The Texas Heart Institute® Journal

Case Reports

Can Significant Coronary Artery Disease Coexist With Transient Takotsubo Cardiomyopathy, and How Does Spasm Interrelate?

Paolo Angelini, MD[1]; Carlo Uribe, MD[1]; Philip A. Salem, MD[2]

[1]Center for Clinical Research, Texas Heart Institute, Houston, Texas
[2]Salem Oncology Center, Houston, Texas

Abstract

An 86-year-old woman being treated for metastatic breast cancer developed severe chest pain at rest during a follow-up visit at a hospital's outpatient oncology clinic. An electrocardiogram showed severe ST-segment elevation. The patient was given sublingual nitroglycerin and was transferred to the emergency department. Diagnostic coronary angiography revealed moderate coronary artery disease with calcific stenoses and transient spastic occlusion of the left anterior descending coronary artery. For this patient, sublingual nitroglycerin aborted the spastic event and apparent transient takotsubo cardiomyopathy. Chemotherapy can potentially cause endothelial dysfunction and increased coronary spasticity, which could result in takotsubo cardiomyopathy.

Keywords: Coronary artery disease; cancer; coronary stenosis; spasm; takotsubo cardiomyopathy; nitroglycerin; chemotherapy

Introduction

The traditional, dominant assumption about the mechanism of transient takotsubo cardiomyopathy (TTC)[1] is that sudden catecholamine surge, regardless of its origin, produces transient cardiomyopathy that disappears spontaneously and completely over a 1- to 3-month period. The presence of coronary artery disease (CAD) has traditionally been considered an exclusion criterium for diagnosing TTC-like syndrome.[2] Nonetheless, angiographic imaging by Napp and colleagues[3] clearly documents the presence of CAD in a significant proportion of patients with TTC.

Our group's initial clinical experience with acetylcholine testing of endothelial dysfunction supports the notion that coronary spasm could be the essential initial pathophysiological mechanism causing myocardial ischemia and secondary stunning (or TTC).[4-6] This report presents a case (exceptionally observed at start of a TTC episode) that appears to document unusually clearly the fundamental role of spasm in producing a TTC-like event and the role of early nitroglycerin administration in aborting the event.

Case Report

An 86-year-old woman of Japanese ethnicity came to the outpatient oncology clinic for evaluation and treatment of newly diagnosed breast cancer with multiple organ metastases. Her history included remote cigarette smoking, untreated hyperlipidemia (but no CAD diagnosis), and remote colon cancer (in remission). She had begun to exhibit severe deterioration of her clinical status, including cachexia, and was advised to undergo aggressive chemotherapy.

Citation: Angelini P, Uribe C, Salem PA. Can significant coronary artery disease coexist with transient takotsubo cardiomyopathy, and how does spasm interrelate? *Tex Heart Inst J*. 2023;50(2):e227941. doi:10.14503/THIJ-22-7941
Corresponding author: Paolo Angelini, MD, Center for Clinical Research, Texas Heart Institute, 6624 Fannin Street, Suite 2780, Houston, TX 77030 (pangelini@texasheart.org)

Treatment was initiated in the outpatient oncology clinic and included vinorelbine, cisplatin, trastuzumab, pertuzumab, paclitaxel, and romiplostim. She tested negative for COVID-19.

During a follow-up 1 week after she began treatment, the patient experienced sudden-onset severe chest pain, dyspnea, new-onset moderate hypertension (190/95 mm Hg), and tachycardia (130 bpm during the upset). Electrocardiography (ECG) revealed monophasic 6-mm ST-segment elevation complexes in the V_1 to V_6 precordial leads (Fig. 1A). Sublingual nitroglycerin administration (800 μg) quickly resolved the chest pain and dramatically improved the ST changes to almost normal in approximately 1 minute (Fig. 1B). She was transferred immediately to the hospital's emergency department.

