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Case Reports

Can Breaking Heroin Addiction Lead to a Broken Heart? A Case of Reverse Takotsubo Cardiomyopathy in a Patient With Heroin Withdrawal

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Abstract

Reverse takotsubo cardiomyopathy is triggered by emotional or physical stress and has a presentation similar to that of acute coronary syndrome. A 39-year-old woman with a history of heroin use disorder presented with intractable nausea, vomiting, and diarrhea. She was diagnosed with heroin withdrawal and started on buprenorphine-naloxone. On day 2 of her hospitalization, she developed chest heaviness and had an elevated troponin I level of 3.2 ng/mL (reference range, 0.015-0.045 ng/mL); electrocardiography showed new T-wave inversions in the anterior and inferior leads. Emergent coronary angiography showed patent coronary arteries, and left ventriculography showed basal hypokinesis and apical hyperkinesis, consistent with reverse takotsubo cardiomyopathy secondary to heroin withdrawal. She was started on antihypertensive agents, and her buprenorphine-naloxone dose was increased. At her 3-month follow-up visit, she reported no symptoms consistent with angina or heart failure. This appears to be the first report of heroin withdrawal causing reverse takotsubo cardiomyopathy. Awareness of this association can lead to earlier recognition and treatment of reverse takotsubo cardiomyopathy.

Keywords: Takotsubo cardiomyopathy; takotsubo syndrome; heroin, adverse effects; heroin, toxicity; heroin, antagonists and inhibitors

Introduction

Takotsubo cardiomyopathy (TC) is a transient, severe left ventricular dysfunction originally characterized in Japan in the early 1990s.[1] "Tako-tsubo" means "octopus trap" and refers to the characteristic apical ballooning shape seen on left ventriculography.[2] The condition was coined "broken heart syndrome" because patients typically present after experiencing emotional or physical stressors.[2] The resulting catecholamine surge leads to catecholamine toxicity and, ultimately, myocardial damage.[1] Takotsubo cardiomyopathy often has a similar presentation to that of acute coronary syndrome (ACS), with chest pain, dyspnea, and elevated troponin I levels.[3] However, unlike ACS, patients with TC have no substantial coronary artery disease.[4] Treatment is largely supportive, but retrospective data have shown improved survival at 1 year with the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[5] Reverse takotsubo cardiomyopathy (RTC) is a variant of TC that features basal akinesis and apical hyperkinesis in the setting of patent coronary arteries.[4] Known triggers of RTC include methamphetamine use, iatrogenic epinephrine overdose, general anesthesia, eating disorders, and neurologic conditions.[4] Treatment is largely supportive, and cardiac recovery occurs within weeks.

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Opioid withdrawal is a result of the physiologic dependence that develops in people who use opioids. Onset of symptoms can occur 8 to 12 hours after last use and peak at 36 to 72 hours.[6] Symptoms of withdrawal typically reflect autonomic hyperactivity with sweating, chills, lacrimation, tremor, pupillary dilatation, and piloerection.[7] Withdrawal is typically also associated with nausea, intestinal cramping, diarrhea, and vomiting.[7] Although opiate withdrawal has been associated with TC, no reports, to the authors' knowledge, have described an association with RTC.[8-13] Knowledge of this association will help in early recognition and treatment of RTC to improve patient outcomes.

Abbreviations and Acronyms

ACS	acute coronary syndrome
ECG	electrocardiogram
RTC	reverse takotsubo cardiomyopathy
SICM	stress-induced cardiomyopathy
TC	takotsubo cardiomyopathy

Case Report

A 39-year-old woman with a history of heroin use was admitted to the hospital at 9:00 PM with intractable emesis, nausea, and diarrhea. She reported snorting approximately 1 gram of heroin daily for the past 2 years, with last use 2 days before presentation. One day before presentation, she had admitted herself to a detoxification facility where symptom onset occurred. Upon presentation to the emergency department, the patient reported diffuse abdominal discomfort, but she did not have any hematemesis, hematochezia, chest pain, or shortness of breath. She reported a history of hypertension but no other personal or family cardiac history. Her vital signs on admission were notable for a temperature of 101.4 °F, blood pressure of 188/110 mm Hg, pulse rate 70/min, respirations 14/min, and oxygen saturation 98% on room air. On physical examination, she was notably uncomfortable, frequently switching positions in bed. She had excessive lacrimation from both eyes, excessive yawning, and intermittent green emesis, and she made frequent trips to the bathroom for diarrhea and to take hot showers. Cardiovascular examination revealed a regular heart rate and rhythm with an audible S1 and S2; there were no murmurs, rubs, or gallops. Her abdomen was mildly and diffusely tender to palpation. There were no visible injection sites on skin examination.

