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)

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 syndrome1,2; 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, 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. 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.

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

LV = left ventricular; TTC = takotsubo cardiomyopathy
Results

We identified 84 qualifying articles (6 case series and 78 case reports) involving 101 patients (Table I). 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%) (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

![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.](image-url)
### 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 |
|----------|-----------|--------------|-----------|------------|------------|-----------------------|-------------------------------|---------------------|----------------------------------|
| 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

| 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 |
|----------|-----------|--------------|-----------|------------|------------|-----------------------|-------------------------------|---------------------|----------------------------------|
| 9        | 1         | CR           | Battineni A, et al. [13] | US | Yes | 69 | M–A | 1.5 yr | Myasthenia crisis ×2 |
| 10       | 2         | CR           | Kano S, et al. [14] | Japan | Yes | 60 | M–A | 11 yr | NA; emotional stress |
| 11       | 3         | CR           | Mansencal N, et al. [15] | France | Yes | 52 | M–A | 3.6 mo | Death in family; emotional stress |
| 12       | 4         | CR           | Ever-Pinzon O, et al. [16] | US | Yes | 82 | M–A | 8 yr | None; quarrel; psychosis |
| 13       | 5         | CR           | Ghadri JR, et al. [17] | Switzerland | Yes | 65 | M–A–focal | 1 yr | Quarrel ×2 |
| 14       | 6         | CR           | De Gennaro L, et al. [18] | Italy | Yes | 72 | M–A | 3.8 yr | Emotional stress ×2 |

#### Apical-to-Midventricular Recurrence Pattern

| 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 |
|----------|-----------|--------------|-----------|------------|------------|-----------------------|-------------------------------|---------------------|----------------------------------|
| 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*
### Apical-to-Basal Recurrence Pattern

| 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 |
|----------|---------|--------------|-----------|---------|--------|-----|----------------------|-----------------------------|------------------------|-------------------------------|
| 29       | 1       | CR           | Sharrett J, et al. | US      | Yes    | 59  | A−B                 | 3 mo                         | COPD exacerbation ×2     |                               |
| 30       | 2       | CS           | Korabathina R, et al. | US      | Yes    | 75  | A−B−B               | 5 mo                         | Gastritis; cholecystitis; gastritis |
| 31       | 3       | CR           | Mugnai G, et al. | Italy   | Yes    | 64  | A−B−B               | 7 mo                         | Seizures ×3            |                               |
| 32       | 4       | CR           | Rodriguez F, et al. | US      | Yes    | 56  | A−A−B               | 2 mo                         | Job stress; emotional stress ×2 |
| 33       | 5       | CR           | Fiąkowska M, et al. | Poland  | Yes    | 51  | A−B−B               | 3 yr                         | Family quarrel; knee surgery; panic attack |
| 34       | 6       | CR           | Pergolini A, et al. | Italy   | Yes    | 76  | A−B                 | 4 yr                         | None ×2                  |                               |
| 35       | 7       | CR           | Izumo M, et al. | Japan   | No     | 78  | A−B                 | 2 yr                         | Pneumonia ×2             |                               |
| 36       | 8       | CS           | Ikeda E, et al. | Japan   | Yes    | 55  | A−B                 | 2 mo                         | Rhabdomyolysis ×2        |                               |
| 37       | 9       | CS           | Ikeda E, et al. | Japan   | No     | 75  | A−B                 | 3 mo                         | Asthma; pneumonia        |                               |
| 38       | 10      | CR           | Kaushik M, et al. | US      | Yes    | 59  | A−A−A−A−A−A−B      | 5 mo                         | Cannabis hyperemesis syndrome; hyperemesis ×5 |
| 39       | 11      | CR           | Tait J, et al. | Canada  | Yes    | 55  | A−B                 | 24 d                        | Pelvic surgery; argument  |                               |
| 40       | 12      | CS           | Singh K, et al. | US      | Yes    | 57  | A−B                 | 8 mo                        | GI distress ×2            |                               |

### Basal-to-Apical Recurrence Pattern

| 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 |
|----------|---------|--------------|-----------|---------|--------|-----|----------------------|-----------------------------|------------------------|-------------------------------|
| 41       | 1       | CR           | Blessing E, et al. | Germany | No     | 70  | B−A                 | 3 mo                         | Emotional stress ×2     |                               |

