

# Risk factors for Takotsubo Syndrome Following Cardiac Surgery: A Case–Control Study

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## Research article

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# Abstract

**Background:** Takotsubo syndrome following cardiac surgery is a rare occurrence. However, early diagnosis is essential to prevent treatment which could increase the left ventricular outflow tract pressure gradient in patients with Takotsubo syndrome, and lead to cardiogenic shock. Therefore, our study aimed to identify the incidence of Takotsubo syndrome after cardiopulmonary bypass and the associated risk factors and prognosis.

**Methods:** We retrospectively studied 5,773 patients who underwent cardiopulmonary bypass between February 2007 and July 2017. Among these, Takotsubo syndrome was diagnosed in 52 (0.9%). To evaluate the risk factors for Takotsubo syndrome, 104 of the remaining 5,721 patient were randomly selected as the control group (1:2 ratio). Univariate and multivariate logistic regression analyses were used for risk factor analysis.

**Results:** Majority of patients (69.2%) in the Takotsubo syndrome group underwent mitral valve surgery, compared to 32.7% in the control group. The following risk factors of Takotsubo syndrome were identified: atrio-ventricular valve surgery (odds ratio (OR), 10.5; 95% confidence interval (CI), 2.6-42.5;  $P=0.001$ ); and the immediate postoperative use of epinephrine (OR, 3.3; 95%CI, 1.0-10.7;  $P=0.05$ ) and dobutamine (OR, 4.8; 95%CI, 1.72-13.3;  $P=0.003$ ). Hypertension was a significant protective factor against Takotsubo syndrome following cardiac surgery (OR, 0.22; 95%CI, 0.06-0.73;  $P=0.01$ ).

**Conclusions:** Takotsubo syndrome following cardiac surgery is rare. Immediate postoperative use of epinephrine and dobutamine, as well as atrio-ventricular valve surgery were factors associated with the development of Takotsubo syndrome.

## Background

Takotsubo syndrome was first described in Japan in 1991 (1). The term 'Takotsubo' in traditional Japanese means 'octopus trap with a wide base' (2). Owing to the shape of the left ventricle, Takotsubo syndrome is also sometimes referred to as ampullary-shaped cardiomyopathy. Although the pathophysiology of Takotsubo syndrome is not fully understood yet, sympathetic over-activation, excessive catecholamine release, and coronary microcirculatory dysfunction, induced by emotional or physical stress, have been suggested as important contributing factors (3–5).

Certain types of surgeries may act as a physiological stressor, triggering Takotsubo syndrome (6). In 2007, Itoh et al. (7) reported on Takotsubo syndrome following cardiac surgery (mitral valve repair), leading the authors to suggest that myocardial stunning, caused by cardiopulmonary bypass, might be a cause of Takotsubo syndrome (7). Takotsubo syndrome preceded by cardiac surgery, however, is a very rare occurrence with only a few cases having been reported in the literature. Despite the low prevalence of Takotsubo syndrome after cardiac surgery, accurate diagnosis of the syndrome, and its differential diagnosis from low cardiac output syndrome following cardiac surgery, is essential as the use of catecholamines and beta-receptor agonists may increase the left ventricular outflow tract (LVOT)

pressure gradient in patients with Takotsubo syndrome and lead to cardiogenic shock (8). In addition, catastrophic complications, such as ventricular tachycardia (3.0%) or ventricular rupture (0.2%), may occur without proper management based on early detection of Takotsubo syndrome (9). However, early detection of Takotsubo syndrome is challenging due to the rarity of the syndrome and lack of knowledge about the associated risk factors. Therefore, our aim in this study was to identify the risk factors and prognosis of Takotsubo syndrome after cardiopulmonary bypass..

## Methods

### Study population

From February 2007 to July 2017, a total of 9,037 consecutive cardiac surgeries were performed at Asan Medical Center, Seoul, Korea. Among these cases, 3,264 patients who were diagnosed with coronary artery disease pre-operatively or who underwent heart transplantation were excluded. Of the remaining 5,773 patients, Takotsubo syndrome was revealed postoperatively in 52 patients (0.9%). To perform a case-control study, we randomly selected 104 patients of the remaining 5,721 patients (without Takotsubo syndrome) as the control group (with a 2:1 ratio to the Takotsubo syndrome) to identify risk factors. The analysis of risk factors was performed retrospectively. The study was approved by the Institutional Review Board of Asan Medical Center and the requirement for informed consent was waived (IRB number: 2017 - 1144) owing to the retrospective design of our study.

