



# A Case of Takotsubo Cardiomyopathy Possibly Induced by Cilostazol Administration

Fukata M<sup>1\*</sup>, Hatakeyama K<sup>1</sup>, Yokoyama T<sup>1</sup>, Nakamura H<sup>1</sup>, Yasuda S<sup>1</sup>, Muta T<sup>1</sup>, Odashiro K<sup>1</sup>, Maruyama T<sup>1,2</sup> and Akashi K<sup>1</sup>

<sup>1</sup>Department of Medicine and Biosystemic Science, Kyushu University Faculty of Medicine, Japan

<sup>2</sup>Division for Student Counseling and Guidance, Faculty of Arts and Science, Japan

## Abstract

Takotsubo cardiomyopathy is a transient cardiac syndrome that involves left ventricular apical akinesis typically triggered by a significant emotional or physical stress. Here, we report a patient who presented with strong chest discomfort with left ventricular apical akinesis following cilostazol administration and was diagnosed with Takotsubo cardiomyopathy. Sudden onset of the disease immediately after cilostazol administration and no preceding emotional or physical stressors suggested that the pharmacological activity of cilostazol had triggered Takotsubo cardiomyopathy. Following the discontinuation of cilostazol and heart failure treatment, left ventricular dysfunction had fully recovered.

**Keywords:** Takotsubo cardiomyopathy; Cilostazol; Cyclic AMP; Left ventricular obstruction

## Introduction

Takotsubo cardiomyopathy is characterized by transient and regional left ventricular dysfunction, which does not correspond anatomically to coronary distribution, without obstructive coronary lesions. The onset of the disease frequently follows episodes of emotional or physiological stress. However, the preceding stressor is not clearly identifiable in part of the patients [1,2]. In the patients without preceding emotional or physiological stressors, several drugs are reported as the possible triggers [3]. We present here a case in which preceding cilostazol administration and underlying left ventricular outflow tract obstruction (LVOTO) were noted to precipitate Takotsubo cardiomyopathy.

## OPEN ACCESS

### \*Correspondence:

Mitsuhiro Fukata, Department of Medicine and Biosystemic Science, Kyushu University Faculty of Medicine, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan,  
E-mail: mfukata-circ@umin.net

**Received Date:** 02 Apr 2016

**Accepted Date:** 29 Apr 2016

**Published Date:** 05 May 2016

### Citation:

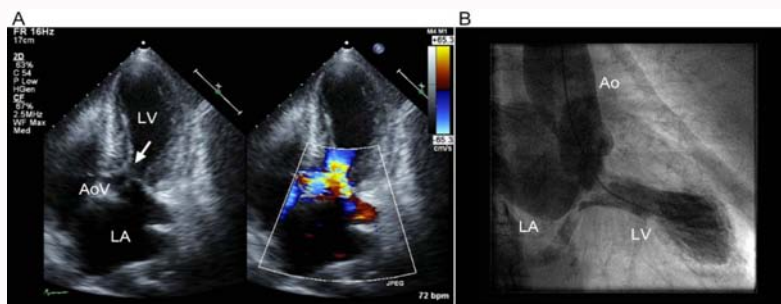
Fukata M, Hatakeyama K, Yokoyama T, Nakamura H, Yasuda S, Muta T. A Case of Takotsubo Cardiomyopathy Possibly Induced by Cilostazol Administration. *Clin Surg*. 2016; 1: 1010.