### Apical-to-Apical Recurrence Pattern

| 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 |
|----------|---------|--------------|-----------|---------|--------|-----|----------------------|-----------------------------|------------------------|-------------------------------|
| 42       | 1       | CR           | Abu-Fanne R, et al. | Israel  | Yes    | 73  | A−A                 | 3 yr                         | NA; asthma exacerbation  |                               |
| 43       | 2       | CR           | Adigun R, et al. | US      | No     | 71  | A−A                 | 10 yr                        | Surgery ×2              |                               |
| 44       | 3       | CR           | Ahmed AE, et al. | Saudi Arabia | Yes | 46  | A−A−A               | 2 yr                         | Emotional stress ×3     |                               |
| 45       | 4       | CR           | Akutsu Y, et al. | Japan   | Yes    | 72  | A−A                 | 1 yr                         | Emotional stress ×2      |                               |
| 46       | 5       | CR           | Brenes Salazar JA | US      | Yes    | 66  | A−A                 | 6 mo                         | Esophageal spasm; emotional distress |                               |
### 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.\(^{a,9}\) | Italy        | Yes        | 64                    | A–A                      | 4 yr                | COPD exacerbation x2            |
| 48       | 7        | CR           | Cattaneo M, et al.\(^{a,46}\) | Switzerland  | No         | 66                    | A–A–A                    | 1 yr                | High altitude; none; cold-weather fishing |
| 49       | 8        | CR           | Cemin R and Oberhollenzer R\(^{a,47}\) | Netherlands | Yes        | 68                    | A–A                      | 1 yr                | Mugging; anniversary of 1st TTC event |
| 50       | 9        | CR           | Cerrito M, et al.\(^{a,48}\) | Italy        | Yes        | 73                    | A–A                      | 10 yr               | Husband’s death; family quarrel   |
| 51       | 10       | CR           | Chaparro-Munoz M, et al.\(^{a,49}\) | England      | Yes        | 56                    | A–A                      | 6 yr                | Emotional stress; family argument |
| 52       | 11       | CR           | Cherian J, et al.\(^{a,50}\) | US           | Yes        | 42                    | A–A                      | 13 yr               | Father’s death; domestic stress   |
| 53       | 12       | CR           | Dahdouh Z, et al.\(^{a,51}\) | France       | Yes        | 53                    | A–A                      | 0.05                | Graves disease x2               |
| 54       | 13       | CR           | Dande AS, et al.\(^{a,52}\) | Switzerland  | Yes        | 67                    | A–A                      | 4 yr                | GI illness x2                   |
| 55       | 14       | CS           | Desmet WJ, et al.\(^{a,53}\) | Belgium      | Yes        | 60                    | A–A                      | 6 yr                | Unknown; stroke                  |
| 56       | 15       | CS           | El-Battrawy I, et al.\(^{a,8}\) | Germany      | Yes        | 77                    | A–A                      | 3 yr                | None; emotional stress           |
| 57       | 16       | CS           | El-Battrawy I, et al.\(^{a,8}\) | Germany      | Yes        | 77                    | A–A                      | 1 yr                | None x2                         |
| 58       | 17       | CS           | El-Battrawy I, et al.\(^{a,8}\) | Germany      | Yes        | 86                    | A–A                      | 2                   | Physical stress x2              |
| 59       | 18       | CS           | El-Battrawy I, et al.\(^{a,8}\) | Germany      | Yes        | 71                    | A–A                      | 1 yr                | NA; emotional stress             |
| 60       | 19       | CS           | El-Battrawy I, et al.\(^{a,8}\) | Germany      | Yes        | 73                    | A–A                      | 1 yr                | Emotional stress; physical stress |
| 61       | 20       | CR           | Fabbriocchi F, et al.\(^{a,54}\) | Italy        | Yes        | 64                    | A–A                      | 7 yr                | Family argument; violent job argument |
| 62       | 21       | CR           | Fineschi M and Gori T\(^{a,55}\) | Italy        | No         | 51                    | A–A                      | 5 yr                | NA; emotional stress             |
| 63       | 22       | CR           | Finsterer J, et al.\(^{a,56}\) | Austria      | Yes        | 47                    | A–A                      | 10 mo               | Surgery; NA                     |
| 64       | 23       | CR           | Gogas BD, et al.\(^{a,57}\) | Greece       | Yes        | 75                    | A–A                      | 8 yr                | NA; emotional stress             |
| 65       | 24       | CR           | Gotyo N, et al.\(^{a,58}\) | Japan        | No         | 70                    | A–A                      | 2 mo                | Pneumonia; pneumonia + adrenal insufficiency |
| 66       | 25       | CR           | Hefner J, et al.\(^{a,59}\) | Germany      | Yes        | 43                    | A–A–A–A–A               | 9 mo                | Emotional stress x4             |
| 67       | 26       | CR           | Hinkelbein J, et al.\(^{a,60}\) | Germany      | Yes        | 61                    | A–A–A–A–A               | 2 mo                | Anesthesia induction x5          |
| 68       | 27       | CR           | Jenab Y, et al.\(^{a,61}\) | Iran         | Yes        | 58                    | A–A                      | 4 mo                | Emotional stress; physical stress while dancing |
| 69       | 28       | CR           | Kleinfeldt T, et al.\(^{a,62}\) | Germany      | Yes        | 67                    | A–A                      | 1 mo                | Near-drowning; agoraphobia       |
| 70       | 29       | CR           | Lagan J, et al.\(^{a,63}\) | UK           | No         | 80                    | A–A–A                   | 2 yr                | Wife’s death; emotional stress x2 |

