A Shocking Development in a Young Male Athlete With Chest Pain

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Foreword
Information about a real patient is presented in stages (boldface type) to an expert clinician (Dr Deepak L. Bhatt), who responds to the information, sharing his reasoning with the reader (regular type). A discussion by the authors follows.

Patient presentation: A 32-year-old male endurance athlete with no significant past history was admitted after experiencing multiple episodes of chest tightness while training for a triathlon. Occasionally, when running up hills, he noted substernal chest pressure that radiated to his left arm and was associated with severe shortness of breath. His past medical history includes seasonal allergic rhinitis and childhood asthma. He takes cetirizine/pseudoephedrine occasionally, but has not taken it recently, and denies taking any other medication or over-the-counter supplement. He admits to occasional binge drinking of 6 to 10 beers once or twice a month. He quit smoking 2 years ago but previously smoked a pack a week for 5 years. He also endorsed a remote history of cocaine use and recent marijuana and energy drink (1–2 small cans; 80 mg of caffeine per 8.4-oz can) use. His family history is only notable for a maternal grandmother who had a myocardial infarction in her 60s and a sister diagnosed with an atrial tachycardia. There is no history of premature coronary artery disease, heart failure, or sudden death. His biological parents and brother are alive and well.

Dr Bhatt: At this point, the differential diagnosis for chest pain in a young, otherwise healthy patient is broad. Certainly, the exertional component of his symptoms is concerning and raises the possibility of premature coronary artery disease, although the family history obtained does not suggest a strong predisposition for atherosclerosis. Coronary artery vasospasm would be another possibility, and he has several potential triggers, including alcohol, pseudoephedrine, caffeine, and marijuana use. Vasospasm can occur with exertion, even though we often think of it as occurring at rest. Forms of structural heart disease, such as hypertrophic or infiltrative cardiomyopathy or an anomalous coronary artery, should be entertained. I would also consider an arrhythmia, either supraventricular or ventricular. The appropriate next steps are a targeted physical examination, an ECG, and a transthoracic echocardiogram to evaluate for structural heart disease.

Patient presentation (continued): His vital signs were as follows: temperature, 96.0°F; blood pressure, 136/88 mmHg; heart rate, 56 beats per minute and regular; respiratory rate, 14 breaths per minute; and oxygen saturation, 98% on room air. He was well appearing. His jugular venous pressure was 6 cm H2O. His lungs were clear to auscultation bilaterally. His cardiac examination revealed normal S1 and S2 heart sounds, no murmurs or gallops, no heaves, and a nondisplaced apical impulse. His extremities were warm and without edema. Serial troponin-T concentrations were undetectable. An ECG showed normal sinus rhythm with normal intervals and no evidence of hypertrophy or ischemia (Figure 1). His urine toxicology screen was negative. A transthoracic echocardiogram revealed a left ventricular ejection fraction of 65%, normal left ventricular and right ventricular size and function, and no significant valvular dysfunction. The following morning at 6 AM, he experienced 2 brief episodes of chest pain, similar in quality to his presenting symptoms, associated with a nonsustained, regular, wide complex monomorphic tachycardia on telemetry. There was no sign of hemodynamic compromise, and his chest discomfort resolved quickly without any intervention. He was subsequently transferred to our tertiary care hospital for further evaluation.

Dr Bhatt: These brief episodes of chest pain provide valuable clues for the most likely potential etiologies of his presentation. The reported telemetry findings are consistent with ventricular tachycardia, although a supraventricular tachycardia with aberrant conduction is possible. The question arises whether his episodes of chest pain are caused by a primary arrhythmic etiology or by another process leading to his chest pain and ventricular tachycardia. Interestingly, his ECG shows J-point elevation and notching on the downslope of the QRS (J wave) in the inferior leads, potentially representing a Haissaguerre pattern, which has been associated with idiopathic ventricular fibrillation. However, this is controversial,
and distinguishing between normal early repolarization and pathological J waves has been challenging. The short duration of the tachycardia and lack of hemodynamic instability make the possibility of an arrhythmia as the primary etiology for his symptoms less likely. Regarding conditions associated with chest pain and resulting ventricular arrhythmias, coronary artery vasospasm should be strongly considered. Unlike his previous chest pain, these in-hospital episodes are more characteristic of vasospasm, occurring in the early morning when vagal tone is greater and at rest. Nevertheless, other conditions, such as coronary artery disease, myocarditis, and infiltrative cardiomyopathy, are still possible, necessitating further evaluation. Given his age and normal ECG, obtaining a nonimaging exercise treadmill test would be a reasonable way to evaluate for ischemia and exercise-induced arrhythmias. Although the transthoracic echocardiogram was unrevealing, further investigation for structural heart disease with cardiac MRI should be considered to exclude late gadolinium enhancement, which would suggest myocarditis, previous infarct, or an infiltrative process. Furthermore, cardiac MRI can delineate the origin and proximal course of the coronary arteries and exclude anomalous coronary arteries.