### Data Collection

Takotsubo syndrome was diagnosed based on the criteria of the Mayo clinic (6, 10). ECG was performed every day postoperatively during hospitalization. Cardiac enzymes were routinely checked every day until those decreased to a normal range. Transthoracic echocardiography (TTE) was routinely performed at least 4-days after surgery and performed immediately if patients showed unstable vital signs.

Once Takotsubo syndrome was diagnosed, follow-up TTE was performed on a daily or weekly basis, depending on the severity of LV dysfunction. All TTE was reviewed by dedicated cardiologists of our institute.

### Statistical Analysis

Statistical analyses were performed using R program (version 3.1.2). Data are expressed as the mean  $\pm$  standard deviation for continuous variables, with categorical variables reported as a count and percentage. Comparison between the Takotsubo syndrome group and the control group was performed using Student's *t*-test or the Mann-Whitney *U*-test for continuous variables and the Chi-squared or Fisher's exact test for categorical variables. For all analyses, a P-value < 0.05 was considered statistically significant. Univariable logistic regression analyses were performed to identify risk factors for Takotsubo syndrome in the entire study cohort. Clinically relevant variables with a P < 0.15 on univariable analysis were included in a multivariable analysis, using a backward elimination method to retain predictive variables.

# Results

## Baseline Characteristics

The baseline characteristics for the Takotsubo syndrome and control groups are summarized in Table 1. The mean interval from the cardiac surgery to the diagnosis of Takotsubo syndrome was  $5.0 \pm 4.5$  days. The mean age was similar in both groups, but with a greater proportion of females in the Takotsubo syndrome than control group ( $P = 0.08$ ). In the Takotsubo group, the majority of patients (69.2%) had undergone mitral valve operation, compared to 32.7% in the control group ( $p < 0.05$ ). With regard to intra-operative variables, the time of cardiopulmonary bypass or aortic cross-clamping was comparable between the two groups. Of note, vasoactive inotropic agents, with the exception of vasopressin, were used in a greater proportion of patients in the Takotsubo syndrome than control group ( $P < 0.05$ ). The length of intensive care unit (ICU) stay and the rate of early mortality were similar in both groups.

Table 1  
Clinical characteristics between groups

	<b>Takotsubo (N = 52)</b>	<b>Control (N = 104)</b>	<b>Total (N = 156)</b>	<b>p-value</b>
Age, years	55.8 ± 14.4	58.2 ± 15.1	57.4 ± 14.9	0.35
Female, N (%)	39 (75.0)	62 (59.6)	101 (64.7)	0.08
Hypertension, N (%)	5 (9.6)	38 (36.5)	43 (27.6)	0.001
Diabetes mellitus, N (%)	4 (7.7)	11 (10.6)	15 (9.6)	0.77
Hemodialysis, N (%)	0	1 (1.0)	1 (0.6)	1.00
Cerebrovascular accident, N (%)	0	1 (1.0)	1 (0.6)	1.00
Laboratory findings				
Hemoglobin, g/dL	12.2 ± 1.9	12.5 ± 2.0	12.4 ± 2.0	0.30
Creatinine, mg/dL	1.2 ± 2.1	1.2 ± 1.7	1.2 ± 1.8	0.89
Albumin, g/dL	3.5 ± 0.7	3.7 ± 0.5	3.6 ± 0.6	0.04
Electrocardiography				0.005
Sinus rhythm, N (%)	18 (40.0)	57 (66.3)	75 (57.3)	
Atrial fibrillation, N (%)	23 (51.1)	28 (32.6)	51 (38.9)	
Permanent pacemaker, N (%)	4 (8.9)	1 (1.2)	5 (3.8)	
Preoperative ventilator, N (%)	1 (1.9)	2 (1.9)	3 (1.9)	1.00
Preoperative inotropes, N (%)	2 (3.8)	2 (1.9)	4 (2.6)	0.85
LVEF, N (%)	57.2 ± 9.1	59.5 ± 9.6	58.7 ± 9.5	0.15
Type of operation				< 0.001
Aortic valve, N (%)	6 (11.5)	32 (30.8)	38 (24.4)	
Mitral valve, N (%)	36 (69.2)	34 (32.7)	70 (44.9)	
Aortic and mitral valve, N (%)	4 (7.7)	9 (8.7)	13 (8.3)	
Tricuspid valve, N (%)	4 (7.7)	4 (3.8)	8 (5.1)	
Aorta, N (%)	1 (1.9)	17 (16.3)	18 (11.5)	
Others, N (%)	1 (1.9)	8 (7.7)	9 (5.8)	