An electrocardiogram (ECG) showed normal sinus rhythm with a heart rate of 70/min (Fig. 1). Her initial troponin I level was 0.973 ng/mL (reference range, 0.015-0.045 ng/mL) and brain natriuretic peptide level was 669 pg/nL (reference range, 0-450 pg/nL). The patient was given a single dose of aspirin (325 mg). When her troponin I level rose to 2,440 ng/mL at 6 hours later, the cardiology team was consulted. They attributed the troponin I elevation to demand ischemia in the setting of hypertension and active drug withdrawal, and they recommended blood pressure control with lisinopril and treatment of her opioid withdrawal.

On the second hospital day, the psychiatry team was consulted to help with her withdrawal symptoms. Buprenorphine-naloxone (Suboxone) was initiated at 12:10 PM on hospital day 2 at a dose of 4/1 mg with a

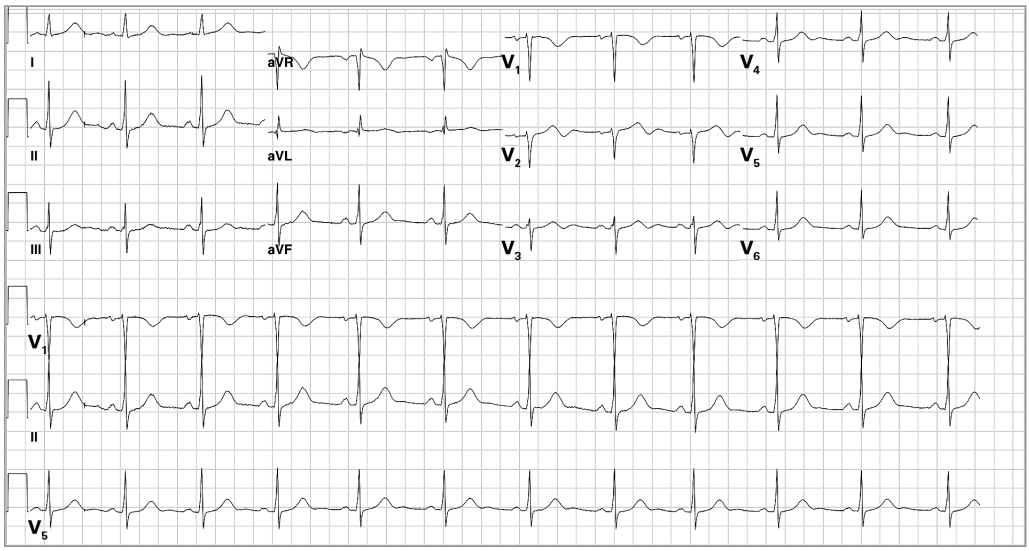

Fig. 1 Electrocardiogram shows normal sinus rhythm with a pulse rate of 70/min.

plan for uptitration if needed. She began to experience new symptoms of chest heaviness and promptly received sublingual nitroglycerin 0.4 mg at 12:20 PM. The patient received another 4/1-mg dose of buprenorphine-naloxone at 3:36 PM. Repeat ECG at 4:43 PM showed new T-wave inversions in the anterior and inferior leads (Fig. 2), and a repeat troponin I level was 3,200 ng/mL. The patient was transferred to the cardiac care unit and started on an intravenous nitroglycerin drip at 7:55 PM. She was then taken to the catheterization laboratory for emergent coronary angiography.

