery of LV systolic dysfunction. The most prevalent LV ballooning pattern is the apical; less prevalent are midventricular and basal (nonapical) patterns. Isolated TTC events are diagnosed in 1.7% to 3.5% of patients who present with suspected acute coronary syndrome[1,2]; TTC recurs in only 1.5% of all cases, according to the largest meta-analysis to date.[3] Although individual case reports and small case series describe clinical profiles of patients with recurrent TTC, few data are available for cohort comparisons of various recurrent LV ballooning patterns. It is unknown whether apical and nonapical ballooning patterns in recurrent TTC identify epidemiologically distinct groups of patients. Accordingly, we analyzed data from documented cases of recurrent TTC to improve our understanding of the clinical profiles and outcomes of this at-risk patient population.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to conduct our study (Fig. 1). We searched for all listings be-

fore and through December 2018 in PubMed, Google Scholar, and Ovid Medline Complete with use of the following search phrases: (*takotsubo cardiomyopathy* OR *apical ballooning syndrome* OR *stress cardiomyopathy*) AND (*recurrence* OR *recurrent* OR *relapse*). No limits were placed on article type or publication date. Requirements for initial selection were English-language articles including adults (age, ≥18 yr). Articles were included if the diagnosis of TTC met the Mayo Clinic criteria,[4] and if details of LV ballooning patterns during initial and recurrent TTC episodes were provided. For meta-analysis, we used established definitions of the 3 predominant TTC patterns: apical, midventricular, and basal LV ballooning.[5] Myocardial ballooning patterns involving the focal LV segments and the right ventricle were excluded. At least 2 authors fully reviewed each article and extracted the data.

We collected these data: 1) article type, country, and year of publication; 2) each patient's sex, age, and age at first TTC episode; 3) number and pattern of each recurrence, and time between episodes; 4) clinical characteristics (presence of chest pain or of emotional or physical stresses during each episode); 5) use of angiotensin-converting enzyme inhibitors (ACEIs) or β-blockers at the time of recurrence; 6) cardiac troponin elevation; 7) electrocardiographic (ECG) ST-segment changes, T-wave changes, or QTc interval prolongation at hospital admission; 8) LV ejection fraction (LVEF) obtained from echocardiograms at presentation, and the time to LVEF recovery after each episode); 9) hemodynamic profiles (shock necessitating vasopressor therapy or cardiac arrest necessitating advanced cardiopulmonary life support); and 10) survival to discharge from the hospital.

When data were missing, we asked for help from corresponding authors who could be reached by e-mail. We reviewed original ECGs when they were available, to corroborate the findings. We used LVEF values stated in each article and evaluated them for accuracy by reviewing online videos (when available) that showed LV contractility. Ultimately, the percentages of reports that were missing data were as follows: medications, 37.1%; echocardiographic findings, 23.8%; cardiac troponin elevation, 21.8%; hemodynamic profiles, 15.3%; ECG changes at admission, 12.4%; clinical characteristics, 9.2%; and survival to hospital discharge, 1%.

For the primary analysis, we divided cases into typical and atypical. The typical group presented exclusively with the apical LV ballooning pattern during their initial and recurrent TTC episodes; the atypical group had at least one nonapical LV ballooning pattern (midventricular or basal) during any TTC episode.