The patient was pain free at hospital admission (30 minutes after onset). Blood pressure was low (85/60 mm Hg), probably because of nitroglycerin's effects. Portable echocardiography revealed extensive anteroapical/lateral hypokinesia (left ventricular ejection fraction [LVEF] was approximately 30%). A high-sensitivity troponin assay showed a mildly elevated level (34 ng/L) at admission, but 18 hours later, it had increased to 1,948 ng/L. Similarly, basic natriuretic protein levels were 113 pg/mL at admission and 1,530 pg/mL the next day. Her ECG ST changes had normalized completely by day 2 (Fig. 1C).

Despite the patient's poor prognosis, her family wished to proceed with diagnostic coronary angiography, along with percutaneous coronary intervention if indicated and if anticipated to be low risk. Angiography revealed moderately severe atherosclerotic stenosis (80%; 16 mm long) of the postdiagonal left anterior descending coronary artery. Intravascular ultrasonography confirmed that the culprit stenosis was complicated by calcium, lipid deposits, and probably some clots, with an eccentric residual small lumen opposite the complex plaque, subjacent to a plaque-free arterial wall segment (Fig. 2A and 2B).

The patient and family wished to proceed with the percutaneous stent intervention, which was completed without complications. However, postrevascularization runoff was sluggish, suggesting persistent microvascular dysfunction. A transthoracic echocardiogram obtained 20 hours after onset showed impaired apical function (akinetic, symmetrical inferoapical, and lateroapical segments involving approximately 25% of the left ventricular circumference; LVEF, 40%) (Fig. 3A). At 44 hours, a contrast transthoracic echocardiogram showed complete left ventricular recovery, with an LVEF of 60% (Fig. 3B).

The patient and her family opted for a protocol of palliative treatment only, given her cachexia and the exhaustion of available oncological treatments. She died 2 days later.

Abbreviations and Acronyms

CAD	coronary artery disease
ECG	electrocardiography
LVEF	left ventricular ejection fraction
TTC	transient takotsubo cardiomyopathy

Discussion

This cardiac episode was interpreted as (1) de novo onset of acute coronary syndrome in a patient with previously asymptomatic CAD during aggressive chemotherapy for stage IV metastatic breast cancer[7]; (2) probable endothelial dysfunction onset[6] leading to spontaneous coronary spasm (sudden onset of angina and anterior ST-segment elevation) that resolved substantially, quickly, and dramatically after early sublingual nitroglycerin administration; (3) residual CAD-related asymmetric stenosis; and (4) a probable episode of nitroglycerin-aborted TTC, suggested by persistent near akinesia (symmetrical apical stunning) early after stenosis resolution (nitroglycerin and angioplasty). The episode resolved after 44 hours, which is early for typical TTC.

In this case, a TTC diagnosis is unfortunately circumstantial and would have required acetylcholine testing to confirm whether abnormal spasticity was present and caused by new-onset endothelial dysfunction.[6-8] Transient takotsubo cardiomyopathy is transiently reproducible by acetylcholine testing, which frequently replicates coronary spasm and transient myopathy pathophysiology.[6-8] This patient's hemodynamic instability contraindicated acetylcholine testing. In her case, CAD did not seem to be able to prevent TTC manifestation (by inducing a stenting effect[6]), and catecholamine-based pathophysiology did not appear to be the initial causative factor but rather a concomitant, secondary element.[1,3]

This case is especially interesting to students of TTC because it highlights spasm in the early phase of TTC that sublingual nitroglycerin was able to interrupt. The