**Copyright** © 2016 Fukata M. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

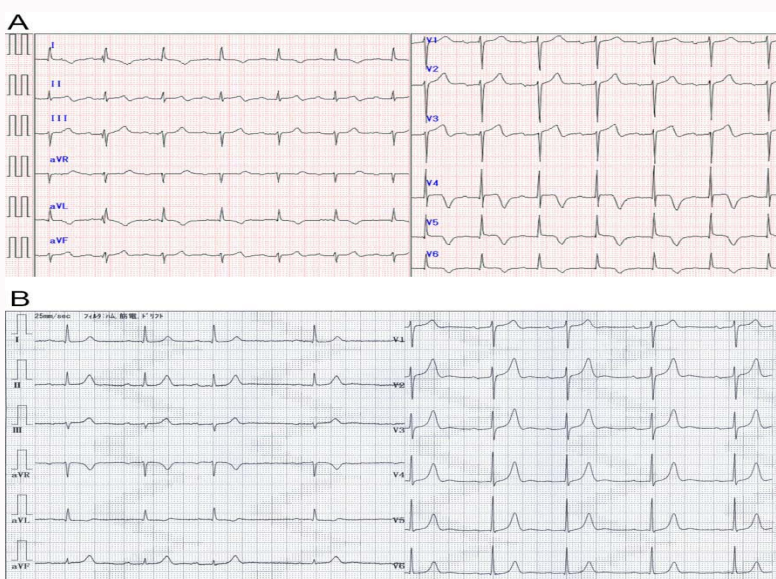
## Case Presentation

An 81-year-old woman presented with strong chest discomfort to our hospital on October 28, 2013. A physical examination revealed both an ejection systolic murmur (Levine II/VI, max at the third intercostal space along the left sternal border) and regurgitant systolic murmur (Levine III/VI, max at the apex). The electrocardiogram exhibited an elevated ST segment in leads II, III, aVF, and V2-5 and negative T wave in leads I, aVL, and V4-6 (Figure 1A). The echocardiography showed apical akinesis and basal hyperkinesis, LVOTO (pressure gradient = 55 mmHg), and severe mitral regurgitation with systolic anterior movement (SAM) of the anterior mitral leaflet (Figure 2A, see supplementary movie file). The left ventricular ejection fraction was decreased to 53.0%, as evaluated by the biplane method of disks. Serum CK, CK-MB, and Troponin T were mildly elevated to 210 U/L, 21 U/L, and 0.447 ng/mL, respectively. Emergent cardiac catheterization was performed to eliminate the possibility of acute coronary syndrome. Coronary artery stenosis and occlusion were not found on coronary angiography. Left ventriculography confirmed apical akinesis, circumferential severe hypokinesis of the mid ventricle, basal hyperkinesis, and severe mitral regurgitation (Figure 2B). The intra-left ventricular pressure gradient was approximately 50 mmHg by catheterization. Based on these findings, the patient was diagnosed with Takotsubo cardiomyopathy.

The patient had been diagnosed with ventricular septal hypertrophy with LVOTO (pressure gradient = 14 mmHg) and sick sinus syndrome by her family doctor one month previously. She was administered 100mg cilostazol per day from October 25 to treat symptomatic sinus bradycardia, and the dose was increased to 200mg per day from October 26. Takotsubo cardiomyopathy was presumed to have developed suddenly following the dose increase in cilostazol because neither electrocardiogram nor echocardiography exhibited an ST-T abnormality or apical hypokinesis, respectively, on October 26 (Figure 1B). She was hospitalized following cardiac catheterization.



**Figure 1:** An electrocardiogram on admission (A) exhibited an elevated ST segment in leads II, III, aVF, and V2-5 and negative T wave in leads I, aVL, and V4-6. No ST-T abnormality was present in an electrocardiogram 2 days before admission (B).



**Figure 2:** Apical 5 chamber view of echocardiographic image at systole (A) showed left ventricular outflow tract obstruction (LVOTO) with acceleration flow and systolic anterior movement (SAM, indicated by an arrow) of the anterior mitral leaflet with severe mitral regurgitation. Left ventriculography at end-systole (B) demonstrated apical ballooning and basal hyper-contraction. The left ventricular chamber adopted a characteristic configuration that mimics Takotsubo. Abbreviations: LA, left atrium; LV, left ventricle; AoV, aortic valve; Ao, ascending aorta. Wall motion abnormality and dynamic obstruction in LV is shown in the movie (supplementary file).

Cilostazol was discontinued from the date of admission. The administration of cibenzoline was initiated to ameliorate LVOTO. She developed acute pulmonary edema and was treated with diuretics and human atrial natriuretic peptide. A permanent pacemaker was implanted for the treatment of excessive bradycardia. Her symptoms were gradually improved along with the amelioration of the left ventricular wall motion abnormality. Neither LVOTO nor SAM could be detected on echocardiography at discharge. Serum BNP level dropped from 1047.2pg/mL on admission to 139.1pg/mL before discharge.

### Discussion

Takotsubo cardiomyopathy is a well-described disease entity that is characterized by transient apical or mid-ventricular left ventricular dysfunction in response to sudden, unexpected emotional distress and is relatively common in elderly woman. Enhanced cardiomyocytes stimulation by catecholamines related to emotional or physical distress is considered to play a major role in the pathogenesis of this cardiomyopathy from the findings in the human study and the experiment using the animal model [4,5]. Catecholamine-induced myocardial stunning in Takotsubo cardiomyopathy is possibly

