A 42-year-old woman is playing golf with her family and friends on a late Sunday afternoon. She has no past medical history, but she has been a smoker for the past 20 years. On the golf course, she collapses suddenly. Bystander cardiopulmonary resuscitation is administered immediately, and emergency medical services arrive within 10 minutes. The initial rhythm is polymorphic ventricular tachycardia with no palpable pulse. She is defibrillated once, and cardiopulmonary resuscitation is performed for an additional 3 minutes with return of spontaneous circulation. She is initially combative and inconsistently follows verbal commands, and she is promptly intubated for airway protection. She is taken to a local community hospital emergency department for medical stabilization before being transferred to our intensive care unit for further management.

At our facility, her temperature is 98.3°F, pulse is 140 bpm, blood pressure is 134/66 mm Hg, and respiratory rate is 26 breaths per minute with oxygen saturation of 95% while on 60% FiO2 on the ventilator in assist-control mode with a tidal volume of 500 mL. She is sedated but not paralyzed. Corneal, gag, and deep tendon reflexes are intact. She withdraws to painful stimuli but does not follow commands. There is no thyromegaly or lymphadenopathy. Jugular venous pressure is 8 cm H2O, and blood urea nitrogen of 11 mg/dL and creatinine of 1.0 mg/dL, and mild anemia with hemoglobin of 10.9 g/dL and hematocrit of 33.4%. Her cardiac biomarkers include a creatine kinase of 780 U/L, creatine kinase MB of 12 ng/mL, and troponin I of 1.82 ng/mL.

A chest x-ray from the referring emergency department reveals clear lung fields, an appropriately positioned endotracheal tube, and no cardiomegaly. A noncontrast head computed tomogram revealed no hemorrhage. Her initial ECG (Figure 1A) shows sinus tachycardia with anterolateral T-wave inversions and a prolonged corrected QT interval. On telemetry, she has frequent runs of nonsustained polymorphic ventricular tachycardia and intermittent ventricular bigeminy. Additionally, ST-segment elevations are seen on telemetry, motivating a repeat ECG (Figure 1B). This shows sinus tachycardia with 5-mm anterior ST-segment elevations and 2-mm reciprocal inferior ST-segment depressions, and the catheterization laboratory was activated. Minutes later, ST-segment elevations were absent on telemetry, and a subsequent ECG (Figure 1C) demonstrated normal sinus rhythm with anterior T-wave inversion without ST-segment deviation.

Dr Parikh: The differential diagnosis for a patient with transient ST-segment elevation in the setting of ventricular tachycardia (VT) arrest is relatively short. Acute myocardial infarction from atherosclerosis and plaque rupture is the most common cause. However, in a young patient without significant risk factors for atherosclerosis, alternative diagnoses should be considered. Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy can be characterized with ST-segment elevations after a ventricular tachyarrhythmia. In this patient, the corrected QT interval is prolonged. She does not, however, have the classic right bundle branch block pattern seen with Brugada syndrome or arrhythmogenic right ventricular cardiomyopathy, and she has no epsilon waves. Furthermore, transient ST-segment elevations lasting seconds to minutes are not commonly reported in the aforementioned conditions. Instead, these changes are most classically seen in Prinzmetal, or variant, angina (PVA).

The presentation of PVA may vary from traditional atherosclerotic coronary disease. Patients are typically younger than those with angina from atherosclerosis. They have severe substernal chest pressure that tends to occur in...
the early morning or late evening in a cyclic fashion.\textsuperscript{6,7} This is in contrast to chronic stable angina, which typically occurs mid-day. Although the presentation of angina is typical, patients with PVA also may present with syncope from complete heart block or VT. Early Holter studies have shown arrhythmia incidence of \(\approx 12\%\) during episodes of ST-segment elevations. These include VT (sustained and nonsustained), bigeminy, and complete heart block.\textsuperscript{7,8} The majority of these arrhythmias occur during painful episodes; however, clinically silent episodes of nonsustained VT can occur.

