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# Takotsubo cardiomyopathy and flecainide toxicity: a case report and brief literature review

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**Abstract. – OBJECTIVE: Takotsubo syndrome, also known as stress cardiomyopathy, is predominantly reported in postmenopausal women and it is often triggered by a physical or emotional stressor.**

**CASE REPORT: We present the case of a 44-year-old Caucasian woman admitted to the emergency department after voluntary intake of 20 tablets of flecainide 150 mg to commit suicide. During the in-hospital stay in the Cardiac Intensive Care Unit, the patient developed Takotsubo syndrome.**

**CONCLUSIONS: The relative role of flecainide as a possible trigger of the syndrome is discussed in the context of the current literature evidence.**

*Key Words:*
Takotsubo cardiomyopathy, Heart failure, Flecainide, Drug-related side effects and adverse reactions.

## Introduction

Takotsubo syndrome, also known as stress cardiomyopathy, is a disease mimicking a myocardial infarction with an acute onset associated with left ventricular apical dyskinesia ("ballooning") not related to a coronary artery occlusion[1]. It is predominantly reported in postmenopausal women and it is often triggered by a physical or emotional stressor. Moreover, Takotsubo-like syndromes can be observed in different disease where endogenous catecholamines play a role (strokes, cerebral tumors, head traumas, catecholamine-secreting tumors) or sympathomimetic drugs are administered (cardiac arrest, shock, cardiovascular stress tests, anesthesia)[2].

### Case Presentation

A 44-year-old Caucasian woman without previous history of systemic disease was admitted to the emergency department after voluntary intake of 20 tablets of flecainide 150 mg to commit suicide. The drug was available in her home because her husband was on antiarrhythmic treatment. No information was given by the patient's relatives about any possible emotional distress or mental disorder that could have precipitated the suicide attempt.

She had a syncopal episode associated with sphincter release and a bifocal fracture of the jaw.

She was in cardiogenic shock, pale, cold and with sweaty skin. Hemodynamics was characterized by blood pressure (BP) of 70/50 mmHg and heart rate (HR) of 40 bpm. Glasgow Coma Scale (GCS) was 9. Soon after, the patient presented a pulseless ventricular tachycardia and then ventricular fibrillation promptly interrupted by cardiopulmonary resuscitation and 200 J DC shock. Spontaneous sinus rhythm with wide QRS at 38 bpm was restored. Therefore, a transvenous pacemaker (PM), set to VVI 80 bpm, was placed.

In the meantime, GCS dropped to 7 so she was sedated and curarized while orotracheal intubation for mechanical ventilation was performed.

BP was 60/30 mmHg; HR was 80 bpm in PM-induced rhythm. A condition of metabolic acidosis (pH 7.25, $pO_2$176, $pCO_2$ 36, $HCO_3$ 16.2, BE -10.3) was present. Hence, infusion of noradrenalin 0.1 mcg/Kg/min was started with improvement of hemodynamic conditions.

Blood tests and chest X-ray examinations did not detect any abnormalities. Flecainide (or another drug) serum levels were not measured. Therefore, she was referred to the Cardiac Intensive Care Unit.

A first transthoracic echocardiogram showed a normal-sized left ventricle with an ejection fraction (LVEF) of 45% and global hypokinesia.

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A second echocardiogram performed on the second day showed an uncoordinated movement of interventricular septum due to the PM stimuli and a slightly reduced global systolic function (LVEF 45%) with severe hypokinesia of apical and periapical segments.

Because of the improvement of the clinical conditions and hemodynamics on the third day, PM output frequency was lowered to 50 bpm and, shortly after, it was removed. A narrow QRS sinus rhythm at 63 bpm was observed in presence of marked ventricular repolarization changes: negative T waves with symmetrical branches in II, III, aVF, V1-V6 and a QTc of 560 ms.

The patient underwent daily ECG monitoring showing the persistence of all the ECG abnormalities described above.

On the tenth day, because of the clinical suspicion of Takotsubo syndrome, cardiac magnetic resonance imaging (MRI) was performed and showed diffuse edematous changes in the apical hypokinetic segments. The injection of gadolinium highlighted patchy areas of late gadolinium enhancement (LGE) in the apical segments with a mid-wall pattern and a non-ischemic distribution (Figure 1, Column A). These findings were suggestive of a stress-induced cardiomyopathy.

