Multiple Unfavorable Echocardiographic Findings in Takotsubo Cardiomyopathy Are Associated with Increased In-Hospital Events and Mortality

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Background: Various unfavorable echocardiographic findings other than apical ballooning, such as right ventricular involvement, mitral regurgitation, left ventricular outflow tract obstruction, and left ventricular thrombus, occur in takotsubo cardiomyopathy. Occasionally, these findings are observed simultaneously in a single patient. This study was performed to investigate the prevalence and characteristics of patients with multiple unfavorable echocardiographic findings in takotsubo cardiomyopathy and their associations with adverse outcomes.

Methods: The echocardiographic images of 113 patients with takotsubo cardiomyopathy (mean age, 72.7 ± 11.4 years; 29 men) were retrospectively reviewed. According to the number of unfavorable echocardiographic findings, patients were classified into a low-risk group (zero or one finding), an intermediate-risk group (two findings), and a high-risk group (three or more findings). In-hospital events were defined as a composite of acute heart failure, shock, ventricular tachyarrhythmia, and in-hospital death.

Results: Apical ballooning, right ventricular involvement, mitral regurgitation, left ventricular outflow tract obstruction, and left ventricular thrombus were observed in 92 (81.4%), 21 (18.6%), 17 (15.0%), 11 (9.7%), and three (2.7%) patients, respectively. There were 77 (68.1%), 25 (22.1%), and 11 (9.7%) patients in the low-, intermediate-, and high-risk groups, respectively. Logistic regression analysis indicated that being in the high-risk group had a significant association with in-hospital events (odds ratio, 8.74, $P = .003$) and death (odds ratio, 16.9; $P = .027$) compared with being in the low-risk group. Net reclassification improvement indicated that adding this risk group classification to known clinical factors that are associated with adverse outcomes could yield incremental information regarding patients with takotsubo cardiomyopathy with in-hospital events (net reclassification improvement, 0.59; $P = .002$).

Conclusions: Multiple unfavorable echocardiographic findings in takotsubo cardiomyopathy are not uncommon and are associated with increased in-hospital events and mortality. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Takotsubo cardiomyopathy, Echocardiography

Takotsubo cardiomyopathy is a clinical entity originally characterized by a transient and unique left ventricular (LV) wall motion abnormality mimicking a *takotsubo* (Japanese octopus pot) or apical ballooning, often triggered by emotional or physical stress.[1-3] Although takotsubo cardiomyopathy is recognized as a self-limiting and relatively benign condition, recent studies have indicated the occurrence of some critical complications,[4-6] including acute heart failure,[3,7] cardiogenic shock,[8,9] ventricular tachyarrhythmia,[10,11] and cardiac rupture,[12] in the acute period. The in-hospital mortality rate of takotsubo cardiomyopathy reached 4.2% in one large population-based study.[13]

Previous studies suggested associations between poor prognosis and atypical and/or unfavorable echocardiographic findings other than apical ballooning, such as right ventricular (RV) involvement,[14,15] mitral regurgitation (MR),[16,17] LV outflow tract obstruction (LVOTO),[18,19] and LV thrombus.[20] These unfavorable echocardiographic findings are sometimes observed simultaneously in a single

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Abbreviations

LV = Left ventricular

LVOTO = Left ventricular outflow tract obstruction

MR = Mitral regurgitation

NRI = Net reclassification improvement

OR = Odds ratio

RV = Right ventricular

patient. However, there have been no previous reports regarding patients with takotsubo cardiomyopathy showing two or more of these findings. This study was performed to investigate the prevalence and characteristics of patients with multiple unfavorable echocardiographic findings in takotsubo cardiomyopathy and their associations with adverse outcomes.

METHODS

Population and Data Collection

A total of 128 consecutive patients with takotsubo cardiomyopathy were admitted to Kawasaki Medical School Hospital between October 1999 and June 2013. After exclusion of 15 patients because of insufficient echocardiographic images, we retrospectively studied the clinical and echocardiographic data of 113 patients. This population of the present study was the same as in our previous study.[14] The diagnosis of takotsubo cardiomyopathy was based on the Mayo Clinic criteria: (1) transient hypokinesis, akinesis, or dyskinesis in the LV midsegment with or without apical involvement, regional wall motion abnormalities extending beyond a single epicardial vascular distribution, and frequently, but not always, a stressful trigger; (2) the absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) new electrocardiographic abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation of cardiac troponin; and (4) the absence of pheochromocytoma and myocarditis.[21] Patients who met all four criteria were diagnosed with takotsubo cardiomyopathy. Modest elevation of cardiac troponin was defined as serum troponin level >99th percentile of the general population (0.014 ng/mL). Pheochromocytoma and myocarditis were ruled out in a clinically standard manner, based mainly on clinical history, such as the absence of antecedent flu, fever, medical history of hypertension (especially episodic high blood pressure), and so on. Some patients who were suspected to have myocarditis and/or pheochromocytoma underwent blood tests for viral antibodies and adrenergic hormone and/or imaging tests such as magnetic resonance imaging or computed tomography.