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. | Korea   | Yes    | 78  | A–A                  | 2 mo                        | Chemoembolization ×2     |                                  |
| 72       | 31      | CS           | Lee PH, et al. | Korea   | Yes    | 42  | A–A                  | 5 mo                        | Gout attack; infectious colitis |                                 |
| 73       | 32      | CR           | Legriel S, et al. | France | Yes    | 54  | A–A                  | 6 mo                        | Seizure ×2            |                                  |
| 74       | 33      | CR           | Leung Ki EL, et al. | Switzerland | Yes   | 76  | A–A                  | 4 mo                        | COPD exacerbation ×2     |                                  |
| 75       | 34      | CR           | Marabotti C, et al. | Italy | Yes    | 65  | A–A                  | 24 d                       | Antidepressant withdrawal; none |                                  |
| 76       | 35      | CR           | Mendoza I and Novaro GM | US | Yes    | 76  | A–A–A               | 7 mo                        | COPD exacerbation ×3     |                                  |
| 77       | 36      | CR           | Mulleners T, et al. | Belgium | Yes   | 62  | A–A                  | 8 yr                        | Emotional stress ×2      |                                  |
| 78       | 37      | CR           | Novo G, et al. | Italy   | Yes    | 61  | A–A                  | 2 mo                        | Emotional stress; none    |                                  |
| 79       | 38      | CR           | Opolski G, et al. | Poland | Yes    | 62  | A–A–A–A             | 10 yr                       | Emotional stress; physical stress; emotional stress ×2 |                                  |
| 80       | 39      | CR           | Patel K, et al. | US      | Yes    | 55  | A–A                  | 4 mo                        | Graves disease ×2        |                                  |
| 81       | 40      | CR           | Pathak H, et al. | US      | Yes    | 79  | A–A                  | 4 yr                        | Physical stress ×2       |                                  |
| 82       | 41      | CR           | Rennyson SL, et al. | US   | Yes    | 66  | A–A                  | 6 mo                        | COPD exacerbation ×2      |                                  |
| 83       | 42      | CR           | Rotondi F, et al. | Italy    | Yes   | 58  | A–A                  | 7 yr                        | None; emotional stress    |                                  |
| 84       | 43      | CR           | Rovetta R, et al. | Italy    | Yes   | 62  | A–A                  | 3 yr                        | Emotional stress ×2      |                                  |
| 85       | 44      | CR           | Santoro F, et al. | Italy    | Yes   | 74  | A–A                  | 4 yr                        | GI illness; digoxin toxicity |                                  |
| 86       | 45      | CR           | Santoro F, et al. | Italy    | Yes   | 74  | A–A                  | 24 d                        | Emotional stress; hypovolemia |                                  |
| 87       | 46      | CR           | Sardar MR, et al. | US       | Yes   | 76  | A–A                  | 7 mo                        | Stroke; vertebrobasilar insufficiency |                                  |
| 88       | 47      | CS           | Sharkey SW, et al. | US       | Yes    | 51  | A–A                  | 3 wk                        | Emotional stress ×2      |                                  |
| 89       | 48      | CS           | Sharkey SW, et al. | US       | Yes    | 53  | A–A–A–A             | 9.5 mo                      | Emotional stress ×4       |                                  |
| 90       | 49      | CS           | Sharkey SW, et al. | US       | Yes    | 65  | A–A                  | 2.9 yr                      | Emotional stress; none    |                                  |
| 91       | 50      | CS           | Sharkey SW, et al. | US       | Yes    | 78  | A–A                  | 13 mo                       | Physical stress ×2       |                                  |
| 92       | 51      | CS           | Sharkey SW, et al. | US       | Yes    | 83  | A–A                  | 2.3 yr                      | Physical stress; emotional stress |                                  |
| 93       | 52      | CR           | Tokunou T and Sadamatsu K | Japan | Yes    | 54  | A–A                  | 12 yr                       | Coronary spasm; emotional stress |                                  |
| 94       | 53      | CR           | Ueki Y and Higa K | Japan   | Yes    | 53  | A–A                  | 5 d                         | Motor weakness; respiratory failure |                                  |
| 95       | 54      | CR           | Venditti F, et al. | Italy   | Yes   | 81  | A–A                  | 6 mo                        | Emotional stress; COPD exacerbation |                                  |
| 96       | 55      | CR           | Vriz O, et al. | Italy   | Yes    | 84  | A–A                  | 10 d                        | Asthma exacerbation ×2    |                                  |

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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 are counted only once

Data are presented as number and percentage or as mean ± SD. P <0.05 was considered statistically significant.
been observed in 16.8% to 40% of all isolated TTC cases,\textsuperscript{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.\textsuperscript{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

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**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 (68)       | 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 (42.5)        | 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 (94.4)     | 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.
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.\(^9\) 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.\(^2,9,5\)

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\(^5\); 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.\(^5,6\)

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.\(^9,4\) 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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