**Patient presentation (continued):** During an exercise treadmill test, he achieved 22.9 metabolic equivalents without recurrent chest pain, ischemic ECG changes, or arrhythmias. A cardiac MRI showed no structural abnormalities or areas with late gadolinium enhancement. However, there was moderate narrowing of the mid left anterior descending and mid right coronary arteries (Figure 2A and 2B). It is noteworthy that the patient later mentioned that he transiently experienced chest pain during the scan.

**Dr Bhatt:** The absence of ECG changes on the exercise treadmill test make flow-limiting coronary artery disease less likely as the etiology of his symptoms. The MRI findings are very informative. A structurally normal heart and the absence of late gadolinium enhancement make many of the previously discussed diagnoses on the differential less likely. The images are of good quality and allow for characterization of the mid to distal coronary artery segments, revealing abnormalities that may represent coronary artery disease, dissection, or vasospasm. Therefore, coronary angiography (ie, computed tomography or invasive angiography) is necessary to distinguish among these possibilities. Invasive angiography would allow for subsequent diagnostic testing at the time of the procedure, if warranted. If angiography does not reveal any obstructive coronary artery disease or dissection, provocative testing with methylergonovine or ergonovine (depending on availability) or acetylcholine could be performed to determine if significant coronary artery vasospasm is present.

**Patient presentation (continued):** The following morning, again at 6 AM, he experienced recurrent chest pain associated with multiple episodes of nonsustained polymorphic ventricular tachycardia with the presence of ST elevation (Figure 3A and 3B). The patient was taken urgently to the cardiac catheterization laboratory. Coronary angiography was performed by using a right femoral artery approach. The left main coronary artery was engaged first, and there was a 99% tubular stenosis in the mid left anterior descending artery that improved to a 40% stenosis with intracoronary administration of nitroglycerin (Figure 4A through 4C). He also had another 40% mid left anterior descending artery stenosis and a 40% mid right coronary artery stenosis.

**Dr Bhatt:** The telemetry tracings reveal episodes of nonsustained polymorphic ventricular tachycardia and frequent ventricular ectopy. ST elevation can be seen in leads I and aVL. Taken together, these findings are consistent...
with ongoing myocardial ischemia. Sublingual nitroglycerin should be administered. Given that his presentation is not consistent with an acute coronary syndrome, β-blockers should be avoided because of their potential to exacerbate coronary artery vasospasm through unopposed α-adrenergic vasoconstriction.

A reversible severe coronary artery lesion confirms the diagnosis of coronary artery vasospasm and is consistent with his presentation. Multifocal coronary vasospasm is possible because his right coronary artery was examined after the administration of intracoronary nitroglycerin. Medical management should include the use of a calcium channel blocker with addition of a long-acting nitrate as tolerated. The medications should be timed to avoid periods of low concentrations, particularly overnight and in the early morning, given the diurnal pattern of vasospasm as in this patient.

In addition to vasospasm, his coronary angiogram revealed a significant amount of atherosclerosis, especially for his age. He should undergo an evaluation for premature atherosclerosis, including a lipid panel, inflammatory markers, and a thyroid-stimulating hormone level.

Patient presentation (continued): A subsequent lipid panel revealed the following: total cholesterol, 148 mg/dL; high-density lipoprotein, 44 mg/dL; low-density lipoprotein, 81 mg/dL; and triglyceride, 116 mg/dL. His high-sensitivity C-reactive protein was 1.5 mg/L. Serum lipoprotein (a) [Lp(a)] was significantly elevated at 158 mg/dL (normal ≤30 mg/dL). His thyroid-stimulating hormone level was 0.94 μIU/mL, hemoglobin A1C was 5.4%, and homocysteine concentration was 9.1 μmol/L (normal, 0–14 μmol/L). Extended-release nifedipine and isosorbide mononitrate were started and titrated to maximally tolerated doses. He also received atorvastatin 80 mg and aspirin 81 mg. For his ventricular tachycardia, given the absence of myocardial scar, the presence of a reversible cause, and the patient’s clear preference, placement of an implantable cardioverter defibrillator (ICD) was deferred, although an implantable loop recorder was placed to monitor him for recurrent ventricular arrhythmia. He was monitored in the hospital for 4 days after initiating his antivasospasm regimen without recurrent chest pain or ventricular ectopy. He was counseled to engage only in light activity and to avoid potential precipitants of coronary vasospasm, such as tobacco, alcohol, or caffeine.

