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# Prevalence of diastolic function and clinical impact on long-term outcome in takotsubo cardiomyopathy

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ABSTRACT

*Background:* Takotsubo cardiomyopathy (TTC) is a syndrome characterized by transient regional systolic dysfunction of the left ventricle (LV). However, far fewer reports focused on the prevalence of left ventricular diastolic function (DF) and its impact on an adverse prognosis in TTC.
*Methods:* From January 2005 to October 2014, 205 consecutive TTC patients (mean age, 70± 12 years; 95% female) were studied. The patients underwent transthoracic echocardiography at the acute phase and recovery phase (mean, 38 ± 16 days after admission).
*Results:* DF was labeled as normal, mild, moderate and severe. At the acute phase, Abnormal DF was present in 108 patients (53%), and left ventricular ejection fraction (LVEF) <50% in 156 patients (76%). At the recovery phase, DF was unchanged for 104 patients (51%), 44 patients (21%) had worsened, 57 patients (28%) had improved in DF grade. 25 patients (12%) had an LVEF <50%. During 2 years of follow-up, 34 patients developed clinical adverse events. Kaplan-Meier analysis estimated that the subgroup with unimproved DF and LVEF <50% at recovery phase had the worst 2-year survival. In multivariable analysis, unimproved DF with LVEF <50% and heart rate (HR) remained predictors of clinical adverse events.
*Conclusions:* The current study demonstrated that consideration of both change of DF and LVEF allows identification of subgroups with divergent long-term prognoses in patients with TTC, and may indicate the need for a different management in the high-risk TTC patients.



## 1. Introduction

Takotsubo cardiomyopathy (TTC) occurs most often in postmenopausal women and is usually triggered by emotional or physical stress. It is characterized by transient apical ballooning of the LV, resulting from systolic dysfunction in the LV apex and midventricle, which usually recovers within a few weeks [1–7]. LV diastolic function becomes markedly abnormal under common pathological conditions, including LV hypertrophy or fibrosis, hypertension, diabetes, and ischemia [8,9], and was also established to be prevalent in TTC [10–12]. Because of the dynamic evolution of the syndrome, comprehensive serial echocardiography examinations should be systematically performed, as they could provide useful information about the LV morphology and global function, both systolic and diastolic. The aim of this study is to evaluate the prevalence and progression of left ventricular DF in TTC, to determine the impact of diastolic functions on the long-term risk of adverse outcomes.

## 2. Methods

### 2.1. Study population

Patients were recruited from Mayo Clinic who had been diagnosed with TTC from January 2005 to October 2014.The diagnosis of TTC required fulfillment of the following Mayo diagnostic criteria [5,6,13]: 1. Transient akinesis or dyskinesis of the LV apical and mid-ventricular segments with regional wall-motion abnormalities extending beyond a single epicardial vascular distribution; 2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; 3. New electrocardiographic abnormalities (either ST-segment elevation or T-wave inversion); 4.Absence of recent significant head trauma, intracranial bleeding, pheochromocytoma, obstructive epicardial coronary artery disease, myocarditis hypertrophic cardiomyopathy. In our study, the first echocardiographic examination was obtained 1 (0, 1) day from the admission. Taking into account the patient's clinical manifestations, the TTC patients underwent transthoracic echocardiography at recovery phase (mean 38 ± 16 days after admission). The study was approved by the institutional review board. Written informed consent was obtained from each participant.

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### 2.2. Echocardiography methods

The echocardiography examinations were performed by an independent investigator, using a Vivid7 Pro (GE Ving med, Horton, Norway) interfaced with a 2.5- to 3.5-MHz phased-array probe. Echocardiographic images of the left lateral decubitus position were analyzed with commercially available systems. DF was assessed in a standardized method and in accordance with the published and relevant guidelines by use of a combination of echocardiographic variables (transmitral in-flow pattern, mitral annular velocities with tissue Doppler imaging, and pulmonary venous flow pattern) [14]. It was based on deceleration time of mitral E-wave velocity and tissue Doppler imaging (i.e., peak early mitral inflow velocity/diastolic early tissue velocity [E/e′]) in patients with atrial fibrillation. When evaluating diastolic function in TTC, a general method with high feasibility and reproducibility is necessary. Left atrial volume is highly feasible and reliable in most echocardiography studies [15], and left atrial volume index (LAVI) is clinically important for its robust relationship between the left atrial remodeling and echocardiography indices of diastolic function. In the Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography [14], it was recommended that LAVI be considered in conjunction with the Doppler parameter of LV relaxation when diastolic function was evaluated. In our article, the practical approach to grading diastolic dysfunction is to classify it according to the following criteria: normal, mild (grade I): mitral E/A ratio <0.8, decelerating time (DT) >200 ms, E/e′ ratio <8, LAVI ≥34 mL/m$^2$; moderate (grade II): mitral E/A ratio 0.8–1.5(pseudo normal), DT 160–200 ms, E/e′ ratio 9–12, LAVI ≥34 mL/m$^2$; and severe or (grade III): E/A ratio ≥2, DT <160 ms, LAVI ≥34 mL/m$^2$. Due to the dramatic change of systolic function in enrolled TTC patients, we determined the LV filling pressure and grade of diastolic dysfunction according to the recommendations for clinical laboratories in the guideline. Furthermore, for patients in whom grade III dysfunction could not be determined from a single examination, 2 Doppler echocardiography procedures were required. Parameters suggestive of, but not definitive for, abnormal DF was classified as indeterminate rather than as normal.