ACC, aortic cross clamp; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LVEF, left ventricular ejection fraction; VIA, vasoactive inotropic agent. \*Vasoactive inotropic agent administered on the day of surgery.

	Takotsubo (N = 52)	Control (N = 104)	Total (N = 156)	p-value
CPB time, min; mean ( $\pm$ SD)	172.3 $\pm$ 66.7	163.8 $\pm$ 113.5	166.7 $\pm$ 99.9	0.53
ACC time, min; mean ( $\pm$ SD)	106.5 $\pm$ 49.1	100.5 $\pm$ 55.9	102.6 $\pm$ 53.6	0.54
Immediate postoperative VIA*				
Epinephrine, N (%)	15 (28.8)	12 (11.5)	27 (17.3)	0.01
Norepinephrine, N (%)	24 (46.2)	28 (26.9)	52 (33.3)	0.02
Dopamine, N (%)	24 (46.2)	69 (66.3)	93 (59.6)	0.02
Dobutamine, N (%)	23 (44.2)	17 (16.3)	40 (25.6)	< 0.001
Vasopressin, N (%)	1 (1.9)	2 (1.9)	3 (1.9)	1.00
Ventilator duration	2.1 $\pm$ 3.5	2.0 $\pm$ 5.0	2.0 $\pm$ 4.6	0.83
ECMO, N (%)	1 (2.0)	0	1 (0.6)	0.71
ICU stay; mean ( $\pm$ SD)	8.0 $\pm$ 15.2	4.3 $\pm$ 8.1	5.5 $\pm$ 11.1	0.11
Early mortality, N (%)	2 (3.8)	8 (7.7)	10 (6.4)	0.58
ACC, aortic cross clamp; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LVEF, left ventricular ejection fraction; VIA, vasoactive inotropic agent. *Vasoactive inotropic agent administered on the day of surgery.				

Troponin-I was increased up to mean value of 108.4  $\pm$  118.8 ng/ml and newly developed electrocardiographic abnormalities (ST-segment changes or T-wave inversion) were documented in 94% (n = 49) of the patients.

In the Takotsubo group, the left ventricular systolic function was recovered to normal values on echocardiography at a mean duration of 7.1  $\pm$  1.3 months after diagnosis (Fig. 1).

## Univariable and multivariable analyses to identify risk factors of Takotsubo syndrome following cardiac surgery

On univariable analyses, female sex, pre-operative atrial fibrillation and/or pacemaker insertion were identified as risk factor for Takotsubo syndrome. Atrio-ventricular valve surgery, such as mitral and tricuspid valve surgery, was also identified as a significant risk factor for Takotsubo syndrome (Odds ratio (OR), 5.61; 95% confidence interval (CI), 2.11–14.9; P = 0.001). Immediate postoperative use of vasoactive inotropic agents was also a risk factor for Takotsubo syndrome. Hypertension was identified as a preventive factor against Takotsubo syndrome (OR, 0.18; 95%CI; 0.06–0.46; P = 0.001). On multivariable analysis, the following variables were retained as independent risk factors for Takotsubo syndrome: Atrio-

ventricular valve surgery (OR, 10.5; 95%CI, 2.6–42.5; P = 0.001), and the immediate postoperative use of epinephrine (OR, 3.3; 95%CI, 1.0-10.7; P = 0.05) and dobutamine (OR, 4.8; 95%CI, 1.72–13.3; P = 0.003). Hypertension was retained as a significant protective factor against Takotsubo syndrome (OR, 0.22; 95%CI, 0.06–0.73; P = 0.01). These findings are summarized in Table 2.