The patient was questioned about the presence and regularity of her menstrual cycle and replied that she had regular menses.

After discharge, on the 23$^{rd}$ day, a follow-up control ECG showed persistent negative T waves in anterior leads. A transthoracic echocardiogram showed mild improvement of LVEF (50%) and mild apical and periapical hypokinesia (Figure 2, Column B). A second cardiac MRI performed on the 46$^{th}$ day showed a resolution of the edematous changes. Furthermore, LGE areas were no longer appreciable in the left ventricle, corroborating

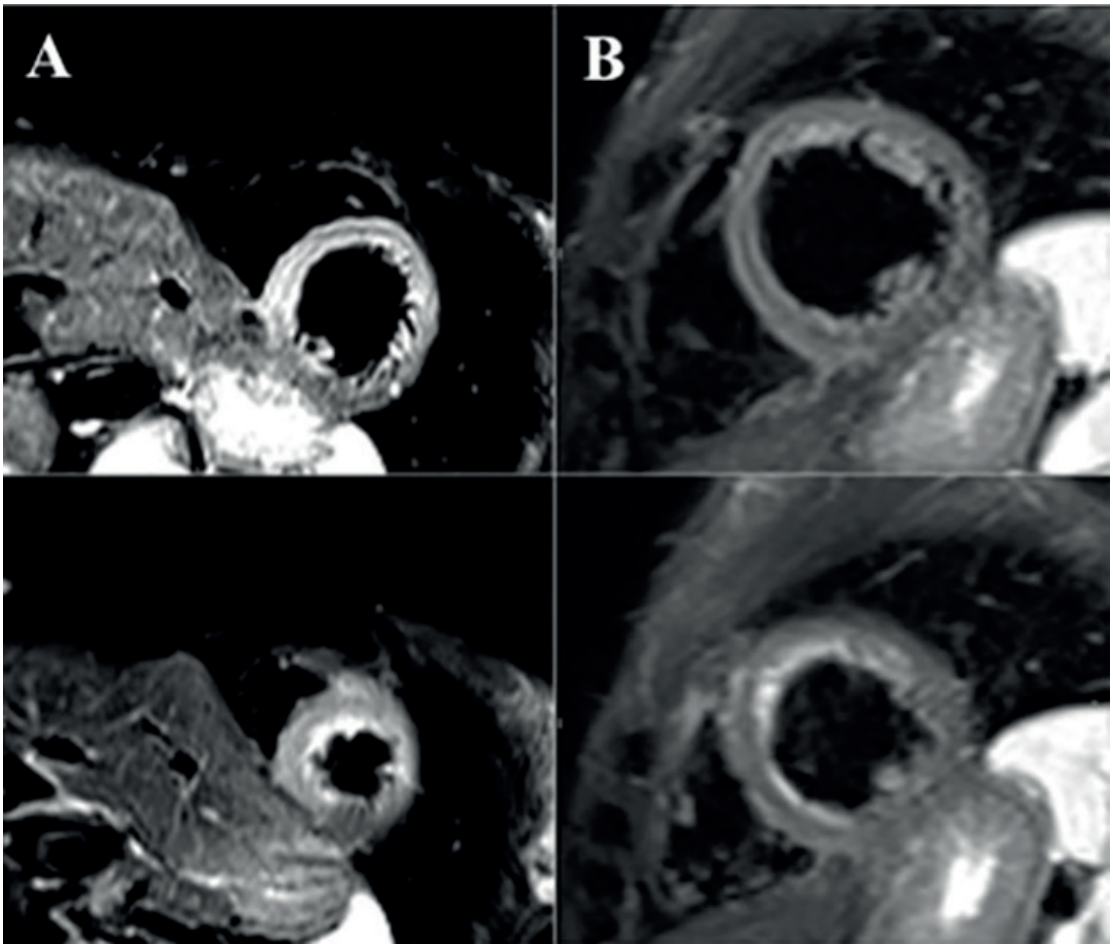


***Figure 1.*** Magnetic Resonance Imaging. **A,** Short axis, T2-weighted images show a diffuse edematous involvement of the mid ventricular and apical segments. **B,** After 1 month T2-weighted images show the absence of edema.