mediated by a switch in  $\beta_2$  adrenoceptor coupling from Gs protein signaling to Gi protein signaling [6]. Since it had been demonstrated that intracellular cyclic adenosine monophosphate (cAMP)-dependent protein kinase A phosphorylation of the  $\beta_2$  adrenoceptor initiate this switch in signal trafficking [7], cAMP increases in the ventricular myocardium can exert not only positive inotropism in the base via  $\beta_1$  adrenoceptor-Gs signaling, but also negative inotropism in the apex via  $\beta_2$  adrenoceptor-Gi signaling [6]. Additionally, negative inotropism by catecholamines is possibly induced by cAMP-mediated calcium overload [8]. Therefore, cilostazol, a selective inhibitor of phosphodiesterase III, could cause Takotsubo cardiomyopathy by suppressing cAMP degradation with the resultant accumulation of intracellular cAMP. In addition to neurohumoral factors, an intra-left ventricular dynamic gradient, as was observed in this case, was previously shown to be a prerequisite for the development of Takotsubo cardiomyopathy [9]. Since this patient had no episode of significant mental distress before the onset of chest discomfort, the pharmacological action of cilostazol to increase cAMP in a heart possessing a structural prerequisite could have likely precipitated Takotsubo cardiomyopathy.

To our best knowledge, this is the first report that cilostazol could

induce Takotsubo cardiomyopathy. Most of the drugs that have been reported as a possible trigger of Takotsubo cardiomyopathy are considered to precipitate Takotsubo cardiomyopathy by catecholamine surge or by overstimulation of the sympathetic nerve system [3]. We suppose that in addition to these sympathetic agonists or sympathomimetic drugs, the drugs that upregulate the molecules mediating adrenoceptor signaling could cause this cardiomyopathy. Supporting this supposition, there are three case reports of Takotsubo cardiomyopathy induced by the administration of the cAMP increasing drugs (levothyroxine [10], anagrelide [11], dipyridamole [12]). The pathophysiological role of cAMP in Takotsubo cardiomyopathy should be specifically examined in future to further understand the disease.

This study describes an informative case in which cilostazol, a commonly used drug in the cardiovascular field, could have triggered Takotsubo cardiomyopathy. This case highlights the role of intracellular cAMP levels in the pathogenesis of Takotsubo cardiomyopathy and suggests the need for careful observation following the administration of a phosphodiesterase inhibitor as well as other cAMP-increasing agents, especially to a patient with an intra-left ventricular obstruction.

## References

1. Sharkey SW, Windenburg DC, Lesser JR, et al. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. *J Am Coll Cardiol*. 2010; 55: 333-341.
2. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA*. 2011; 306: 277-286.
3. Amariles P. A comprehensive literature search: drugs as possible triggers of Takotsubo cardiomyopathy. *Curr Clin Pharmacol*. 2011; 6: 1-11.
4. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005; 352: 539-548.
5. Ueyama T, Kasamatsu K, Hano T, Yamamoto K, Tsuruo Y, Nishio I. Emotional stress induces transient left ventricular hypocontraction in the rat via activation of cardiac adrenoceptors: a possible animal model of 'tako-tsubo' cardiomyopathy. *Circ J*. 2002; 66: 712-713.
6. Lyon AR, Rees PS, Prasad S, Poole-Wilson PA, Harding SE. Stress (Takotsubo) cardiomyopathy - a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat Clin Pract Cardiovasc Med*. 2008; 5: 22-29.
7. Daaka Y, Luttrell LM, Lefkowitz RJ. Switching of the coupling of the beta2-adrenergic receptor to different G proteins by protein kinase A. *Nature*. 1997; 390: 88-91.
8. Mann DL, Kent RL, Parsons B, Cooper G 4th. Adrenergic effects on the biology of the adult mammalian cardiocyte. *Circulation*. 1992; 85: 790-804.
9. Merli E, Sutcliffe S, Gori M, Sutherland GG. Tako-Tsubo cardiomyopathy: new insights into the possible underlying pathophysiology. *Eur J Echocardiogr*. 2006; 7: 53-61.
10. Kwon SA, Yang JH, Kim MK, Park SW, Kim SH, Park KH, et al. A case of Takotsubo cardiomyopathy in a patient with iatrogenic thyrotoxicosis. *Int J Cardiol*. 2010; 145: e111-113.
11. Proietti R, Rognoni A, Ardizzone F, Maccio S, Santagostino A, Rognoni G. Atypical Takotsubo syndrome during anagrelide therapy. *J Cardiovasc Med (Hagerstown)*. 2009; 10: 546-549.
12. Koh AS, Kok H, Chua T, Keng F. Takotsubo cardiomyopathy following dipyridamole pharmacologic stress. *Ann Nucl Med*. 2010; 24: 497-500.