# Pretreatment With Low-Dose β-Adrenergic Antagonist Therapy Does Not Affect Severity of Takotsubo Cardiomyopathy

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ABSTRACT

*Background:* Takotsubo cardiomyopathy is a syndrome of transient left ventricular dysfunction following acute emotional or physical stress without obstructive coronary artery disease. The leading hypothesis for the etiology is stress-induced catecholamine surge.

*Hypothesis:* People taking outpatient β-adrenergic receptor antagonist therapy have less-severe presentation and clinical course of Takotsubo cardiomyopathy.

*Methods:* We identified patients diagnosed with Takotsubo cardiomyopathy from October 2005 to January 2011 by analyzing our cardiac-catheterization database. Clinical records and angiograms were reviewed by 2 experienced observers independently to confirm the diagnosis. We collected clinical, demographic, laboratory, and angiographic data for the identified patients. We then compared the severity of myocardial dysfunction or damage (cardiac enzymes, left ventricular end diastolic pressure, and left ventricular ejection fraction) between patients taking outpatient β-adrenergic antagonist therapy upon admission vs those who were not. Arrival and peak values for cardiac enzymes were analyzed when available. Analysis of parameters related to the severity of myocardial dysfunction or damage was conducted using the Mann-Whitney *U* test. Means for age were compared using the Student *t* test. Statistical significance was set at $P < 0.05$ (2-tailed).

*Results:* Out of 64 patients identified, 16 (25%) were on one of 3 β-adrenergic antagonists on presentation: metoprolol succinate, metoprolol tartrate, or atenolol, with mean doses of 75 mg daily, 52.5 mg twice daily, and 37.5 mg daily, respectively. Patients on β-blockers were older (mean age 73.1 years vs 66 years; $P < 0.05$). There was no statistically significant difference in levels of cardiac enzymes, left ventricular end diastolic pressure, or left ventricular ejection fraction between the 2 groups.

*Conclusions:* Prior therapy with low-dose β-adrenergic antagonists does not affect the severity of presentation and clinical course of Takotsubo cardiomyopathy as measured by common markers of myocardial dysfunction.

## Introduction

Takotsubo or stress cardiomyopathy is a syndrome of transient left ventricular (LV) dysfunction in the absence of obstructive coronary artery disease that occurs after acute emotional or physical stress.[1] It is clinically indistinguishable from acute coronary syndrome and accounts for 1%–2% of all cases of suspected acute myocardial infarction.[2] The classic pattern seen on left ventriculography is a large area of anterior, apical, and inferior akinesis with hypercontractile bases and apical ballooning[1] (where it resembles a Japanese octopus trap,[3] or "takotsubo"). Variants involving akinesis of the anterior and inferior midventricular[4] or basal[5] segments (inverted Takotsubo) have been identified. One hallmark of this condition is the extension of wall-motion abnormalities beyond the distribution of a single coronary artery. Although the exact pathophysiology is unknown, Takotsubo cardiomyopathy has been reported in states of catecholamine excess due to stress,[6] disease,[3,7] or exogenous administration.[8] β-Adrenergic receptor–antagonist therapy in the acute phase of Takotsubo cardiomyopathy[9] has some benefit in reducing intraventricular pressure gradient in patients with midventricular obstruction. There is little data to guide the management of patients with Takotsubo cardiomyopathy once the LV dysfunction has resolved; however, many physicians intuitively continue β-adrenergic–antagonist therapy in these patients. The

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purpose of this study was to analyze the effect of outpatient β-adrenergic–antagonist therapy on the presentation and clinical course of Takotsubo cardiomyopathy.