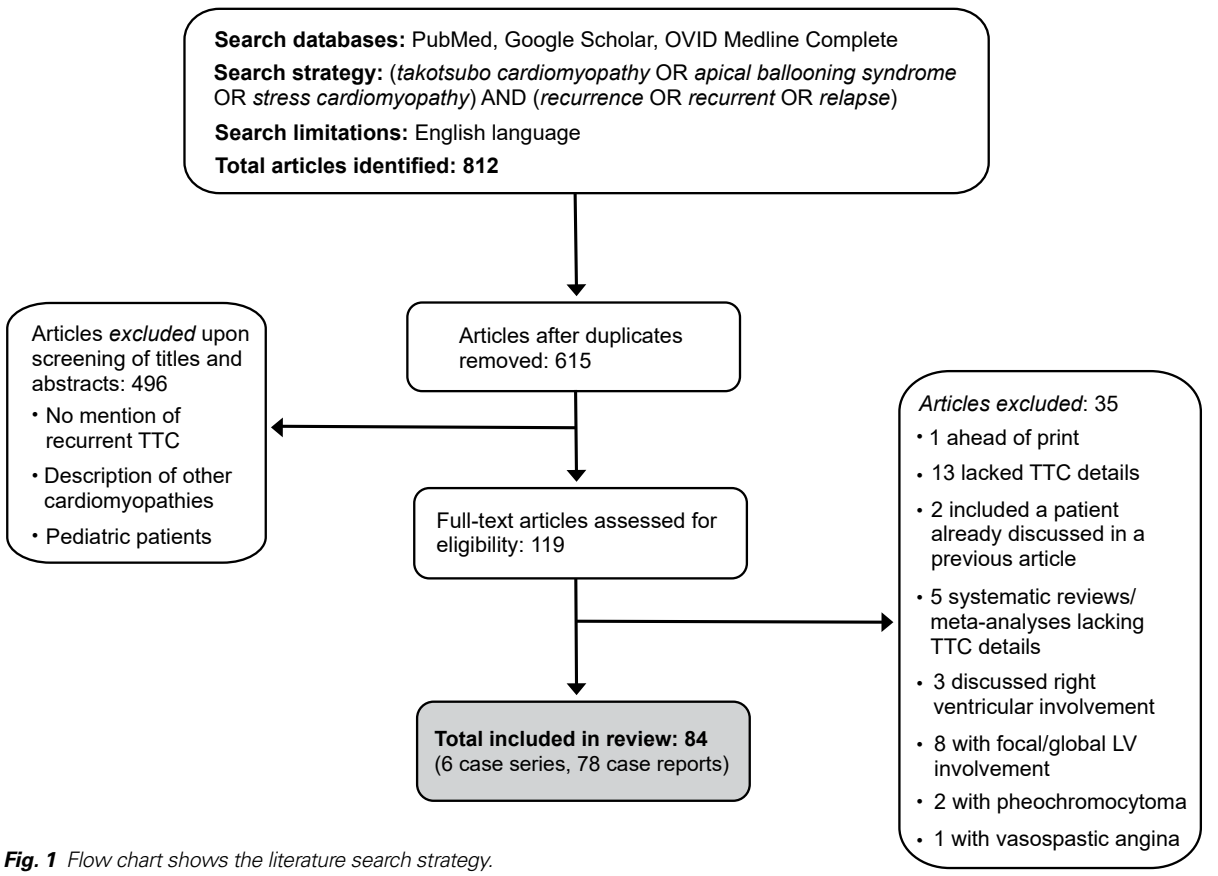

Fig. 1 *Flow chart shows the literature search strategy.*

LV = left ventricular; TTC = takotsubo cardiomyopathy

Statistical Analysis

Univariate analysis was used to compare demographic and clinical characteristics between the groups: the Student *t* test or Wilcoxon rank sum test for continuous variables, and χ^2 tests for categorical variables. To determine whether there was an independent relationship between either type of LV ballooning and severe cardiac events, we used logistic regression models to accommodate sample-size limitations and the relatively few instances of shock and cardiac arrest. Baseline biologic variables were then examined for univariate association with cardiac arrest at a significance level of P <0.20. These variables were age, ACEI use, β-blocker use, emotional triggers, physical triggers, ECG changes (such as ST-segment changes), and LVEF. Of these, LVEF, β-blocker use, and ST-segment changes were selected, and atypical presentation was added to each model. We used χ^2 analysis to compare the percentages of typical and atypical patients who had cardiogenic shock, cardiac arrest, or both. For all patients who initially presented with an apical LV ballooning pattern, a second parallel univariate analysis was conducted (as described above) by comparing patients who presented with apical ballooning based on whether recurrent episodes were apical or nonapical (midventricular or basal LV ballooning). In all univariate analyses, P <0.05 was considered statistically significant. Analyses were performed with use of Statistical Analysis Software 9.4M6 (SAS Institute Inc.).

Results

We identified 84 qualifying articles (6 case series and 78 case reports) involving 101 patients (Table I).[6-89] Of those patients, 60 (59.4%) had only the typical apical ballooning pattern initially and on recurrence, and 41 (40.6%) had an atypical nonapical pattern at least once (Fig. 2).

The study included 93 women (92.1% of the population; mean age, 64.2 ± 11.5 yr) and 8 men (7.9%; mean age, 70.1 ± 9 yr). The mean time between initial and recurrent TTC episodes was similar between the groups (2.6 ± 3.1 yr for all recurrences combined). The groups were similar in terms of demographic and clinical characteristics, except that the typical group had a larger number of emotional or physical triggers at initial presentation (n=51; 96.2%) than did the atypical cohort (n=32; 84.2%) (*P*=0.046). Of the recurrent cases, 51 (50.5%) occurred in Europe and 31 (30.7%) in North America (Table II).

The incidence of cardiogenic shock during hospitalization was similar between groups for initial and recurrent TTC episodes (*P*=0.072); however, during recurrence, it was higher in the typical group (n=11; 20.8%) than in the atypical group (n=2; 6.3%). In the typical group, the likelihood of shock presentation during recurrence was slightly higher at recurrence (n=11; 20.8%) than at initial presentation (n=4; 7.6%)

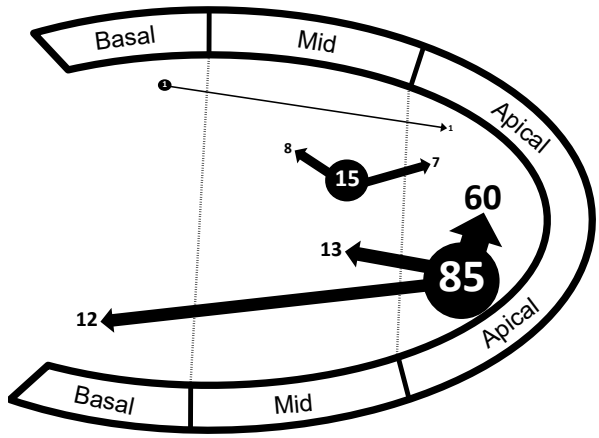

Fig. 2 *Diagram shows distribution of the 101 instances of recurrent takotsubo cardiomyopathy by left ventricular ballooning location during initial and recurrent episodes. In 85 instances, the initial ballooning pattern was apical; at recurrence, the pattern was apical in 60, midventricular (mid) in 13, and basal in 12. In 15 instances, the initial pattern was midventricular; at recurrence, the pattern was midventricular in 8 and apical in 7. Only one patient had an initial basal pattern and apical recurrence.*