Table 2  
Risk analysis for Takotsubo syndrome following cardiac surgery

Preoperative variables	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age, years	0.98	0.96–1.01	0.34			
Sex (female)	2.03	0.98–4.37	0.06			
Diabetes mellitus	0.70	0.18–2.18	0.56			
Hypertension	0.18	0.06–0.46	0.001	0.22	0.06–0.73	0.01
Ventilator support	1.00	0.04–10.67	>0.99			
Inotropic support	2.04	0.23–17.41	0.48			
LVEF	0.97	0.94–1.01	0.16			
Arrhythmia						
Atrial fibrillation	2.60	1.21–5.66	0.01			
Permanent pacemaker	12.6	1.73–256.5	0.03			
Hemoglobin	0.91	0.77–1.08	0.30			
Creatinine	0.98	0.79–1.18	0.89			
Albumin	0.52	0.29–0.92	0.03			
<b>Operative variables</b>						
Type of operation						
Atrio-ventricular valve	5.61	2.11–14.93	0.001	10.54	2.63–42.54	0.001
Others	0.94	0.27–3.22	0.92			
CPB time	1.00	1.00–1.00	0.53			
ACC time	1.00	0.99–1.01	0.53			
Postoperative use of VIA						
Epinephrine	3.11	1.33–7.39	0.009	3.36	1.04–10.73	0.05
Norepinephrine	2.33	1.16–4.69	0.02			
Vasopressin	1.00	0.05–10.68	1.00			
Dopamine	0.43	0.22–0.85	0.02			

ACC, aortic cross clamp; CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; VIA vasoactive inotropic agent.

	Univariable analysis			Multivariable analysis		
Dobutamine	4.06	1.92–8.76	< 0.001	4.84	1.72–13.35	0.003

ACC, aortic cross clamp; CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; VIA vasoactive inotropic agent.

## Discussion

To the best of our knowledge, this is the first case-control study to report Takotsubo syndrome after cardiac surgery. We also identified that of the patients who developed Takotsubo syndrome, 69.2% had undergone mitral valve surgery. We identified atrio-ventricular valve surgery, and the immediate postoperative use of epinephrine or dobutamine as specific risk factors for Takotsubo syndrome following cardiac surgery. Our findings are consistent with those previously reported. In the literature, 14 cases of Takotsubo syndrome after cardiac surgery have been reported, with the majority of these cases (n = 10, 71.4%) occurred after mitral valve surgery (2, 7, 11–22). Like all other surgeries, cardiac surgery can cause emotional and/or physiological stress which may trigger Takotsubo syndrome. In addition, cardiopulmonary bypass needed during cardiac surgery induces a systemic inflammatory response which may also cause coronary microvascular dysfunction and excessive catecholamine release (7). Direct manipulation and incision of the heart also increases its vulnerability to catecholamine-induced cardiac toxicity (21). We note, however, that the reason why Takotsubo syndrome occurs more frequently after mitral valve surgery than other cardiac surgery is unknown.

Several differential diagnoses for Takotsubo syndrome have previously been presented. Of these, papillo-annular discontinuity after mitral valve replacement, which leads to a spherical LV and, thus, decreases LV systolic function, should be differentiated from ‘transient’ Takotsubo syndrome (12, 23). Other causes of myocardial stunning after cardiac surgery, such as suboptimal myocardial protection or coronary air embolism, should also be considered as differential diagnoses of Takotsubo syndrome. These differential diagnoses should be identified intra-operatively, using transesophageal echocardiography, based on the characteristic echocardiographic finding of Takotsubo syndrome, namely apical ballooning that extends beyond a single coronary territory (15).