Patients with PVA may also have systemic manifestations of vasospasm including migraine headaches and Raynaud’s phenomenon.\textsuperscript{9} Observational data suggest that traditional risk factors for coronary atherosclerosis such as hypertension, diabetes mellitus, dyslipidemia, and obesity are not significant risk factors for coronary vasospasm, with the notable exception of smoking as a well-established trigger. Although this patient had no known history of migraines or Raynaud’s phenomenon, she was a known smoker, which puts her at elevated risk for vasospasm. Given this presentation, a diagnostic coronary angiogram is indicated to delineate coronary anatomy.

The patient underwent emergent coronary angiography (Figure 2A), initially with visualization of a normal right coronary artery, followed by injection of the left coronary artery. This revealed a \(95\%\) proximal left anterior descending artery (LAD) stenosis of 10 mm in length with otherwise angiographically normal coronaries. Given her presentation, 200 \(\mu\)g of intracoronary nitroglycerin was administered with near-total resolution of the stenosis, suggestive of vasospasm as the likely etiology (Figure 2B).

Dr Parikh: Coronary vasospasm is defined as \(>75\%\) lumen loss with reversibility with vasodilator agents. Vasospasm is often demonstrated on coronary angiography in the absence of significant atherosclerotic disease in the majority of PVA patients. Although some reports suggest that vasospasm is superimposed on a fixed atherosclerotic lesion, \(50\%\) of patients have angiographically normal coronary arteries.\textsuperscript{10} The right coronary artery is most commonly involved, followed by the LAD and then the left circumflex artery. If clinical uncertainty remains despite ECG tracings and angiography, provocative testing may be pursued in select cases. Provocative testing is performed via use of ergonovine analogues,\textsuperscript{10} acetylcholine derivatives, or hyperventilation and is not recommended in patients with high-grade stenoses given the risk of prolonged vasospasm that may be difficult to reverse despite vasodilator therapy.\textsuperscript{11,12}

After coronary angiography and administration of intracoronary nitroglycerin, optical coherence tomography (OCT) images were obtained of the LAD (Figure 3). This showed a normal vessel distally (A), mild atherosclerotic changes closer to the spasm site (B), intimal and medial thickening at the spasm site (C), and a normal-appearing left main artery (D).

Dr Parikh: Publications on intracoronary images of vasospasm are sparse but raise important questions about pathophysiology. Intracoronary imaging at the spasm site via intravascular ultrasound or OCT may distinguish normal vascular architecture from underlying atherosclerosis as well as identify arterial remodeling due to chronic, recurrent vasospasm.\textsuperscript{13–16} The presence of atherosclerosis may have therapeutic implications.
In our patient, given resolution of the vasospasm with nitroglycerin and no evidence of significant obstructive atherosclerotic disease, no further intervention was performed.

At the conclusion of the case, femoral angiography revealed a focal stenosis in the external iliac artery (Figure 2C). This also appeared to improve with intra-arterial nitroglycerin (Figure 2D). OCT images were obtained of the iliac artery and revealed no evidence of atherosclerosis at the site of vasospasm and in the proximal reference segment (Figure 4). There was, however, significant luminal loss with a concurrent increase in medial wall thickness at the site of vasospasm.

Dr Parikh: It has been reported previously that patients with PVA may have peripheral vasospasm, including Raynaud’s phenomenon and migraine headaches. To our knowledge, this is the first report of OCT-documented vasospasm in an otherwise normal iliac artery. The iliac artery images reveal a vessel free of atherosclerotic changes. The site of vasospasm shows a relative thickening of the medial layer consistent with smooth muscle contraction.