(*P*=0.051). Cardiac arrest necessitating advanced cardiopulmonary support was higher in the typical group (n=10; 18.9%) than in the atypical group (n=2; 6.1%) (*P*=0.096).

Survival to hospital discharge, although similar between groups, was lower in the typical group: 53 (88.3%) compared with 40 (97.5%) (*P*=0.098). Eight patients, all women, died during hospitalization. Of those patients, 7 were in the typical group; the cause of death was cardiac arrest with anoxic encephalopathy in 1 patient, cerebrovascular accident in 1, sepsis in 2, and unknown causes in 3. The patient in the atypical group died of cardiac arrest with consequent anoxic encephalopathy.

In multivariable analysis, after adjustment for baseline ejection fraction, medication use, and ECG changes, the odds of cardiac arrest were estimated to be 78% lower in the atypical group than in the typical group (adjusted odds ratio [OR]=0.22; 95% CI, 0.04–1.18; *P*=0.08). Similarly, the estimated odds of shock were 56% lower in the atypical group (adjusted OR=0.44; 95% CI, 0.13–1.49; *P*=0.19). When severe cardiac events were combined, shock and cardiac arrest events were significantly less frequent in the atypical group than in the typical group (Fig. 3), with an estimated 63% lower odds (adjusted OR=0.37; 95% CI, 0.14–0.97; *P*=0.039).

Comparison of Recurrent Patterns After Initial Apical Pattern

Of the 101 patients, 85 first presented with the typical apical ballooning pattern (Table III). At recurrence, 60 patients had another apical pattern and 25 had a nonapical pattern (13 midventricular and 12 basal). No

TABLE I. Characteristics of Patients With Recurrent Takotsubo Cardiomyopathy

Case No.	Pt. No.*	Article Type	Reference	Country	Female Sex	Age at 1st Event (yr)	Initial and Recurrence Type	Time Between Events	Initial and Recurrence Triggers
Midventricular-to-Midventricular Recurrence Pattern									
1	1	CS	Korabathina R, et al.[6]	US	Yes	67	M–M–M	1 yr	COPD exacerbation; gastritis; colitis
2	2	CR	Sager HB, et al.[7]	Germany	Yes	66	M–M–M	8 mo	COPD exacerbation; family dispute; angioplasty
3	3	CS	El-Battrawy I, et al.[8]	Germany	Yes	50	M–M	6 yr	Physical stress ×2
4	4	CS	El-Battrawy I, et al.[8]	Germany	Yes	63	M–M	2 yr	Physical stress ×2
5	5	CR	Fenster BE, et al.[9]	US	Yes	37	M–M	3 yr	Emotional stress; received mammogram results
6	6	CR	Kato K, et al.[10]	Japan	Yes	65	M–M	3 yr	Choking on water ×2
7	7	CR	Lal Y, et al.[11]	US	Yes	53	M–M	5 mo	Job stress ×2
8	8	CS	Sharkey SW, et al.[12]	US	Yes	53	M–M	1.2 yr	Emotional stress ×2
Midventricular-to-Apical Recurrence Pattern									
9	1	CR	Battineni A, et al.[13]	US	Yes	69	M–A		Myasthenia crisis ×2
10	2	CR	Kano S, et al.[14]	Japan	Yes	60	M–A	1.5 yr	Emotional stress ×2
11	3	CR	Mansencal N, et al.[15]	France	Yes	52	M–A	11 yr	NA; emotional stress
12	4	CR	Wever-Pinzon O, et al.[16]	US	Yes	82	M–A	3.6 mo	Death in family; emotional stress
13	5	CR	Ghadri JR, et al.[17]	Switzerland	Yes	65	M–A–focal	8 yr	None; quarrel; psychosis
14	6	CR	De Gennaro L, et al.[18]	Italy	Yes	72	M–A	1 yr	Quarrel ×2
15	7	CS	Sharkey SW, et al.[12]	US	Yes	66	M–A	3.8 yr	Emotional stress ×2
Apical-to-Midventricular Recurrence Pattern									
16	1	CR	Bridgman PG, et al.[19]	New Zealand	Yes	76	A–M	5 mo	Earthquake ×2
17	2	CR	From AM, et al.[20]	US	Yes	65	A–M	3 yr	NA ×2
18	3	CR	Koeth O, et al.[21]	Germany	Yes	66	A–M	1 yr	NA; none
19	4	CR	Xu B, et al.[22]	Australia	Yes	52	A–M	11 yr	Family argument ×2
20	5	CR	Gach O, et al.[23]	Belgium	Yes	70	A–M–A	6 yr	None; thunderstorm; hip replacement
21	6	CS	Singh K, et al.[24]	US	Yes	66	A–M	2 yr	None; husband's death
22	7	CS	Singh K, et al.[24]	US	Yes	63	A–M	7 yr	None ×2
23	8	CR	Migliore F, et al.[25]	Italy	Yes	67	A–M	6 yr	Relative's death ×2
24	9	CR	Miller GA, et al.[26]	US	Yes	49	A–M	6 mo	Seizures ×2