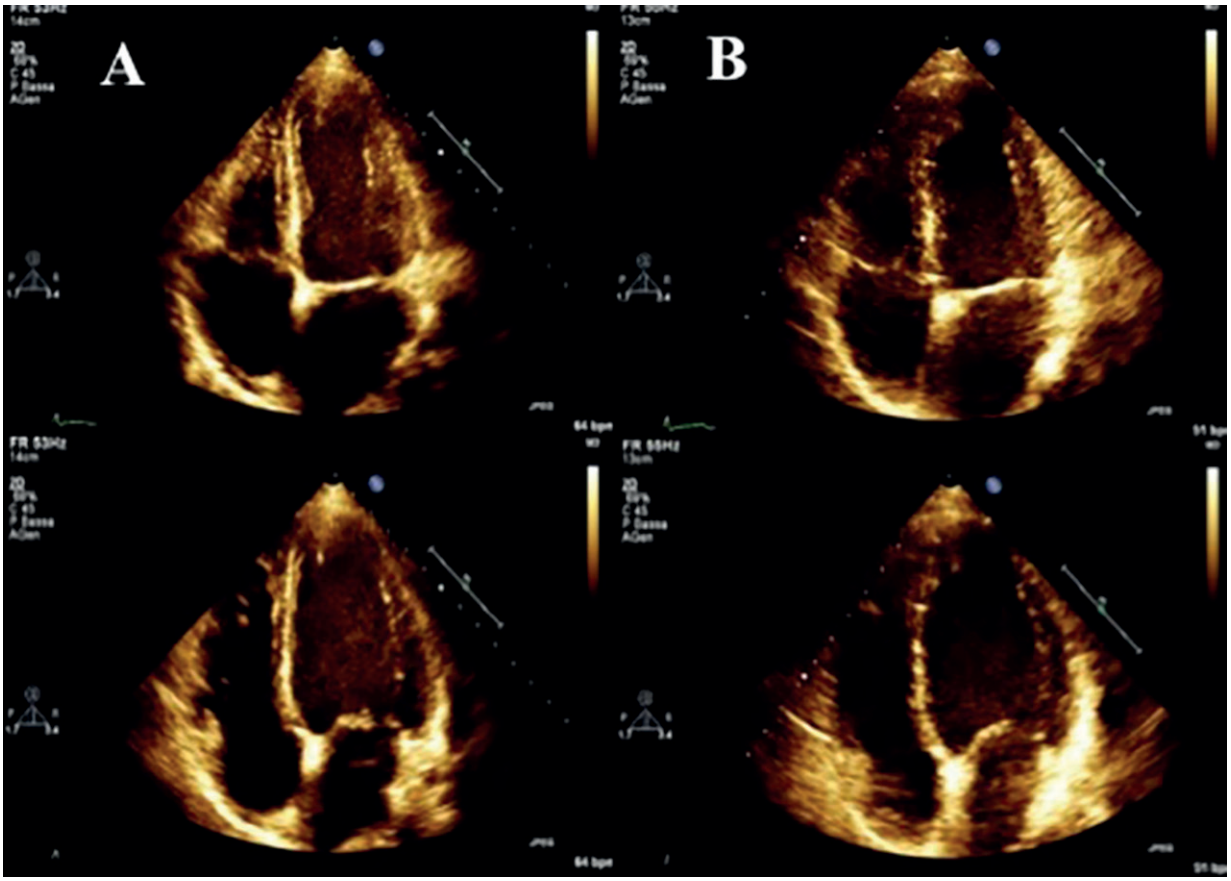


**Figure 2.** Echocardiogram. **A,** The apical four chamber view shows an apical ballooning in end-systole. **B,** After 1 month, recovery of ventricular shape.

the diagnosis of Takotsubo syndrome (Figure 1, Column B). On the 78th day, the ECG repolarization phase was completely restored, and, at the transthoracic echocardiogram, only inferior segments of the interventricular septum were mildly hypokinetic.