We retrospectively reviewed the echocardiographic images and findings of these patients and investigated their relationships with clinical background and in-hospital outcomes. The detailed definitions of clinical characteristics, medical history, and laboratory data were reported previously.[14] Briefly, clinical characteristics and medical history were determined by chart review. Laboratory data collected on admission and digitally recordings of echocardiography performed within 12 hours after admission were reviewed. The echocardiographic equipment was managed according to the guidelines of the Japanese Society of Echocardiography.[22]

Definitions of Unfavorable Echocardiographic Findings

The following echocardiographic findings were defined as unfavorable: (1) apical ballooning—akinesis or dyskinesis of the LV apex (Figure 1 and Video 1; available at www.onlinejase.com); (2) RV involvement—the presence of akinesis or dyskinesis of the RV free wall with sparing of the RV basal segments with or without apical involvement[14] (Figure 2 and Video 2; available at www.onlinejase.com); (3) significant MR—presence of moderate or severe MR on the basis of published guidelines[23,24] (Figure 3 and Videos 3 and 4; available at www.onlinejase.com) (i.e., a comprehensive approach using a combination of the criteria of color Doppler regurgitant jet area to left atrial area ratio $\geq$ 20%, effective regurgitant orifice area ≥ 0.20 cm^2, regurgitant volume $\geq$ 30 mL, and vena contracta width ≥ 0.3 cm, as previously stated[16]); (4) LVOTO—a dynamic intraventricular pressure gradient (cutoff value, 30 mm Hg) detected by continuous-wave Doppler using a modified Bernoulli equation (Figure 4 and Video 5; available at www.onlinejase.com); and (5) LV thrombus—an intra-LV mass with margins distinct from ventricular endocardium and distinguishable from papillary muscles, chordae, trabeculations, or technical artifacts (Figure 5 and Video 6; available at www.onlinejase.com). The patients were classified into three groups according to the number of unfavorable findings: a low-risk group, including patients with zero or one finding; an intermediate-risk group, including patients with two findings; and a high-risk group, including those with three or more findings. This classification was done before the initiation of the analysis of characteristics and outcome. The characteristics and outcomes were compared among these groups.

Outcomes

An in-hospital clinical event was defined as a composite of acute heart failure (Killip class $\geq$ III), cardiogenic shock (systolic blood pressure $<$ 90 mm Hg with signs of tissue hypoperfusion), cardiac rupture, sustained ventricular tachyarrhythmia, and in-hospital death of any cause.

The study protocol was approved by the ethics committee of Kawasaki Medical School. This study was performed in compliance with the Declaration of Helsinki with regard to investigations in human subjects.

Statistical Analysis

Data are presented as mean $\pm$ SD for continuous variables with normal distributions, as median (interquartile range) for continuous variables not normally distribution, and as frequency (percentage) for categorical variables. The Kolmogorov-Smirnov test was used to assess the normality of the distribution. One-way analysis of variance and Kruskal-Wallis test with post hoc Bonferroni correction was used to compare continuous variables with normal and non-normal distributions among the three groups, respectively. The χ^2 test was used to compare categorical variables. To investigate associations between multiple unfavorable echocardiographic findings and in-hospital events or deaths, only a univariate logistic regression model was used, because the number of events was too small to apply to a multivariate model. To confirm the incremental value of the multiple unfavorable echocardiographic findings over known clinical factors associated with the adverse outcome (age, gender, ST-segment elevation, physical trigger, and LV ejection fraction), we performed receiver operating characteristic curve analysis and compared areas under the curves (AUCs) of the logistic regression models with the clinical factors only and the clinical factors plus the present risk classification on the basis of the number of unfavorable echocardiographic findings using DeLong's method. Continuous net reclassification improvement (NRI) was also calculated.[25] All statistical analyses was performed with R (R Foundation for Statistical Computing, Vienna,