## Methods

We identified patients diagnosed with Takotsubo cardiomyopathy from October 2005 to April 2009 retrospectively from our cardiac-catheterization database. A manual review of clinical records and angiograms of patients undergoing urgent and emergent cardiac catheterizations with a diagnosis of cardiomyopathy and nonobstructive coronary artery disease was performed by 2 experienced observers to identify patients with Takotsubo cardiomyopathy. From April 2009 forward, we prospectively identified patients diagnosed with Takotsubo cardiomyopathy and collected clinical, demographic, angiographic, and laboratory data for all identified patients. We collected data for parameters such as creatine kinase, troponins, and creatine kinase muscle-brain at 2 different periods, including at the time of arrival and the peak values. Left ventricular ejection fraction (LVEF) was calculated from the offline analysis of presentation contrast ventriculograms. We then compared parameters related to the severity of myocardial dysfunction or damage (cardiac enzymes, left ventricular end diastolic pressure [LVEDP], and LVEF) between patients taking outpatient β-adrenergic–antagonist therapy (as documented by their outpatient medication list at the time of admission) and those who were not. Left ventricular end diastolic pressure was obtained during left heart catheterization (AXIOM Sensis; Siemens AG, Germany). Left ventricular ejection fraction was determined by offline analysis of contrast ventriculograms in the right anterior oblique projection (CAAS Left Ventricular Analysis; Pie Medical Imaging BV, The Netherlands). Three independent measurements of LVEF were obtained by manual tracing of LV end-systolic and end-diastolic frames and the results were averaged. Analysis of parameters related to the severity of myocardial dysfunction or damage was conducted using the Mann-Whitney $U$ test. Age was expressed as mean ± SD and compared using the Student $t$ test. Statistical significance was set at $P < 0.05$ (2-tailed). The study was approved by our institutional review board. Because no patient-specific information was disclosed during the study process, the informed-consent requirement was waived by the institutional review board. No external funding source was utilized. Investigations were in accordance with the Declaration of Helsinki.

## Results

In total, 64 patients were diagnosed with Takotsubo cardiomyopathy, of which 16 were taking a β-blocker on presentation. Patients were taking one of 3 preparations of β-blockers: metoprolol succinate (50%), metoprolol tartrate (37.5%), or atenolol (12.5%), with mean doses of 75 mg daily, 52.5 mg twice daily, and 37.5 mg daily, respectively. The baseline characteristics of the study population are depicted in Table 1. Patients on β-adrenergic–antagonist therapy were older (73.1 years vs 66 years; $P < 0.05$) and had more cardiovascular risk factors compared with the other group.

Table 1. Comparison of Baseline Characteristics of the Study Population

| | β-Adrenergic–Antagonist Therapy, n = 16 | No β-Adrenergic–Antagonist Therapy, n = 48 |
|---|---|---|
| Demographics | | |
| Age, mean (± SD), y[a] | 74.1 (±9.0) | 65.9 (±12.1) |
| Gender, n (%) | | |
| M | 2 (12.5) | 4 (8.33) |
| F | 14 (87.5) | 44 (91.66) |
| Race, n (%) | | |
| Caucasian | 11 (68.75) | 47 (97.91) |
| African American | 1 (6.25) | 0 |
| Unknown | 4 (25) | 1 (2.1) |
| Medications | | |
| β-Blocker (%) | Metoprolol tartrate (37.5), metoprolol succinate (50), atenolol (12.5) | None |
| ACEI/ARB, n (%) | 11 (68.75) | 14 (21.53) |
| Statin, n (%) | 9 (56.25) | 20 (41.66) |
| Cardiovascular risk factors, n (%) | | |
| Hypertension | 14 (87.5) | 24 (50) |
| PAD | 2 (12.5) | 1 (2.08) |
| DM | 3 (18.5) | 11 (22.91) |
| Dyslipidemia | 7 (43.75) | 23 (47.91) |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DM, diabetes mellitus; F, female; M, male; PAD, peripheral arterial disease. [a]$P < 0.05$.

There were no statistically significant differences between the 2 groups in measured parameters of myocardial damage or dysfunction, such as levels of cardiac biomarkers, LVEDP, and LVEF (Table 2).

## Discussion

β-Adrenergic receptor antagonists block the effects of catecholamines on the heart and other organs. Detrimental effects of adrenergic stress on the heart include impaired diastolic function, tachycardia and tachyarrhythmia, myocardial ischemia, stunning, apoptosis, and necrosis.[10] High levels of catecholamines have been documented in multiple studies of Takotsubo cardiomyopathy.[11,12] The exact mechanism of the catecholamine-induced myocardial stunning is unclear, and various theories have been suggested, including direct myocyte injury, epicardial coronary artery spasm, and microvascular spasm.[8] It is reasonable to speculate that by opposing the actions of catecholamines, β-adrenergic antagonists would prevent or at least attenuate the intensity of these detrimental cardiac effects in Takotsubo cardiomyopathy.