Continued

TABLE I. Characteristics of Patients With Recurrent Takotsubo Cardiomyopathy (continued)

Case No.	Pt. No.*	Article Type	Reference	Country	Female Sex	Age at 1st Event (yr)	Initial and Recurrence Type	Time Between Events	Initial and Recurrence Triggers
25	10	CR	Eitel I, et al.[27]	Germany	Yes	69	A–M	2 yr	Emotional stress; missed a train
26	11	CR	Jimenez-Lopez J, et al.[29]	Spain	Yes	75	A–M	2 yr	None; bronchospasm (house fire)
27	12	CR	Yamamoto Y, et al.[28]	Japan	Yes	48	A–M	1 yr	Argument with coworker ×2
28	13	CR	Kotla SK and Nathaniel C[30]	US	Yes	64	A–M	4 yr	Mother's death; brother's death
Apical-to-Basal Recurrence Pattern									
29	1	CR	Sharrett J, et al.[31]	US	Yes	59	A–B	3 mo	COPD exacerbation ×2
30	2	CS	Korabathina R, et al.[6]	US	Yes	75	A–B–B	5 mo	Gastritis; cholecystitis; gastritis
31	3	CR	Mugnai G, et al.[32]	Italy	Yes	64	A–B–B	7 mo	Seizures ×3
32	4	CR	Rodriguez F, et al.[33]	US	Yes	56	A–A–B	2 mo	Job stress; emotional stress ×2
33	5	CR	Fijalkowska M, et al.[34]	Poland	Yes	51	A–B–B	3 yr	Family quarrel; knee surgery; panic attack
34	6	CR	Pergolini A, et al.[35]	Italy	Yes	76	A–B	4 yr	None ×2
35	7	CR	Izumo M, et al.[36]	Japan	No	78	A–B	2 yr	Pneumonia ×2
36	8	CS	Ikeda E, et al.[37]	Japan	Yes	55	A–B	2 mo	Rhabdomyolysis ×2
37	9	CS	Ikeda E, et al.[37]	Japan	No	75	A–B	3 mo	Asthma; pneumonia
38	10	CR	Kaushik M, et al.[38]	US	Yes	59	A–A–A–A–A–B	5 mo	Cannabis hyperemesis syndrome; hyperemesis ×5
39	11	CR	Tait J, et al.[39]	Canada	Yes	55	A–B	24 d	Pelvic surgery; argument
40	12	CS	Singh K, et al.[24]	US	Yes	57	A–B	8 mo	GI distress ×2
Basal-to-Apical Recurrence Pattern									
41	1	CR	Blessing E, et al.[40]	Germany	No	70	B–A	3 mo	Emotional stress ×2
Apical-to-Apical Recurrence Pattern									
42	1	CR	Abu-Fanne R, et al.[41]	Israel	Yes	73	A–A	3 yr	NA; asthma exacerbation
43	2	CR	Adigun R, et al.[42]	US	No	71	A–A	10 yr	Surgery ×2
44	3	CR	Ahmed AE, et al.[43]	Saudi Arabia	Yes	46	A–A–A	2 yr	Emotional stress ×3
45	4	CR	Akutsu Y, et al.[44]	Japan	Yes	72	A–A	1 yr	Emotional stress ×2
46	5	CR	Brenes Salazar JA[45]	US	Yes	66	A–A	6 mo	Esophageal spasm; emotional distress

Continued

TABLE I. Characteristics of Patients With Recurrent Takotsubo Cardiomyopathy (continued)