### 2.3. Baseline characteristics

Demographic data and risk factors including age, sex, symptoms, stress triggers, concomitant diseases, discharge medicine, echocardiogram parameters. (1) hypertension (blood pressure >140/90 or treatment with antihypertensive medications); (2) diabetes mellitus (patient history and/or treatment with insulin or oral hypoglycemic agents); (3) hyperlipidemia (total serum cholesterol level ≥240 mg/dL or treatment with lipid-lowering drugs); (4) serum cardiac biomarker, including troponin I and brain natriuretic peptide; (5) data from LV angiography; and (6) patient medications at recovery phase. Medical records, questionnaire and follow-up calls were performed to detect the adverse events as we previously described [4].

### 2.4. Statistical analysis

Continuous variables were presented as means ± standard deviation (SD); skewed data were expressed as median and quantiles. Categorical variables were expressed as percentages and compared by use of the Fisher exact test or $\chi^2$ tests. Comparisons between categorical variables at admission and redo-examination were made with the McNemar test for binary variables and marginal homogeneity for >2 levels. Continuous variables were compared using an unpaired *t*-test. For survival analysis, Kaplan-Meier curves were generated and compared using the log-rank test. Follow-up began on the day acute echocardiography was performed. The effect of diastolic function and its progression was investigated with a Cox proportional hazards regression model. A multivariable model was built using unimproved DF with LVEF <50% adjusted for age, sex, and other variables significant in unadjusted analyses at the 0.10 level. All statistical tests were 2-sided. A P value of <0.05 was set a priori and considered statistically significant. All statistical analyses were performed with the Statistical Package for Social Sciences version 11.5 for Windows (SPSS, Chicago, IL).

## 3. Results

### 3.1. Study participants

Two hundred thirty-nine patients diagnosed with TTC at Mayo clinic were enrolled. Two hundred twenty-seven patients returned to recovery echocardiography evaluation, 22 patients were excluded from the current investigation (14 had incomplete recovery echocardiography data and 8 refused to participate), and 12 patients died during hospitalization. The final study group consisted of 205 patients. The mean (SD) age was 70 ± 12 years. Of the participants, 195 (95%) were female, 141 (69%) had hypertension, 31 (15%) had diabetes, and 27 (13%) had atrial fibrillation. Twenty-six percent suffered from acute heart failure, and 18% needed mechanical ventilator support during hospitalization. Medications taken by patients during hospitalization included beta-blockers (n = 160, 63%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (n = 105, 42%), aspirin (n = 156, 62%), and statins (n = 109, 43%) (Table 1).

### 3.2. Prevalence of diastolic and systolic function

Diastolic dysfunction was associated with increased age and atrial fibrillation. In the acute phase of TTC, 156 patients (76%) presented with LVEF <50% and 108 patients (53%) had diastolic dysfunction. Of those with diastolic dysfunction, 65 (32%) had mild diastolic dysfunction, 30 (15%) had moderate diastolic dysfunction, and 13 (6%) had severe diastolic dysfunction. On the following recovery echocardiography examination (mean [SD], 38 ± 16 days from the acute phase), 180 (80%) had an LVEF ≥50%. Diastolic function was unchanged in 104 (51%), 44 (21%) had worsening DF, and 57 (28%) had improved DF compared to the patients with acute admission diastolic dysfunction. The prevalence of diastolic dysfunction of any degree was not significantly different (P = 0.18) (data not shown). During the admission and recovery phases, LVEF improved from 40 ± 14% to 58 ± 10% (P < 0.001), while HR and left ventricle end- systolic diameter (LVESD) decreased significantly (P < 0.01) (data not shown). As shown in Table 2, we compared the long-term events between the change in DF stratified by the LVEF; the unimproved DF combined with LVEF <50% showed the poorest prognosis during follow-up (P = 0.042).

### 3.3. Long-term outcome

Median follow-up time was 2 years (inter-quartile range, 0.9–3.0). 34 patients underwent adverse events. 12 patients died from cardiac

**Table 1**
Baseline characteristics in TTC patients.

| Variables | Values |
|---|---|
| Age (years) | 70 ± 12 |
| Sex (F/M) | 195/10 |
| Age at acute presentation (years) | 68 ± 12 |
| Chief complaint | |
| Chest pain (No., %) | 124 (60) |
| Shortness of breath (No., %) | 101 (49) |
| Trigger factor (No., %) | |
| Emotional factor | 55 (27) |
| Physical factor | 101 (49) |
| Comitant disease (No., %) | |
| HTN | 141 (69) |
| AF/AF | 27 (13) |
| DM | 31 (15) |
| Hyperlipidemia | 87 (42) |
| Cardiac biomarkers Median (Q1, Q3) | |
| BNP, pg/mL (n = 110) | 618 (245,1547) |
| CK-MB, ng/mL (n = 81) | 11.1 (6.6, 20.1) |
| TNI, ng/mL (n = 327) | 0.45 (0.14, 0.87) |
| Killip class (No., %) | |
| I–II | 146 (71.5) |
| III–IV | 59 (28.5) |
| AHF (No., %) | 53 (26) |
| Intubation (No., %) | 36 (18) |
| IABP (No., %) | 11 (5) |
| ECG change (No., %) | |
| ST elevation | 83 (40) |
| ST depression | 17 (8) |
| T inversion | 85 (41) |
| QTc (ms) | 505 ± 52 |
| Follow-up, years | 2 (0.9, 3.0) |
| Adverse events | 34 |
| Death from heart failure, shock and arrest | 12 |
| Pneumonia | 6 |
| Respiratory failure and COPD | 7 |
| Suspected cardiac deaths | 3 |
| Recurrence | 6 |

Abbreviations: AF/AF: atrial fibrillation and atrial flutter; AHF: acute heart failure; BNP: brain natriuretic peptide; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ECG: electrocardiography; F: female; HTN: hypertension; IABP: intra-aortic balloon counterpulsation; M: male; TNI: troponin.