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Table 2. Comparison of Parameters of Myocardial Dysfunction Between the 2 Groups

| | β-Adrenergic–Antagonist Therapy, Median (n1) | No β-Adrenergic–Antagonist Therapy, Median (n2) | *U* Test | *P* Value |
|---|---|---|---|---|
| Initial CK, U/L | 117 (16) | 120 (45) | 393.5 | 0.586 |
| Peak CK, U/L | 148 (16) | 140 (44) | 375.5 | 0.697 |
| Initial TnT, ng/mL | 0.12 (6) | 0.25 (10) | 42.5 | 0.181 |
| Initial TnI, ng/mL | 0.69 (10) | 1.4 (37) | 235.0 | 0.201 |
| Peak TnT, ng/mL | 0.45 (6) | 0.38 (10) | 32.0 | 0.875 |
| Peak TnI, ng/mL | 1.5 (10) | 2.5 (38) | 214.0 | 0.278 |
| Initial CK-MB, ng/mL | 8.6 (12) | 10.3 (31) | 190.5 | 0.904 |
| Peak CK-MB, ng/mL | 14.7 (12) | 10.8 (32) | 205.0 | 0.744 |
| LV systolic pressure, mm Hg | 136 (15) | 124.5 (46) | 428.5 | 0.164 |
| LVEDP, mm Hg | 10 (15) | 11 (45) | 344.0 | 0.920 |
| LVEF, % | 52.0 (14) | 52.3 (44) | 313.0 | 0.936 |
| Length of hospital stay, d | 4 (16) | 3 (45) | 462.0 | 0.097 |

Abbreviations: CK, creatine kinase; CK-MB, creatine kinase muscle-brain; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; TnI, troponin I; TnT, troponin T.

On the other hand, patients on chronic β-adrenergic–antagonist therapy develop increased sensitivity and upregulation of β-adrenergic receptors,[13] and the effect of a sudden catecholamine surge could be escalated in these patients. β-Adrenergic antagonists are also negative ionotropes that can increase LV end-diastolic pressure and are commonly withheld during management of acute decompensated congestive heart failure. Because of this, one might expect the hemodynamic picture during the acute systolic dysfunction of Takotsubo cardiomyopathy to be worse in patients on chronic β-adrenergic–antagonist therapy.

Studies using intravenous β-adrenergic–antagonist therapy with propranolol or metoprolol in patients presenting with Takotsubo cardiomyopathy have reported improved systolic blood pressure, LVEF, and intraventricular pressure gradient, especially in those with dynamic midventricular obstruction.[9,14–16] However, 30-day treatment with an oral regimen of β-adrenergic antagonists, angiotensin-converting enzyme inhibitors, calcium channel blockers, and aspirin started at the time of diagnosis demonstrated no difference in the rapidity of improvement of LV myocardial dysfunction compared with a nontreated control group.[17]

Markedly higher levels of catecholamine hormones have been demonstrated in patients with Takotsubo cardiomyopathy compared with patients with Killip class III myocardial infarction,[11] and the adrenergic blockade achieved with commonly used doses of β-adrenergic antagonists may not be sufficient to effectively antagonize the supraphysiologic catecholamine surge seen in Takotsubo cardiomyopathy. Other potential confounders such as the degree of stress (and the resultant catecholamine surge), intensity of chest pain, concomitant medication use (such as recent β-agonist nebulizer treatment), and medication compliance could also affect the studied parameters. It is important to note that the 2 groups were unbalanced with respect to age and other comorbidities, with patients on β-adrenergic–antagonist therapy being older (73.1 years vs 66 years; $P < 0.05$) with higher prevalence of cardiovascular risk factors.

Our study has some limitations. This is a single-center analysis, and the β-blocker–treated patients were on 3 different formulations. As with other studies on Takotsubo cardiomyopathy, our study is limited by small sample size. We did not have sufficient power to analyze the effect of the different formulations of β-blockers. We could not study time to recovery of LV function due to wide variation in timing of postdischarge echocardiograms. However, hospital length of stay, which could be a surrogate for the rapidity of clinical recovery, was not significantly different between the 2 groups. As we only studied patients who had urgent or emergent cardiac catheterizations for the diagnosis, there may be patients with milder symptoms who are excluded and may have benefited from β-blocker therapy. In addition, the effect of higher doses of β-blockers on the severity of this condition is unknown.

## Conclusion

Based on our study, we conclude that low-dose β-adrenergic receptor antagonist therapy prior to presentation does not affect the severity of presentation or clinical course of Takotsubo cardiomyopathy as assessed by common laboratory, angiographic, and hemodynamic parameters of myocardial dysfunction or damage. Because of its limitations, the results of our study are inconclusive.

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