## Discussion

We believe that in the reported case the ingestion of high-dose flecainide may have played a role in the onset of Takotsubo cardiomyopathy together with the emotional situation that induced the patient to commit suicide.

Flecainide is one of the Vaughan Williams class I C antiarrhythmic drugs, which are inhibitors of the fast sodium channel, and it is used for the treatment of supraventricular and ventricular arrhythmias. It causes a marked depression of the upstroke of the cardiac action potential, a delay in the inactivation of the slow sodium channel and an inhibition of the rapid repolarizing current IKr[3]. Pro-arrhythmic effects of flecainide relate to the facilitation of reentry in the ventricular tissue and consequent induction of arrhythmias as conventional rapid ventricular tachycardias or *torsades de pointes*. These effects depend on a non-uniform slowing of conduction and appear to be dose-related[4-7]. Moreover, the negative inotropic effect of flecainide may play a role in takotsubo syndrome ventricular dysfunction[8]. In overdose accidents, as the case we describe in this report, mortality is close to 22%[7].

On the other hand, Takotsubo or «broken heart» syndrome, with transient left ventricular apical ballooning, is growing in importance and diagnosis frequency during the last years since it was described by Sato et al[9]. Takotsubo syndrome usually has a good prognosis; however, complications are reported during the acute phase, including heart failure and ventricular arrhythmias[10]. It is characterized by acute chest symptoms, typical

extended left ventricular apical wall motion abnormalities, usually affecting various coronary territories with a disproportionate myocardial necrosis marker release, in absence of "culprit" coronary lesions. The myocardial stunning is probably related to an excessive catecholamine incretion[11]. The syndrome was originally described in postmenopausal women and, over time, has been associated with an increasingly advanced age[12] and a marked gender preference (90% of cases are female with an age range of 62-76 years)[13]. Estrogen deficiency per se does not appear to be a risk factor for the Takotsubo cardiomyopathy, whereas both age-related and estrogen deficiency-related endothelial dysfunction in menopause can play a pathogenetic role[14].

The aforementioned epidemiological features make it unlikely that a 44-year-old fertile woman could develop a takotsubo syndrome without the intervention of drug stimuli such as the combination of high-dose flecainide and noradrenalin resulting from stress incretion or administration in the emergency department. In this context, the most appropriate diagnosis of our clinical case should be Takotsubo-like syndrome or takotsubo syndrome phenocopy[2].

Literature is scant about possible association between flecainide use and the occurrence of takotsubo syndrome. Gabriel et al[15] described a series of 12 patients with takotsubo cardiomyopathy: four of them were treated by flecainide for a long time before. They underlined that flecainide could play a role in triggering Takotsubo syndrome or could increase left ventricular dysfunction or favor occurrence and severity of complications. They suggests that flecainide use should be avoided in patients with a history of Takotsubo syndrome.

In 2009 Zaman et al[16] described a case of a 46-year-old female with a history of atrial fibrillation treated with flecainide 100 mg twice a day who developed ventricular fibrillation during a laparoscopic cholecystectomy and was diagnosed with takotsubo syndrome associated with arrhythmogenic right ventricular cardiomyopathy.

In 2019 Bodziock et al[8] and Viland et al[17] respectively reported the case of a 48-year-old man and a woman in her fifties who attempted suicide by ingesting extra tablets of flecainide they were prescribed for atrial fibrillation. As in our case, both patients developed a takotsubo syndrome.

All cases reported in the literature, such as the one we described, had a favorable prognosis thanks to emergency interventions.