At the end of the procedure, the patient was started on intravenous nitroglycerin and clevidipine, a short-acting intravenous calcium channel blocker, and transferred to the cardiac intensive care unit. Therapeutic hypothermia was initiated. Twenty-four hours later, she was rewarmed and extubated. Her hospital course was complicated by a significant drop in her hematocrit level secondary to a splenic laceration related to her cardiopulmonary resuscitation. It was also complicated by aspiration pneumonia, which necessitated reintubation. She was ultimately discharged on oral isosorbide mononitrate, nifedipine, and atorvastatin.

Dr Parikh: The mainstay of therapy for coronary vasospasm includes calcium channel blockers and nitrates at moderate to high doses. Although nifedipine has been the most extensively studied calcium channel blocker, it is widely believed to be a class effect including other dihydropyridines and nondihydropyridines such as verapamil and diltiazem. Adding fluvastatin to calcium channel blockers in PVA patients has been shown to suppress coronary spasm. The mechanism of this is likely multifactorial as a result of reduction of low-density lipoprotein, improvement of endothelial dysfunction, reduction of inflammation, and perhaps an increase in endothelial nitric oxide production via the RhoA-associated kinase pathway.

Given mild atherosclerotic changes on angiogram and OCT, the patient was started on 81 mg aspirin daily as well.

Dr Parikh: The use of aspirin in PVA is not without consequence and may be beneficial in certain patients. On the one hand, patients with PVA may have underlying atherosclerotic vascular disease and may benefit from primary prevention of atherothrombosis. On the other hand, aspirin is a potent nonselective inhibitor of cyclooxygenase, thereby inhibiting prostaglandin production.
and potentially increasing the risk of vasospasm. Use of a calcium channel blocker together with aspirin has been shown to reduce this risk.

Our patient had no further episodes of ventricular ectopy and no additional chest pain during her hospitalization. After completing a course of antibiotics for aspiration pneumonia, the patient was referred for an implantable cardioverter-defibrillator (ICD).

**Dr Parikh:** Current guidelines do not support the routine use of ICD therapy in PVA patients. Nevertheless, observational data from a 7-year follow-up period of PVA patients report a sudden cardiac death rate of up to 3% to 4%. When one specifically examines the outcomes of patients who initially present with sudden cardiac death, the data are limited. We decided that this patient’s severe presentation warranted ICD implantation.

The ICD was implanted without complications, and the patient was discharged home the following day. In addition to her medical therapy, she was instructed to make several lifestyle and dietary changes including the cessation of any smoking as well as refraining from pseudoephedrine and nonaspirin nonsteroidal anti-inflammatory drug use. She has followed up regularly, without additional symptoms or arrhythmias. She has quit smoking.

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**Discussion**

Prinzmetal et al first described this phenomenon in a 1959 article describing a syndrome of angina that occurred at rest with transient ST-segment elevations. They proposed that episodes of “temporary increased tonus” resulted in an obstruction of a coronary artery. Therefore, typical angina is the most common presentation in these patients. Life-threatening arrhythmias, however, may occur in 10% to 15% of patients. Complete heart block is associated with right coronary artery spasms, and VT is associated with LAD spasms. Coronary spasm may not be the only mechanism for arrhythmias. Variation of the QT-interval duration within an ECG, or QT dispersion, is greater in asymptomatic PVA patients and may further increase susceptibility to ventricular arrhythmias.

The diagnosis of PVA can be made clinically with the use of ECG and Holter/telemetry data; however, coronary angiography is a relatively safe and effective way to resolve diagnostic uncertainty. In the 2011 American College of Cardiology/American Heart Association ST-segment elevation myocardial infarction guidelines, diagnostic evaluation of ischemia including coronary angiography is recommended in patients with a suspicion of coronary vasospasm, particularly in the setting of chest pain and transient ST elevations.