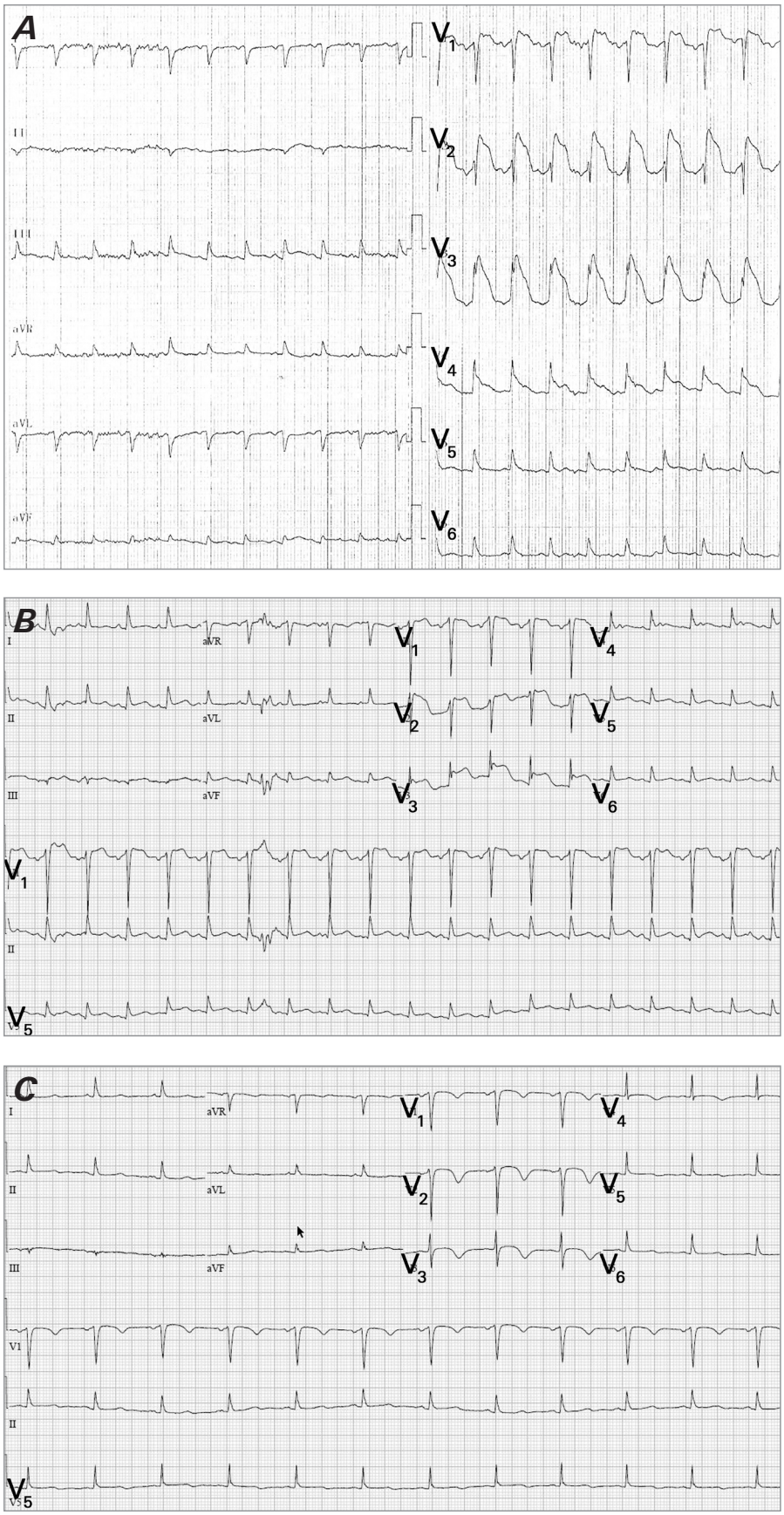

Fig. 1 Electrocardiogram tracings obtained at 3 time points: **A**) at onset of chest pain (monophasic ST-segment elevation), **B**) early after administration of sublingual nitroglycerin (improved ST-segment elevation), and **C**) 2 days after probable transient takotsubo cardiomyopathy onset.