The results of angiography showed patent coronary arteries without substantial coronary artery disease. Left ventriculography showed basal hypokinesis and apical hyperkinesis (Fig. 3). Transthoracic echocardiography showed an ejection fraction of 50% to 55% with hypokinesis of the basal-mid inferoseptal and basal-mid

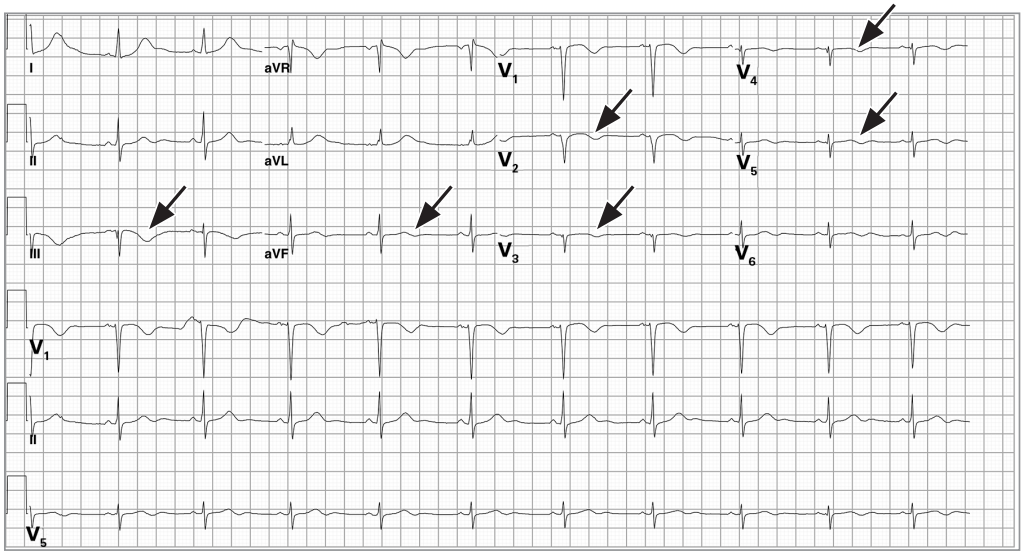

Fig. 2 Electrocardiogram shows normal sinus rhythm with T-wave inversions in the inferior and anterior leads (arrows).

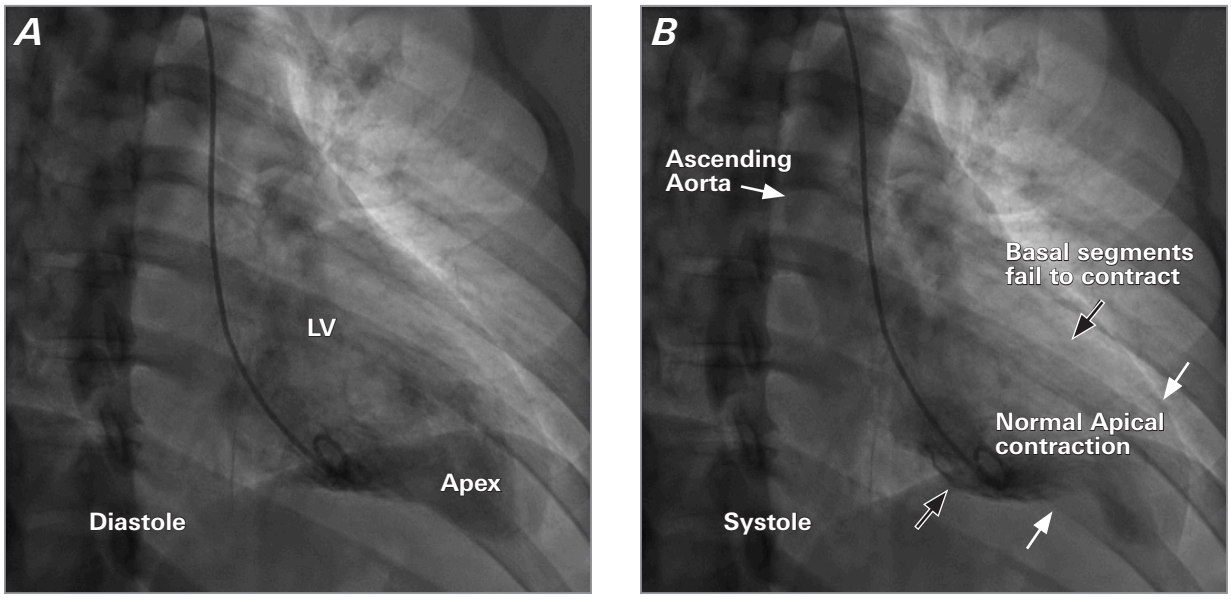

Fig. 3 Left ventriculography in right anterior oblique projection. **A**) Basal hypokinesis and apical hyperkinesis is seen during diastole. **B**) The LV is shown in systole.