Case No.	Pt. No.*	Article Type	Reference	Country	Female Sex	Age at 1st Event (yr)	Initial and Recurrence Type	Time Between Events	Initial and Recurrence Triggers
47	6	CR	Carigi S, et al.[89]	Italy	Yes	64	A–A	4 yr	COPD exacerbation ×2
48	7	CR	Cattaneo M, et al.[46]	Switzerland	No	66	A–A–A	1 yr	High altitude; none; cold-weather fishing
49	8	CR	Cemin R and Oberhollenzer R[47]	Netherlands	Yes	68	A–A	1 yr	Mugging; anniversary of 1st TTC event
50	9	CR	Cerrito M, et al.[48]	Italy	Yes	73	A–A	10 yr	Husband's death; family quarrel
51	10	CR	Chaparro-Munoz M, et al.[49]	England	Yes	56	A–A	6 yr	Emotional stress; family argument
52	11	CR	Cherian J, et al.[50]	US	Yes	42	A–A	13 yr	Father's death; domestic stress
53	12	CR	Dahdouh Z, et al.[51]	France	Yes	53	A–A	0.05	Graves disease ×2
54	13	CR	Dande AS, et al.[52]	Switzerland	Yes	67	A–A	4 yr	GI illness; stroke
55	14	CS	Desmet WJ, et al.[53]	Belgium	Yes	60	A–A	6 yr	Unknown; none
56	15	CS	El-Battrawy I, et al.[8]	Germany	Yes	77	A–A	3 yr	None; emotional stress
57	16	CS	El-Battrawy I, et al.[8]	Germany	Yes	77	A–A	1 yr	None ×2
58	17	CS	El-Battrawy I, et al.[8]	Germany	Yes	86	A–A	2	Physical stress ×2
59	18	CS	El-Battrawy I, et al.[8]	Germany	Yes	71	A–A	1 yr	NA; emotional stress
60	19	CS	El-Battrawy I, et al.[8]	Germany	Yes	73	A–A	1 yr	Emotional stress; physical stress
61	20	CR	Fabbiocchi F, et al.[54]	Italy	Yes	64	A–A	7 yr	Family argument; violent job argument
62	21	CR	Fineschi M and Gori T[55]	Italy	No	51	A–A	5 yr	NA; emotional stress
63	22	CR	Finsterer J, et al.[56]	Austria	Yes	47	A–A	10 mo	Surgery; NA
64	23	CR	Gogas BD, et al.[57]	Greece	Yes	75	A–A	8 yr	NA; emotional stress
65	24	CR	Gotyo N, et al.[58]	Japan	No	70	A–A	2 mo	Pneumonia; pneumonia + adrenal insufficiency
66	25	CR	Hefner J, et al.[59]	Germany	Yes	43	A–A–A–A	9 mo	Emotional stress ×4
67	26	CR	Hinkelbein J, et al.[60]	Germany	Yes	61	A–A–A–A–A	2 mo	Anesthesia induction ×5
68	27	CR	Jenab Y, et al.[61]	Iran	Yes	58	A–A	4 mo	Emotional stress; physical stress while dancing
69	28	CR	Kleinfeldt T, et al.[62]	Germany	Yes	67	A–A	1 mo	Near-drowning; agoraphobia
70	29	CR	Lagan J, et al.[63]	UK	No	80	A–A–A	2 yr	Wife's death; emotional stress ×2

Continued

TABLE I. Characteristics of Patients With Recurrent Takotsubo Cardiomyopathy (continued)

Case No.	Pt. No.*	Article Type	Reference	Country	Female Sex	Age at 1st Event (yr)	Initial and Recurrence Type	Time Between Events	Initial and Recurrence Triggers
71	30	CS	Lee PH, et al.[64]	Korea	Yes	78	A–A	2 mo	Chemoembolization ×2
72	31	CS	Lee PH, et al.[64]	Korea	Yes	42	A–A	5 mo	Gout attack; infectious colitis
73	32	CR	Legriel S, et al.[65]	France	Yes	54	A–A	6 mo	Seizure ×2
74	33	CR	Leung Ki EL, et al.[66]	Switzerland	Yes	76	A–A	4 mo	COPD exacerbation ×2
75	34	CR	Marabotti C, et al.[68]	Italy	Yes	65	A–A	24 d	Antidepressant withdrawal; none
76	35	CR	Mendoza I and Novaro GM[67]	US	Yes	76	A–A–A	7 mo	COPD exacerbation ×3
77	36	CR	Mulleners T, et al.[69]	Belgium	Yes	62	A–A	8 yr	Emotional stress ×2
78	37	CR	Novo G, et al.[70]	Italy	Yes	61	A–A	2 mo	Emotional stress; none
79	38	CR	Opolski G, et al.[71]	Poland	Yes	62	A–A–A–A	10 yr	Emotional stress; physical stress; emotional stress ×2
80	39	CR	Patel K, et al.[72]	US	Yes	55	A–A	4 mo	Graves disease ×2
81	40	CR	Pathak H, et al.[73]	US	Yes	79	A–A	4 yr	Physical stress ×2
82	41	CR	Rennyson SL, et al.[74]	US	Yes	66	A–A	6 mo	COPD exacerbation ×2
83	42	CR	Rotondi F, et al.[75]	Italy	Yes	58	A–A	7 yr	None; emotional stress
84	43	CR	Rovetta R, et al.[76]	Italy	Yes	62	A–A	3 yr	Emotional stress ×2
85	44	CR	Santoro F, et al.[77]	Italy	Yes	74	A–A	4 yr	GI illness; digoxin toxicity
86	45	CR	Santoro F, et al.[78]	Italy	Yes	74	A–A	24 d	Emotional stress; hypovolemia
87	46	CR	Sardar MR, et al.[79]	US	Yes	76	A–A	7 mo	Stroke; vertebrobasilar insufficiency
88	47	CS	Sharkey SW, et al.[12]	US	Yes	51	A–A	3 wk	Emotional stress ×2
89	48	CS	Sharkey SW, et al.[12]	US	Yes	53	A–A–A–A	9.5 mo	Emotional stress ×4
90	49	CS	Sharkey SW, et al.[12]	US	Yes	65	A–A	2.9 yr	Emotional stress; none
91	50	CS	Sharkey SW, et al.[12]	US	Yes	78	A–A	13 mo	Physical stress ×2
92	51	CS	Sharkey SW, et al.[12]	US	Yes	83	A–A	2.3 yr	Physical stress; emotional stress
93	52	CR	Tokunou T and Sadamatsu K[80]	Japan	Yes	54	A–A	12 yr	Coronary spasm; emotional stress
94	53	CR	Uechi Y and Higa K[81]	Japan	Yes	53	A–A	5 d	Motor weakness; respiratory failure
95	54	CR	Venditti F, et al.[82]	Italy	Yes	81	A–A	6 mo	Emotional stress; COPD exacerbation
96	55	CR	Vriz O, et al.[83]	Italy	Yes	84	A–A	10 d	Asthma exacerbation ×2