## Conclusions

It is difficult to discriminate in the case of Takotsubo syndrome that we have presented which pathogenetic factor could have played a major role. Both excessive serum catecholamines, probably secreted in response to suicide-related stressful events, and the proarrhythmic action of high dose flecainide were possible candidates. In particular, the chronology of the events in this case points out the "guilt" of high dose flecainide toxicity in inducing life-threatening ventricular arrhythmias, as it has been already described in a similar case of suicide attempt that did not develop a takotsubo syndrome[18]. In our case, the resulting "stunned" myocardium, possibly sensitized by the excessive catecholamine incretion, developed the features of an apical ballooning syndrome.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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## References

1) Sharkey SW, Lesser JR, Zenovich AG, Maron MS, Lindberg J, Longe TF, Maron BJ. Acute and reversible cardiomyopathy provoked by stress in women from the United States. Circulation 2005; 111: 472-479.
2) Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of takotsubo syndrome. Circulation 2017; 135: 2426-2441.
3) Reiffel JA, Blitzer M. The actions of ibutilide and class Ic drugs on the slow sodium channel: new insights regarding individual pharmacologic effects elucidated through combination therapies. J Cardiovasc Pharmacol Ther 2000; 5: 177-181.
4) The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989; 321: 406-412.
5) Krishnan SC, Antzelevitch C. Flecainide-induced arrhythmia in canine ventricular epicardium. Phase 2 reentry? Circulation 1993; 87: 562-572.
6) Nogales Asensio JM, Moreno Sánchez N, Doncel Vecino LJ, Villar Mariscal C, López-Mínguez JR, Merchán Herrera A. Torsade-de-pointes in

a patient under flecainide treatment, an unusual case of proarrhythmicity. Int J Cardiol 2007; 114: E65-E67.

7) Courand PY, Sibellas F, Ranc S, Mullier A, Kirkorian G, Bonnefoy E. Arrhythmogenic effect of flecainide toxicity. Cardiology J 2013; 20: 203-205.
8) Bodziock G, Armstrong C, Montgomery J. Flecainide overdose presenting with long QT and acute Takotsubo cardiomyopathy. J Electrocardiology 2019; 52: 7-9.
9) Sato H, Taiteishi H, Uchida T: Takotsubo-type cardiomyopathy due to multivessel spasm. In: Clinical aspect of myocardial injury: In Ischemia to Heart Failure, Kodama K, Haze K, Hon M (eds.), Kagakuhyouronsha, Tokyo, Japan 1990. p. 56-64.
10) Núñez-Gil IJ, Mejía-Rentería HD, Martínez-Losas P. Practical update of Takotsubo syndrome. Medicina Clinica (Barc) 2016; 146: 212-217.
11) Ono R and Falcão LM. Takotsubo cardiomyopathy systematic review: Pathophysiologic process, clinical presentation and diagnostic approach to Takotsubo cardiomyopathy. Int J Cardiol 2016; 209: 196-205.
12) Biccirè FG, Pannarale G, Acconcia MC, Torromeo C, Cardillo I, Chianta V, Ferrari I, Gaudio C and Barillà F. Clinical frailty and triggers in Takotsubo syndrome: the notable role of a new classification. J Cardiovasc Med (Hagerstown) 2020; 21: 144-149.
13) Schneider B, Sechtem U. Influence of age and gender in Takotsubo syndrome. Heart Failure Clin 2016; 12: 521-530.
14) Pelliccia F, Gaudio C. The elusive link between sex hormone levels and Takotsubo syndrome. Int J Cardiol 2018; 250: 58-59.
15) Gabriel L, Chenu P, Guédès A, Dangoisse V, Marchandise B, Blommaert D, Jamart J, De Roy L, Schroeder E. A possible association between Takotsubo cardiomyopathy and treatment with flecainide. Int J Cardiol 2011; 147: 173-175.
16) Zaman S, Ramesh N, Kovoor P. Arrhythmogenic right ventricular cardiomyopathy presenting with intra-operative aborted sudden cardiac death and takotsubo-like left ventricular functional abnormalities. Hellenic J Cardiol 2009; 50: 330-334.
17) Viland J, Langørgen J, Wendelbo Ø. A somnolent woman in her fifties with acute circulatory failure. Tidsskr Nor Laegeforen 2019; 139. Norwegian, English. doi: 10.4045/tidsskr.18.0683. Erratum in: Tidsskr Nor Laegeforen 2019; 139: PMID: 31140247.
18) Mandawat A, McCullough SA, Gilstrap LG, Yeh RW. Successful treatment of flecainide overdose with sustained mechanical circulatory support. Heart Rhythm Case Rep 2015; 1: 137-140.