In 2008, Takotsubo syndrome, induced by pharmacological stress (epinephrine infusion), was first described by Wong et al. (11). In the following year, Abraham et al. reported that exogenous catecholamines and beta-receptor agonists (epinephrine, dobutamine), like endogenous catecholamines, could induce Takotsubo syndrome (24). Previous findings that excessive release of catecholamine may cause Takotsubo syndrome (3, 4) are convincing and are consistent with our own results that immediate postoperative use of epinephrine and dobutamine as risk factors for Takotsubo syndrome following cardiac surgery. Previous reports on the occurrence of Takotsubo syndrome after cardiac surgery indicated that, in most cases, the syndrome developed several minutes to several days after the release of cross-clamping (2, 7, 11, 12, 14–22). Of note, Ohata et al. did report on a case of Takotsubo syndrome that developed 1-month after aortic valve replacement in a 70-year-old female (13). In our study, intra-

operative transesophageal echocardiography was performed in all cases, with TTE routinely performed at least 4 days after surgery. We do note that in the case of unstable vital signs, or if the patient complained of chest discomfort, TTE was immediately performed. The median interval between the cardiac surgery and the diagnosis of Takotsubo syndrome in our study cohort was 4.0 (Interquartile range, 3.0–5.0) days. Therefore, our imaging protocol would have been appropriate to detect Takotsubo syndrome in most cases.

Takotsubo syndrome has been known to occur mostly in elderly women (25). Ueyama et al. reported that, in rats, the use of estradiol might be protective against LV dysfunction induced by emotional stress (26). In the present study, there were more female patients in Takotsubo group (75.0%) than in control group (59.6%), although this difference was not significant ( $P = 0.08$ ). However, female sex was identified as a risk factor for Takotsubo syndrome after cardiac surgery on univariable analysis, but was not retained as an independent risk factor on multivariable analysis.

Characteristically, Takotsubo syndrome is a transient heart failure syndrome (27), with a mortality rate of 3.2% having been reported in a previous case-summary study (25). The mortality rate of Takotsubo syndrome after cardiac surgery in our study cohort was 3.8% and, thus, was comparable to previously published data. Of note, the mortality rate in the Takotsubo group (3.8%) was similar to that in the control group (7.7%;  $P = 0.58$ ). Madias reported a low prevalence of diabetes mellitus among patients with Takotsubo syndrome (28). Based on this finding, Madias suggested that diabetic autonomic neuropathy and decreased catecholamine release might have protective effect against Takotsubo syndrome. Madias did report that the prevalence of hypertension in patients with Takotsubo syndrome was comparable to that in the general population. In contrast, in our study, the prevalence of hypertension was lower in the Takotsubo syndrome than control group, while the prevalence of diabetes mellitus was similar between the two groups. In our multivariable analysis, hypertension was identified as having a protective factor against Takotsubo syndrome after cardiac surgery. It is possible that anti-hypertensive medications, such as beta-receptor antagonists, taken before cardiac surgery may lower the risk of Takotsubo syndrome following cardiac surgery. However, data about anti-hypertensive medications prescribed to the patients in our study cohort by their primary-care physician could not be accurately identified and, thus, analysis of the plausible protective role of anti-hypertensive medications was not possible.

## Limitations

This study is a retrospective observational study of patients enrolled from a single center. Although we did use a case-controlled design, in the absence of randomization, effects of selection or detection bias cannot be denied. In addition, due to the retrospective design of the study, the causal relationship between the development of Takotsubo syndrome and the use of epinephrine or dobutamine could not be determined. Finally, we could not completely exclude confounding effect of medications taken pre-operatively, a factor which should be assessed in subsequent, larger, cohort studies.

## Conclusions

Takotsubo syndrome occurred in about 1% of patients who underwent cardiac surgery under cardiopulmonary bypass. Immediate postoperative use of epinephrine and doputamine, as well as atrio-ventricular valve surgery were factors associated with the development of Takotsubo syndrome after cardiac surgery. The resulting left ventricular dysfunction was reversible in the majority of patients, without an increase in the rate of mortality. The findings of our study will need to be verified in a larger, multi-center, prospective studies.

## **Abbreviations**

ECG, electrocardiography

ICU, intensive care unit

LV, left ventricle

LVOT, left ventricular outflow tract

TTE, transthoracic echocardiography

## **Declarations**

### **Ethics approval and consent to participate**

This study was approved and informed consent was waived by the Institutional Review Board of Asan Medical Center (IRB number: 2017-1144).

### **Consent to publication**

Not applicable.

### **Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no competing interests.

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## Authors' contributions

JY and YS have made substantial contributions to the acquisition, analysis, interpretation of data. JB have designed the study and interpreted the data. All authors have approved the submitted version.