Continued

TABLE I. Characteristics of Patients With Recurrent Takotsubo Cardiomyopathy (continued)

Case No.	Pt. No.*	Article Type	Reference	Country	Female Sex	Age at 1st Event (yr)	Initial and Recurrence Type	Time Between Events	Initial and Recurrence Triggers
97	56	CR	Wong CP and Chia PL[84]	Singapore	Yes	62	A–A	1.5 yr	Myasthenia crisis ×2
98	57	CR	Wu BT, et al.[85]	Japan	Yes	62	A–A	1 yr	Emotional stress ×2
99	58	CR	Xu Z, et al.[86]	China	Yes	82	A–A	4 d	Emotional stress ×2
100	59	CR	Yaoita H, et al.[87]	Japan	Yes	67	A–A	4 yr	None; vasodilator noncompliance
101	60	CR	Yoshida T, et al.[88]	Japan	Yes	83	A–A	12 d	Emotional stress; none

A = apical; B = basal; COPD = chronic obstructive pulmonary disease; CR = case report; CS = case series; GI = gastrointestinal; M = midventricular; NA = not available; Pt. = patient; TTC = takotsubo cardiomyopathy

*Restarts for each category

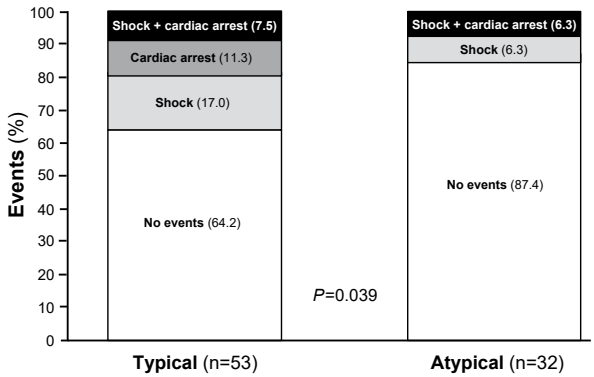

Fig. 3 *Graph shows that fewer patients with atypical takotsubo cardiomyopathy had severe cardiac events. Column totals indicate number of papers that mentioned severe events.*

P *<0.05 was considered statistically significant.*

significant differences between the apical and atypical groups were identified in terms of patient demographics, time between recurrences, medication use at time of recurrence, or ECG findings. However, a significantly larger number of patients in the typical group had an emotional or physical trigger at initial presentation and when an apical pattern recurred: 51 (96.2%) compared with 18 (78.3%) (*P*=0.013). As for severe cardiac events, shock at presentation was similar between the groups but was higher during recurrence in the typical group: 11 (20.8%) compared with 1 (5.3%) (*P*=0.12). Similarly, a larger number of cardiac arrests occurred in the typical group (n=10; 18.9%) than in the atypical group (n=1; 5%) (*P*=0.14), and the survival rate was lower: 53 (88.3%) compared with 24 (96%) (*P*=0.27).

Discussion

Recurrent TTC occurs so infrequently that only case reports and small case series have been available for review, with little or no analysis of recurrence patterns. Our most important finding is that patients with atypical TTC had a nearly two-thirds lower risk of shock and cardiac arrest than did patients in whom only typical TTC developed. This finding was statistically significant when both adverse events were combined. In-hospital mortality rates among patients with atypical TTC were also more favorable; only 1 of 8 total deaths occurred in this cohort.

No demographic or baseline clinical characteristics explained the difference in severe cardiac events and death between groups, even after multivariable adjustment. We speculate that if severe cardiac events are related to the acute coronary syndrome presentation and correlate in linear fashion with the degree of myocardial dysfunction, then the patients with atypical TTC perhaps had less myocardium in jeopardy than did those with typical TTC. Qualitatively determined LVEF was similar between the groups; however, LVEF evaluation performed by varying standards precluded identifying the myocardium at risk. Quantitative echocardiographic methods or magnetic resonance imaging may measure LVEF more precisely when focal myocardial stunning makes qualitative evaluation of contractility challenging.