Supplemental motion images are available for Figure 3A and Figure 3B.

LV, left ventricle.

inferior walls (Fig. 4 and Fig. 5). The patient was diagnosed with RTC secondary to heroin withdrawal, given the transient left ventricular wall motion abnormalities that extended beyond the territory supplied by a single coronary artery.

She was started on lisinopril, carvedilol, and amlodipine, with a plan to increase the lisinopril as needed to control her hypertension. On hospital day 3, the psychiatry team increased her buprenorphine-naloxone dose to 8/2 mg twice daily. The plan was to continue this dose and to set up outpatient follow-up. At the 3-month follow-up visit, she was doing well and remained sober from heroin; she reported no symptoms consistent with angina or heart failure. Bedside ultrasonography showed resolution of the basal inferior and inferoseptal wall motion abnormalities. Unfortunately, the patient cited time constrictions with her occupation and never underwent formal repeat transthoracic echocardiography or attended subsequent appointments, but she reported over the phone that she was doing well.

Discussion

Stress-induced cardiomyopathy (SICM)—also known as TC or "broken heart syndrome"—was first described in Japan in 1990.[2] The condition was originally characterized as an acute, usually reversible, left ventricular apical dysfunction with the wall motion abnormality extending beyond a single coronary artery perfusion territory. Almost all patients are women (90%) and are typically postmenopausal (average age, 66.8 years). Patients present after experiencing emotional or physical stress with characteristics similar to ACS but without evidence of obstructive coronary artery disease on catheterization.[5] Most patients present with chest pain or dyspnea, but up to 8% present with nausea and vomiting.[14] The symptoms of abdominal pain in the patient featured in this report were thought to be more likely related to opioid withdrawal than to TC.

Of all patients with elevated troponin I levels who present with symptoms of ACS, an estimated 2% have TC.[3] Although the exact mechanisms are unknown, the underlying pathophysiology of TC is thought to be related to catecholamine surges resulting from emotional or physical stress.[4] Intracoronary acetylcholine administration has been shown to induce severe multivessel coronary artery spasm with apical ballooning.[15] Specialized centers should consider performing delayed (5-30 days) acetylcholine testing to help elucidate the underlying mechanism of TC.[15]

Treatment is usually supportive, but Patel et al[16] showed that intracoronary administration of nitroglycerin increases the median epicardial diameter in patients with TC by 24.8%. The patient in this report received

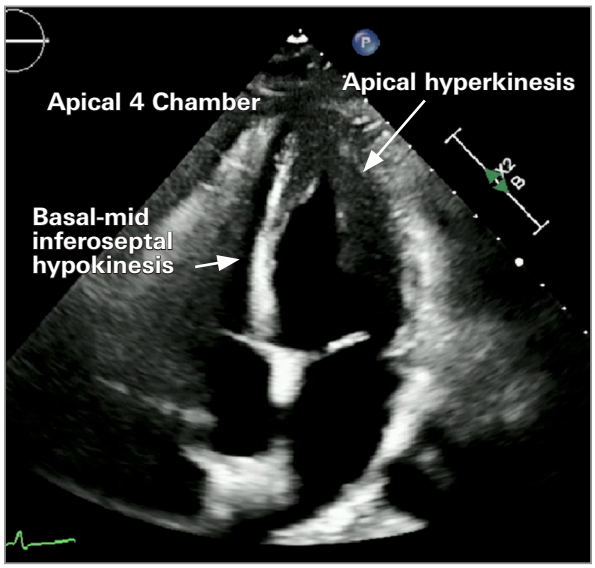

Fig. 4 The apical 4-chamber echocardiogram view shows basal-mid inferoseptal hypokinesis and apical hyperkinesis.

Supplemental motion image is available for Figure 4.