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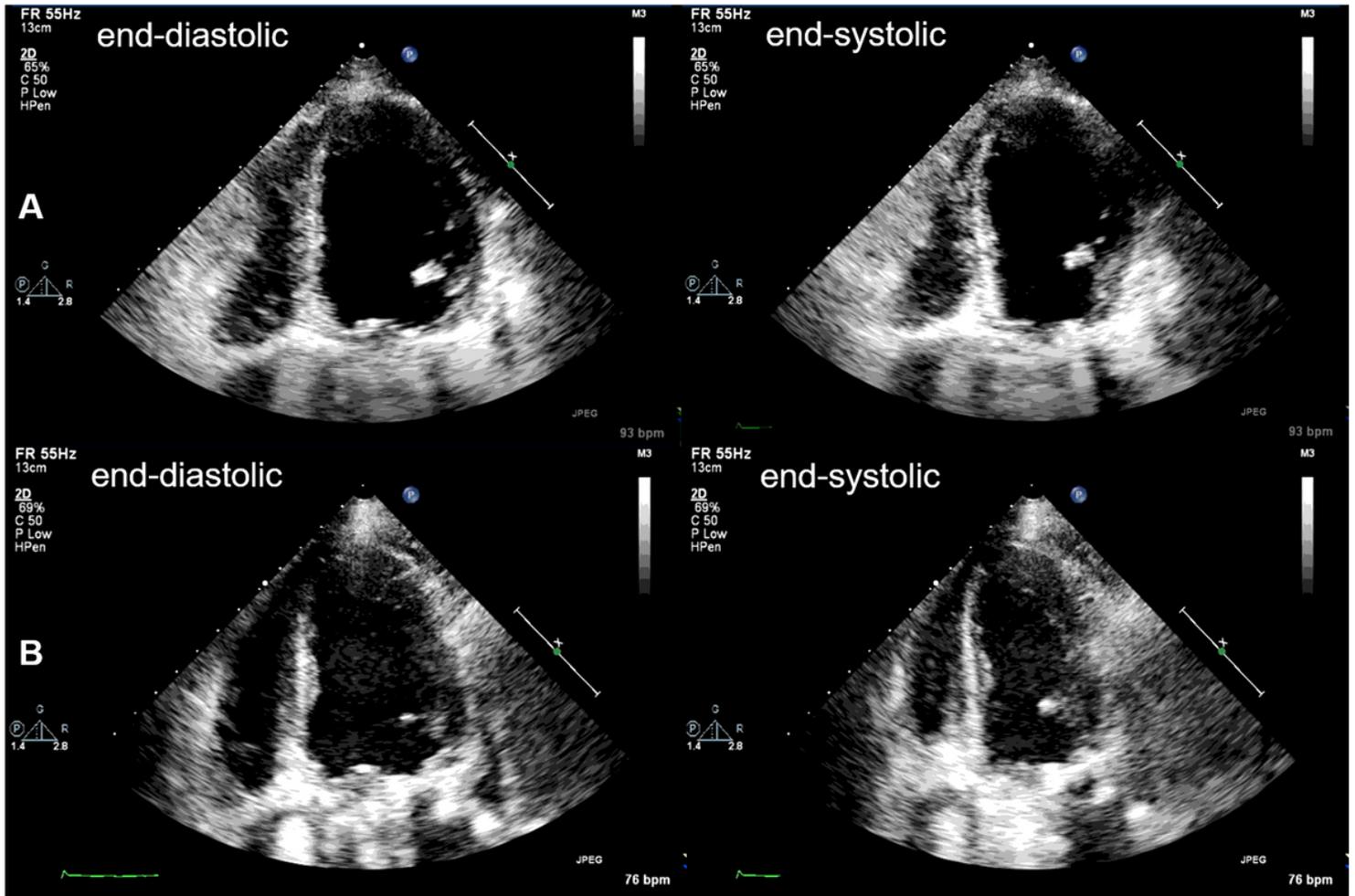
Not applicable.

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## Figures



**Figure 1**

Echocardiographic findings of Takotsubo syndrome. Transthoracic echocardiography showing apical ballooning with decreased left ventricular (LV) systolic function (ejection fraction, 35%) on postoperative day 4 (A). Seven days later, LV systolic function had normalized (ejection fraction, 55%) and apical ballooning is no longer observable (B).