The trends in adverse events may relate to underlying comorbidities and the severity of stress triggers, information that was not consistently obtainable. Nevertheless, our observation of more encouraging outcomes among patients with atypical TTC is novel and in fact differs from that in patients with a single TTC event; the International Takotsubo Registry report of 1,750 isolated TTC cases revealed no significant differences in a composite endpoint of cardiogenic shock, cardiopulmonary resuscitation, or in-hospital death.[5]

The apical LV ballooning pattern is typical in TTC. During the last 2 decades, atypical LV ballooning has

TABLE II. Comparison of the Patients Based on Typical (Apical) or Atypical (Nonapical) Ballooning Patterns

Variable	All (N=101)	Typical (n=60)	Atypical (n=41)	*P* Value
Geographic location				
North America	31 (30.7)	13 (21.7)	18 (43.9)	0.017
Europe	51 (50.5)	36 (60)	15 (36.6)	0.02
Asia or Australia	19 (18.8)	11 (18.3)	8 (19.5)	0.883
Publication time frame				
2001–2010	35 (34.7)	24 (40)	11 (26.8)	—
2011–2018	66 (65.3)	36 (60)	30 (73.2)	—
Time between recurrences (yr)	2.6 ± 3.1	2.7 ± 3.3	2.5 ± 2.9	0.834
>1 Recurrence	17 (16.8)	8 (13.3)	9 (22)	0.26
Female sex	93 (92.1)	55 (91.7)	38 (92.7)	0.854
Age (yr)	64.7 ± 10.8	65.9 ± 11.4	62.9 ± 9.7	0.173
Chest pain	73 (84.9)	41 (82)	32 (88.9)	0.379
ACEI use at recurrence	37 (59.7)	20 (57.1)	17 (63)	0.65
β-blocker use at recurrence	36 (55.4)	20 (52.6)	16 (59.3)	0.603
Serum troponin elevation	76 (96.2)	42 (95.5)	34 (97.1)	0.701
Initial triggers				
Emotional	41 (45.1)	24 (45.3)	17 (44.7)	0.96
Physical	43 (47.3)	27 (50.9)	16 (42.1)	0.405
Any*	83 (91.2)	51 (96.2)	32 (84.2)	0.046
Recurrence triggers				
Emotional	47 (48)	25 (43.1)	22 (55)	0.247
Physical	44 (44.9)	28 (48.3)	16 (40)	0.418
Any*	90 (91.8)	53 (91.4)	37 (92.5)	0.842
Initial ECG findings				
ST-segment changes	47 (54)	26 (52)	21 (56.8)	0.664
T-wave changes	52 (60)	29 (58)	23 (62.2)	0.7
QTc prolongation	16 (18.4)	9 (18)	7 (18.9)	0.914
Recurrence ECG findings				
ST-segment changes	38 (42.2)	24 (44.4)	14 (38.9)	0.606
T-wave changes	57 (63.3)	34 (63)	23 (63.9)	0.93
QTc prolongation	22 (24.4)	15 (27.8)	7 (19.4)	0.373
Initial LVEF (%)	34.8 ± 8.6	34.6 ± 8.9	35.1 ± 8.3	0.795
Recurrence LVEF (%)	36.4 ± 9.5	35.4 ± 10.5	37.8 ± 8	0.237
LV recovery time (mo)				
Initial	1.1 ± 1.3	1 ± 1.5	1.3 ± 1	0.46
Recurrence	1.5 ± 3.3	1.5 ± 4	1.5 ± 1.8	0.92
Cardiogenic shock				
Initial	7 (8.2)	4 (7.6)	3 (9.4)	0.766
Recurrence	13 (15.3)	11 (20.8)	2 (6.3)	0.072
Any episode	20 (11.8)	15 (14.2)	5 (7.8)	0.214
Cardiac arrest	12 (14)	10 (18.9)	2 (6.1)	0.096
Hospital survival	92 (92)	53 (88.3)	40 (97.5)	0.098

ACEI = angiotensin-converting enzyme inhibitor; ECG = electrocardiographic; LV = left ventricular; LVEF = left ventricular ejection fraction

*Two triggers (emotional and physical) in one patient[10] are counted only once

Data are presented as number and percentage or as mean ± SD. $P < 0.05$ was considered statistically significant.

TABLE III. Comparison of 85 Patients With Initial Apical Ballooning Pattern by Group