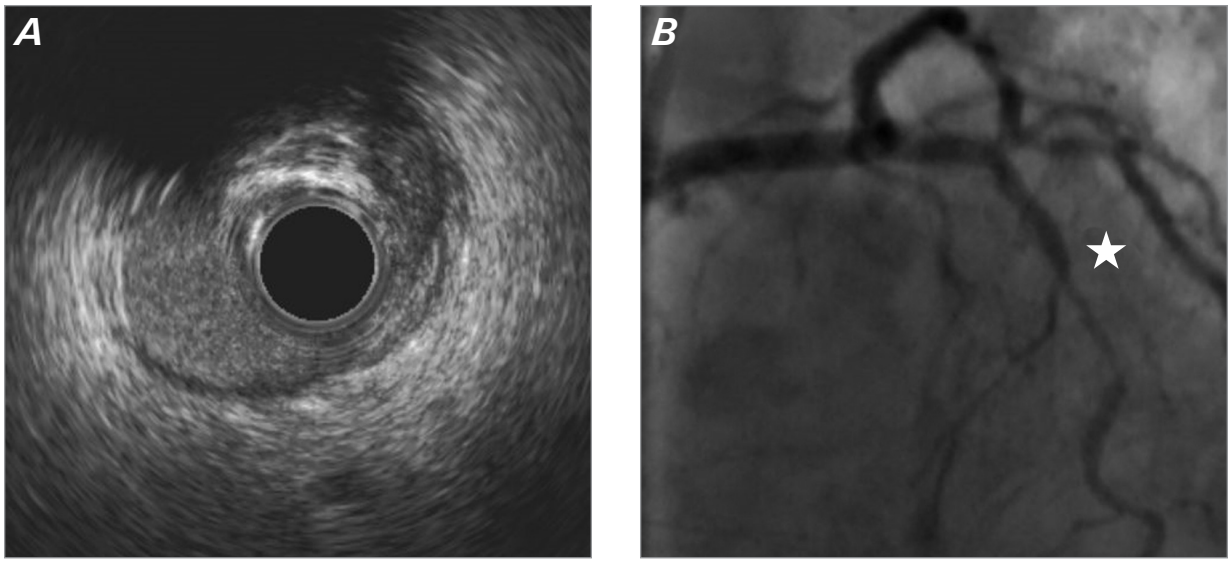

Fig. 2 A) An IVUS still-frame image of the proximal LAD segment shows a cross-section of the LAD that is partially normal, opposite a section of the arterial wall that has been invaded by eccentric calcifications and thick atherosclerotic buildup. It is implied that 1 part of the LAD wall (presenting IVUS-based pulsatile pattern, at star in panel B was able to express spastic contraction (inactive under the effect of nitroglycerin at the time of angiography). **B**) Angiogram of the LAD after nitroglycerin palliation of chest pain. Note that the culprit artery is now patent but chronically stenosed. Star indicates site of worst stenosis.

Supplemental motion image is available for Figure 2A.