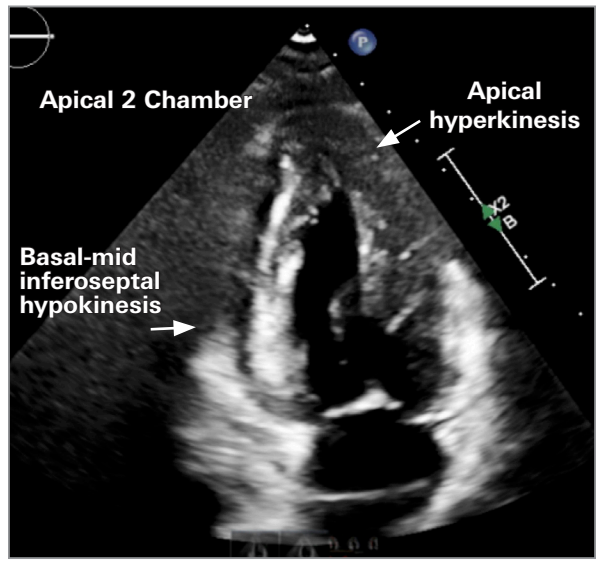

Fig. 5 The apical 2-chamber echocardiogram view shows basal-mid inferior hypokinesis and apical hyperkinesis.

Supplemental motion image is available for Figure 5.

intravenous nitroglycerin on hospital day 2, less than 24 hours after presentation, which may have blunted the occurrence of full TC. The left ventricular phenotype of TC is a moving target, and early administration of nitroglycerin may have led to an incomplete manifestation or postpeak manifestation of TC. The use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers has been shown to improve survival at 1 year.[5] Death rates are estimated at 5.6%, and the risk of major adverse cardiac or cerebrovascular events is 9.9% per patient-year.[17] The cardiac abnormalities associated with TC usually resolve within 4 to 8 weeks, and the rate of recurrence is 1.8% per patient-year.[4,5]

Several variants of TC or SICM have been described, including midventricular, basal, and focal.[5] Basal TC is synonymous with RTC and is characterized by basal hypokinesis with apical hyperkinesis, as experienced by the patient in this report. According to the International Takotsubo Registry, RTC accounts for 2.2% of all patients with TC and usually occurs in younger women than traditional TC, with a mean age of 36 years.[18] Compared with TC, the troponin I elevation is typically higher in RTC; the mean ejection fraction is lower (27.8% vs 34.5%), and the cardiac recovery is quicker (mean, 10.7 days vs 23.6 days).[19,20] One study found that all patients with RTC had experienced either physical or emotional stress, but in other types of TC, 15% of patients had no stressor identified.[19] The outcomes and recurrence of RTC are comparable to those of TC.[4]

Methamphetamine use, iatrogenic epinephrine overdose, general anesthesia, eating disorders, and neurologic conditions have all been described as triggers of the RTC form of SICM.[5] Although opiate and methadone withdrawal have been correlated with the development of TC, this is the first case report, to the authors' knowledge, describing an association of heroin withdrawal with the RTC form of TC.[8-13] Supervised buprenorphine has been used to treat withdrawal symptoms and mitigate the stress of withdrawal.[7] Given that the pathophysiology of TC involves increased concentrations of circulating catecholamines,[1] and given that increased catecholamines arise during heroin or methadone withdrawal, the early administration of buprenorphine (a medication that binds to μ opioid receptors) on hospital day 2 may have blunted the overall stress of withdrawal and thus the full occurrence of RTC in this patient.

This case report describes a unique pattern of RTC in a premenopausal woman who developed chest pain, ECG changes, and elevated troponin I levels while experiencing opiate withdrawal 2 days after last using heroin. Her ventricular wall motion abnormalities were typical of an RTC pattern, with basal-mid inferoseptal and basal-mid inferior wall hypokinesis and apical hyperkinesis. This report will hopefully raise awareness of RTC as a potential complication of heroin withdrawal. Further studies are needed to define the pathophysiology of RTC and to confirm whether early initiation of buprenorphine-naloxone, or other medications used to treat withdrawal, could help prevent RTC when the condition is induced by heroin withdrawal.