In a small intravascular ultrasound series of patients with provoked vasospasm, negative remodeling, as defined by a reduction in external elastic membrane cross-sectional area at
the site of vasospasm, was reported in 67% of patients with PVA. In a study of 202 patients with PVA by Suzuki et al, histological analysis of coronary plaques via atherectomy showed the predominant histopathology to be smooth muscle cell–rich neointimal hyperplasia. Kobayashi et al published a case of a patient with an inferior ST-segment elevation myocardial infarction and right coronary artery vasospasm who underwent OCT imaging, revealing intimal thickening, vascular contraction, and thrombus formation resulting in lumen loss, suggesting an underlying moderate degree of atherosclerosis in the patient. More recently, Tanaka et al demonstrated lumen loss and intimal gathering from medial contraction by using OCT in PVA patients, even when patients were asymptomatic. Thus, the intimal thickening we demonstrated in our patient may be from underlying mild atherosclerosis, from neointimal hyperplasia as a result of recurrent vasospasm, or from redundant intimal tissue as a result of medial contraction. Despite a potential role in select patients who may be candidates for percutaneous coronary intervention (PCI), the routine use of intravascular ultrasound or OCT is not recommended.

Severe presentations of PVA present a therapeutic challenge. Medical therapy with long-acting nitrates and calcium channel blockers is beneficial. The addition of statin therapy and low-dose aspirin in select patients also appears reasonable. Currently, the use of interventions including coronary stenting at the site of spasm or implantation of an ICD for malignant tachyarrhythmias is not universally recommended.

Successful PCI has been reported in patients with medically refractory coronary vasospasm, but concern remains that vasospasm may occur at the stent edge or even at an entirely different site afterward. Some clinicians advocate stenting additional segments that demonstrate vasospasm with provocation after initial PCI to prevent recurrent angina, although this is controversial. Although long-term follow-up on these patients is not available, short-term

![Figure 4. Our patient underwent optical coherence tomography of the external iliac artery (EIA), revealing normal proximal segment with medial thickness of 110 μm (A), near doubling of medial thickness with evidence of intimal thickening at spasm site (B), and return to normal-appearing intima and media distally (C).](image-url)
in-stent restenosis rates appear similar to those in non-PVA patients. As a consequence, the American College of Cardiology/American Heart Association guidelines recommend PCI in PVA if there is a significant coronary artery stenosis present in the appropriate clinical scenario.32 Given the risk of periprocedural complications, we generally believe that PCI should be restricted to refractory cases in which all medical options have been exhausted.

ICD implantation in the PVA patient presenting with malignant tachyarrhythmias has been reported but is controversial because prognostic data on these patients are limited. One case series followed 8 patients with PVA and recurrent angina despite medical therapy for a mean of 3.5 years. All patients had recurrence of ventricular tachyarrhythmia within 15 months of hospital discharge. ICDs were implanted in most patients, with the majority receiving appropriate shocks in this interval. The authors of this study advocate ICD implantation in patients who remain symptomatic despite maximal medical management.33 However, another small series of 7 patients who presented with sudden cardiac death from coronary vasospasm had a favorable prognosis at a mean follow-up of >4 years while on calcium channel blockers and nitrates. The only patient in this series who had recurrent VT and ICD implantation was a woman who continued to smoke and developed a fixed coronary stenosis.

One case series followed 8 patients with PVA and recurrent angina over a 5-year follow-up. These patients were younger survivors over a 5-year follow-up. These patients were younger and had a greater incidence of LAD spasm. In addition to smoking, multivessel spasm, and significant atherosclerotic disease, a history of prior out-of-hospital cardiac arrest appeared to be an independent risk factor for future major adverse cardiac events.35 These results suggest that this population is particularly vulnerable and may benefit more from implantation of an ICD.

PVA is a clinical syndrome that can vary in presentation from mild chest discomfort to sudden cardiac death. Early suspicion in patients with classic symptoms and ECG changes is important, as is excluding life-threatening alternative diagnoses. Medical therapy is beneficial in nearly all patients. The use of interventions such as PCI or ICD implantation should be limited to select patients.

Disclosures

Dr Parikh receives research support from Medtronic and also serves as consultant to and receives honoraria from Medtronic and Boston Scientific.

References


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