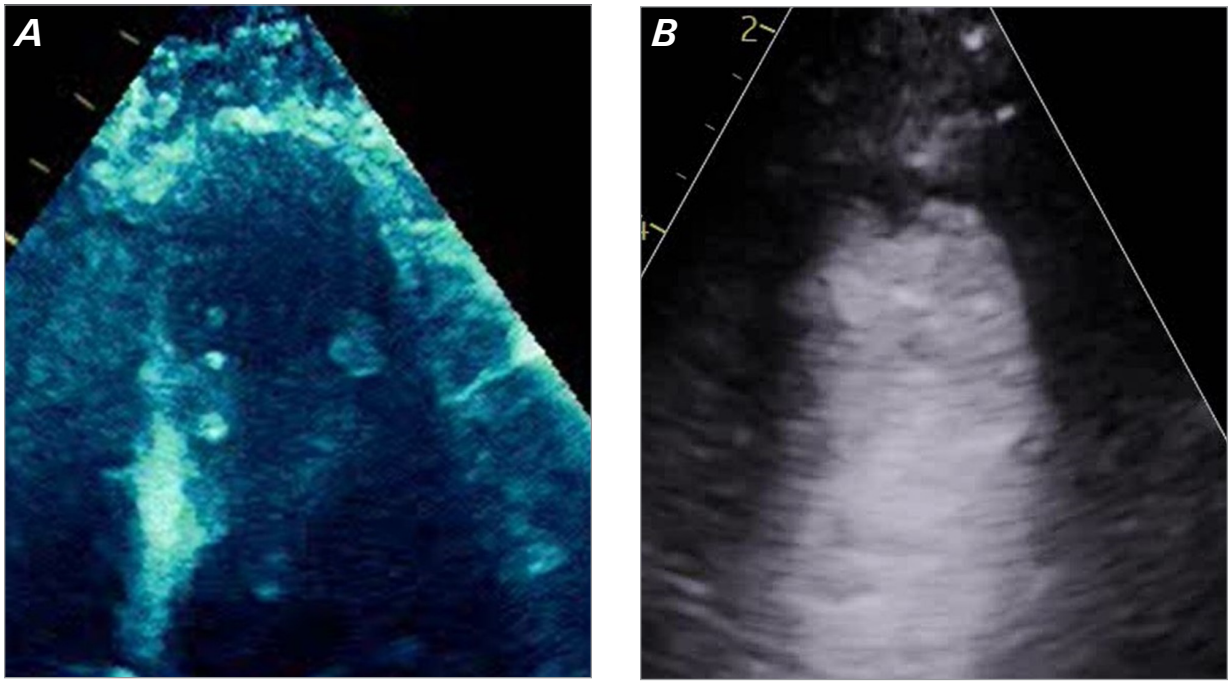

Fig. 3 A) Transthoracic echocardiogram shows apical akinesia 20 hours after onset. **B**) Transthoracic echocardiogram with contrast agent shows complete resolution of akinesia at 44 hours.

Supplemental motion image is available for Figure 3A.

Supplemental motion image is available for Figure 3B.

presence of CAD may have been compatible with severe coronary spasm in this portion of the left anterior descending coronary artery, leading to reversible occlusion at an eccentric plaque. The main reason to publish this case is because spasm was recently proposed to be the essential mechanism leading to TTC because of a reversible, total occlusion of coronary arteries that usually resolves spontaneously before the patient is admitted to the hospital (and who typically is found with "normal" coronary arteries).[6] Quick administration of nitroglycerin can be quite effective in interrupting and resolving a full manifestation of TTC. This is rarely possible in cases that start at home, in the absence of a culture of emergency vasodilatation.

Acknowledgments:

Jeanie F. Woodruff, BS, ELS, of the Scientific Publications Department at the Texas Heart Institute, contributed to the editing of the manuscript.

Published: 30 March 2023

Conflict of Interest Disclosures: The authors declare no potential conflicts of interest.

Funding/Support: This report did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. 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
2. 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
3. Napp LC, Cammann VL, Jaguszewski M, et al. Coexistence and outcome of coronary artery disease in takotsubo syndrome. *Eur Heart J.* 2020;41(34):3255-3268. doi:10.1093/eurheartj/ehaa210
4. 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
5. Angelini P. Transient takotsubo syndrome and its recurrence: Why does it happen, why does it end, and why does it rarely reappear? *Int J Cardiol.* 2021;330:142-144. doi:10.1016/j.ijcard.2021.02.033
6. Angelini P, Uribe C, Tobis JM. Pathophysiology of takotsubo cardiomyopathy: reopened debate. *Tex Heart Inst J.* 2021;48(3):e207490. doi:10.14503/THIJ-20-7490
7. Angelini P, Uribe C. Is transient takotsubo syndrome associated with cancer? Why, and with what implications for oncocardiology? *J Am Heart Assoc.* 2019;8(15):e013201. doi:10.1161/JAHA.119.013201
8. Jabri A, Kalra A, Kumar A, et al. Incidence of stress cardiomyopathy during the coronavirus disease 2019 pandemic. *JAMA Netw Open.* 2020;3(7):e2014780. doi:10.1001/jamanetworkopen.2020.14780