Dr Bhatt: His lipid studies are certainly notable for his Lp(a) concentration. An elevated Lp(a) clearly has been associated with an increased risk of cardiovascular disease and is often seen in patients with premature coronary artery disease. Although the effect of Lp(a)-lowering therapy on cardiovascular outcomes is not well studied, many would advocate for aggressive low-density lipoprotein cholesterol lowering with a high-intensity statin. Drugs that have been shown to lower...
Lp(a) levels, including niacin and perhaps PCSK9 inhibitors in the future, can also be considered. The benefit of aspirin therapy is suggested in a study from the Women’s Health Initiative showing that carriers of an apolipoprotein (a) allele variant, which was associated with an elevated Lp(a), had a significant reduction in the risk of major cardiovascular events with aspirin use.

Patient presentation (continued): Three weeks later, he experienced 2 episodes of chest tightness lasting only for a few seconds. On review of the loop recorder, there were no arrhythmias to correlate with these episodes. The following morning, he was found to be unresponsive by his wife. She initiated cardiopulmonary resuscitation and called emergency medical services. He was found to be in ventricular fibrillation and was subsequently defibrillated. Transient ST elevation was noted on the initial ECG. Therapeutic hypothermia was initiated en route to the hospital, and coronary angiography revealed the same mid left anterior descending artery lesion that partially dilated with intracoronary nitroglycerin.

In the Coronary Care Unit, he was maintained on intravenous nitroglycerin and amiodarone, and completed a therapeutic hypothermia protocol. Interrogation of the loop recorder revealed a self-terminating, 22-minute episode of polymorphic ventricular tachycardia, followed by another 12-minute episode of ventricular tachycardia and ventricular fibrillation, terminated by external defibrillation. He awoke with a mild short-term memory deficit, which gradually resolved throughout his stay. The patient denied medication nonadherence or consumption of alcohol, tobacco, or illicit drugs. A urine toxicology screen was negative. MRI of the head did not reveal any sign of infarction or anoxic injury. Transthoracic echocardiogram showed a depressed ejection fraction at 35% to 40% with global hypokinesia. His vasospasm regimen was intensified with further up titration of nifedipine and isosorbide mononitrate. He underwent implantation of an ICD before discharge.

Several months after hospitalization, he has felt well without recurrent chest pain or side effects from his medication regimen, and has returned to work and light physical activity. Given the heritable nature of Lp(a), his first-degree relatives were screened, and his mother, brother, and sister were found to have an elevated Lp(a). His mother was already taking a statin, and his siblings started statin therapy.

Dr Bhatt: Sudden cardiac death is an uncommon and certainly an unfortunate complication of coronary artery vasospasm. The patient was likely in the midst of a “hot phase” of coronary artery vasospasm, which has been described as a period lasting days to weeks in which angina symptoms require increasing doses of calcium channel blockers and nitrates and may still be refractory. The mechanism for this hot phase of vasospastic angina is not well understood. During this time, patients are at a greater risk of complications, including myocardial infarction, ventricular arrhythmias, and sudden cardiac death. In the long term, spontaneous remission of coronary artery vasospasm is fairly common. Complete resolution of ischemia/angina 12 months after discontinuation of calcium channel blocker therapy has been reported in 76% and 65% of patients by Holter monitoring and ergonovine testing, respectively. However, the chance of remission is lower in those with underlying coronary artery disease.