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References

1. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of takotsubo syndrome. *Circulation.* 2017;135(24):2426-2441. doi:10.1161/CIRCULATIONAHA.116.027121
2. Sato H, Tateishi H, Uchida T, Dote K, Ishihara M. Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm. In: Kodama K, Haze K, Hori M, eds. *Clinical Aspect of Myocardial Injury: From Ischemia to Heart Failure* (in Japanese). Kagaku Hyoronsha; 1990:56-64.
3. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (tako-tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J.* 2008;155(3):408-417. doi:10.1016/j.ahj.2007.11.008
4. Awad HH, McNeal AR, Goyal H. Reverse takotsubo cardiomyopathy: a comprehensive review. *Ann Transl Med.* 2018;6(23):460. doi:10.21037/atm.2018.11.08
5. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *N Engl J Med.* 2015;373(10):929-938. doi:10.1056/NEJMoa1406761
6. Surmaitis RM, Khalid MM, Vearrier D, Greenberg MI. Takotsubo cardiomyopathy associated with buprenorphine precipitated withdrawal. *Clin Toxicol (Phila).* 2018;56(9):863-864. doi:10.1080/15563650.2018.1437921
7. Shulman M, Wai JM, Nunes EV. Buprenorphine treatment for opioid use disorder: an overview. *CNS Drugs.* 2019;33(6):567-580. doi:10.1007/s40263-019-00637-z
8. Revelo AE, Pallavi R, Espana-Schmidt C, Visco F, Pekler G, Mushiyev S. "Stoned" people can get stunned myocardium: a case of heroin withdrawal precipitating takotsubo cardiomyopathy. *Int J Cardiol.* 2013;168(3):e96-e98. doi:10.1016/j.ijcard.2013.07.120
9. Sarcon A, Ghadri JR, Wong G, Lüscher TF, Templin C, Amsterdam E. Takotsubo cardiomyopathy associated with opiate withdrawal. *QJM.* 2014;107(4):301-302. doi:10.1093/qjmed/hct219
10. Spadotto V, Zorzi A, Elmaghawry M, Meggiolaro M, Pittoni GM. Heart failure due to 'stress cardiomyopathy': a severe manifestation of the opioid withdrawal syndrome.

Eur Heart J Acute Cardiovasc Care. 2013;2(1):84-87. doi:10.1177/2048872612474923
11. Lemesle F, Lemesle F, Nicola W, Pierre Jonville-Béra A. First case of stress cardiomyopathy as a result of methadone withdrawal secondary to drug-drug interaction. *Am J Emerg Med.* 2010;28(3):387.e5-387.e6. doi:10.1016/j.ajem.2009.07.007
12. Olson PC, Agarwal V, Lafferty JC, Bekheit S. Takotsubo cardiomyopathy precipitated by opiate withdrawal. *Heart Lung.* 2018;47(1):73-75. doi:10.1016/j.hrtlng.2017.10.001
13. Saiful FB, Lafferty J, Jun CH, et al. Takotsubo cardiomyopathy due to iatrogenic methadone withdrawal. *Rev Cardiovasc Med.* 2011;12(3):164-167.
14. Sanchez-Jimenez EF. Initial clinical presentation of Takotsubo cardiomyopathy with-a focus on electrocardiographic changes: a literature review of cases. *World J Cardiol.* 2013;5(7):228-241. doi:10.4330/wjc.v5.i7.228
15. Angelini P. Transient left ventricular apical ballooning: a unifying pathophysiologic theory at the edge of Prinzmetal angina. *Catheter Cardiovasc Interv.* 2008;71(3):342-352. doi:10.1002/ccd.21338
16. Patel SM, Lerman A, Lennon RJ, Prasad A. Impaired coronary microvascular reactivity in women with apical ballooning syndrome (Takotsubo/stress cardiomyopathy). *Eur Heart J Acute Cardiovasc Care.* 2013;2(2):147-152. doi:10.1177/2048872613475891
17. Ghadri JR, Wittstein IS, Prasad A, et al. International expert consensus document on takotsubo syndrome (part II): diagnostic workup, outcome, and management. *Eur Heart J.* 2018;39(22):2047-2062. doi:10.1093/eurheartj/ehy077
18. Ghadri JR, Cammann VL, Napp LC, et al; International Takotsubo (InterTAK) Registry. Differences in the clinical profile and outcomes of typical and atypical takotsubo syndrome: data from the International Takotsubo Registry. *JAMA Cardiol.* 2016;1(3):355-340. doi:10.1001/jamacardio.2016.0225
19. Ramaraj R, Movahed MR. Reverse or inverted takotsubo cardiomyopathy (reverse left ventricular apical ballooning syndrome) presents at a younger age compared with the mid or apical variant and is always associated with triggering stress. *Congest Heart Fail.* 2010;16(6)284-286. doi:10.1111/j.1751-7133.2010.00188.x
20. Song BG, Chun WJ, Park YH, et al. The clinical characteristics, laboratory parameters, electrocardiographic, and echocardiographic findings of reverse or inverted takotsubo cardiomyopathy: comparison with mid or apical variant. *Clin Cardiol.* 2011;34(11):693-699. doi:10.1002/clc.20953