Variable	Apical (n=60)	Nonapical (n=25)	*P* Value
Time between recurrences (yr)	2.7 ± 3.3	2.3 ± 2.7	0.646
>1 Recurrence	8 (13.3)	6 (24)	0.232
Female sex	55 (91.7)	23 (92)	0.854
Age (yr)	65.9 ± 11.4	63.6 ± 9.2	0.371
Chest pain	41 (82)	20 (90.9)	0.333
ACEI use at recurrence	20 (57.1)	11 (61.1)	0.781
β-blocker use at recurrence	20 (52.6)	10 (55.6)	0.838
Serum troponin elevation	42 (95.5)	21 (95.5)	0.999
Initial trigger			
Emotional	24 (45.3)	8 (34.8)	0.394
Physical	27 (50.9)	10 (43.5)	0.55
Any	51 (96.2)	18 (78.3)	0.013
Recurrence trigger			
Emotional	25 (43.1)	10 (41.7)	0.905
Physical	28 (48.3)	11 (45.8)	0.84
Any	53 (91.4)	21 (87.5)	0.59
Initial ECG findings			
ST-segment changes	26 (52)	12 (54.5)	0.842
T-wave changes	29 (58)	14 (63.6)	0.653
QTc prolongation	9 (18)	4 (18.2)	0.985
Recurrence ECG findings			
ST-segment changes	24 (44.4)	7 (33.3)	0.38
T-wave changes	34 (63)	13 (61.9)	0.932
QTc prolongation	15 (27.8)	4 (19)	0.435
LVEF (%)			
Initial	34.6 ± 8.9	33.3 ± 7.3	0.539
Recurrence	35.4 ± 10.5	36.7 ± 7.8	0.573
LV recovery time (mo)			
Initial episode	1 ± 1.5	1.3 ± 1	0.46
Recurrence	1.5 ± 4	1.5 ± 1.8	0.92
Cardiogenic shock			
Initial episode	4 (7.6)	3 (15.8)	0.298
Recurrence	11 (20.8)	1 (5.3)	0.12
Any episode	15 (14.2)	4 (10.5)	0.571
Cardiac arrest	10 (18.9)	1 (5)	0.14
Hospital survival	53 (88.3)	24 (96)	0.27

ACEI = angiotensin-converting enzyme inhibitor; ECG = electrocardiographic; LV = left ventricular; LVEF = left ventricular ejection fraction

Data are presented as mean ± SD or as number and percentage. $P<0.05$ was considered statistically significant.

been observed in 16.8% to 40% of all isolated TTC cases,[5,12,90] challenging earlier definitions of stress-induced cardiomyopathy and theories regarding its pathophysiology. We found that 84.2% of all initial TTC cases were apical, but that almost 1 in 3 recurrences was basal or midventricular. Of the few initially atypical cases (almost all, midventricular), the recurrent pattern was apical in almost half. Apical recurrence was the predominant clinical course overall, whereas the recurrence of atypical TTC usually involved mixed variants; we found only 8 cases of purely midventricular recurrence. It is unclear whether the various ballooning patterns of recurrent TTC indicate unique disease entities; however, it is more likely that they are a continuum of the same disease process, because LV ballooning patterns can change within a few hours.[91]

In our analysis, more cases of atypical recurrent TTC were reported from North America than from Europe or from Asia and Australia. The geographic differences suggest an association between ethnicity and disease presentation; the effects of environmental and socioeconomic factors are unknown.

The Elusive Pathophysiology of Takotsubo Cardiomyopathy

Both the cause and the pathophysiology of stress-induced cardiomyopathy are elusive. The often-mentioned theory

that catecholamine surges may cause TTC has rarely been corroborated by serum catecholamine measurement, so the most plausible theoretical cause is coronary spasm and focal myocardial stunning from endothelial dysfunction.[92] In addition, because most cases of recurrent TTC seem to occur in postmenopausal women and because all of the midventricular events that we found were in women, hormonal influence is possible.[2,93]

Other than avoiding the inciting trigger (if even identifiable), there are no convincing recommendations for preventing recurrent TTC. In our analysis, when an emotional or physical stress trigger was identified, 76% of recurrent events were due to the same type of trigger and <10% to a crossover trigger. Renin-angiotensin system inhibitors were thought to be protective[3]; however, about 60% of subjects in our analysis were taking an ACEI when TTC recurred. Apart from this observation, the impact of medication use on preventing TTC recurrence cannot be elucidated from this meta-analysis of recurrence-only patients without a control group. Nonetheless, the overall rate of recurrent TTC appears to be low.[3,5]

The population of patients in which TTC recurs provides valuable insight into the pathophysiology of the disease and in clarifying cause and effect. Acetylcholine tests, which clinically reproduce the coronary spasm in TTC, have distinct promise in revealing endothelial dysfunction.[94] This diagnostic approach may enable a better understanding of how catecholamine surge affects coronary vasomotor function.

Limitations

The chief limitation in our meta-analysis was the inability to determine the merit of information within individual studies; incomplete data may have influenced trends, outcomes, and other variables. Article search-and-selection bias was possible, despite efforts to minimize it. Attempts to understand true TTC recurrence rates were hindered by a lack of uniform protocols to monitor TTC subjects prospectively with use of standardized imaging methods. Finally, between-group comparisons of LV recovery time and other variables may have been affected by varying timing protocols for reassessing LV contractile function.

Conclusions

Our meta-analysis adds meaningfully to the natural history of TTC by revealing implications of specific recurrence patterns. Strikingly, we found no major differences between baseline variables in comparing apical with nonapical groups of patients and recurrence patterns. Single and even multiple recurrences occurred in 1 of 6 cases. Defined clinical outcomes seem to be influenced by LV ballooning pattern, and patients in whom atypical variants occur may have more favorable outcomes in terms of combined severe cardiac events and death. Regardless, just as in isolated TTC episodes, recurrent TTC is associated with a substantial clinical risk. Further study into the pathophysiology of this enigmatic cardiomyopathy is warranted.

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