Discussion
Coronary artery vasospasm, initially described by Prinzmetal as variant angina, is a condition characteristic of vasospasm likely associated with endothelial dysfunction leading to signs of myocardial ischemia in the form of chest pain, ST elevation on ECG, and, in severe cases, myocardial infarction, ventricular arrhythmias, and sudden cardiac death. The cause of endothelial dysfunction is likely multifactorial, and several mechanisms have been proposed, including abnormal nitric oxide activity and nitric oxide availability, increased phospholipase C activity in vascular smooth muscle cells, and enhanced Rho-kinase activity leading to increased myosin light chain phosphorylation and vascular smooth muscle constriction. In addition, numerous substances have been described as causing coronary artery vasospasm, including cigarette smoke, alcohol, illicit drugs (cocaïne, amphetamines, heroin, ecstasy, marijuana, butane), pseudoephedrine, sumatriptan, ergotamine and its derivatives, anesthetics (propofol, sevoflurane),...
Spasm can occur in focal coronary artery segments or diffusely, involving multiple arteries, and is often seen in areas with underlying atherosclerosis. Indeed, even in angiographically normal coronary arteries, atherosclerotic lesions, often with a negative remodeling pattern, can be detected at the spasm site by intravascular ultrasound. Moreover, intracoronary imaging by optical coherence tomography has greater resolution and may provide further insight into the characteristics of vasospastic segments, such as increased basal smooth muscle tone in the media. Studies using Holter monitoring or exercise testing have described a diurnal pattern with many episodes of coronary artery vasospasm occurring in the early morning, as in our patient’s case.

Although not necessary in this case, provocative testing using intravenous or intracoronary injection of methylergonovine or ergonovine or intracoronary injection of acetylcholine can be useful in diagnosing coronary artery vasospasm in the patients with normal-appearing coronary arteries on angiography but a clinical presentation concerning for vasospasm; such provocative testing holds a class IIB recommendation from the American Heart Association/American College of Cardiology and a class IIA recommendation by the European Society of Cardiology for this indication. A lumen reduction of 75% to 99% is considered to be diagnostic for coronary artery vasospasm.

The literature on coronary vasospasm continues to evolve with several key recent publications. A contemporary study of 921 patients, who were found to have nonobstructive coronary artery disease on invasive angiography and subsequently underwent acetylcholine provocation testing demonstrated the relative safety of the procedure with a 1% rate of minor complications, including symptomatic bradycardia, nonsustained ventricular tachycardia, paroxysmal atrial fibrillation, and catheter-induced vasospasm.

The treatment of coronary artery vasospasm focuses on antagonism of pathways known to mediate smooth muscle vasoconstriction and avoidance of substances associated with vasospasm (Table). Calcium channel blockers are the mainstay of treatment and have been shown to be effective in reducing symptoms in >90% of patients. A maximally tolerated dose of a calcium channel blocker combined with a long-acting nitrate is effective in reducing symptoms and preventing severe episodes of angina. However, a registry study showed that chronic nitrate therapy in patients already on a calcium channel blocker did not reduce major cardiac events. Statins have also been proposed to have a benefit, potentially through Rho-kinase inhibition and increased nitric oxide synthase activity. In a prospective study, 64 patients with acetylcholine-induced vasospasm received standard therapy with a calcium channel blocker (extended release diltiazem or nifedipine) and were randomly assigned to receive fluvastatin. The statin group had significantly reduced acetylcholine-induced vasospasm in comparison with the nonstatin group. Recently, a randomized, controlled trial of 50 patients evaluated the addition of the phosphodiesterase inhibitor cilostazol to amiodipine and found a significant improvement in angina frequency and severity in the cilostazol group.

Percutaneous coronary intervention and stent placement are not routinely performed in the absence of obstructive coronary artery disease because of the high rate of recurrent vasospasm in other coronary artery segments, although stent placement has been described in patients with symptoms refractory to aggressive medical management or severe ischemia on an exercise stress test. Similarly, coronary artery bypass grafting is not routinely performed because of the risk of recurrent vasospasm distal to the grafts.

Major complications of coronary artery vasospasm include myocardial infarction, ventricular arrhythmias, and sudden death. A proposed mechanism of myocardial infarction attributable to coronary artery vasospasm is related to coronary thrombosis. Furthermore, a histological examination of coronary atherectomy samples from patients with coronary artery vasospasm revealed signs of intimal damage, including thrombosis, intimal hemorrhage, and neo-intimal hyperplasia, perhaps increasing the risk of progressive stenosis in the

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affected segments in the future. Elevated Lp(a) levels have been associated with a lower threshold for provoked coronary vasospasm. Patients who have coronary artery vasospasm with an elevated Lp(a) may have an increased risk of myocardial infarction, possibly because of impaired fibrinolysis. Potentially, new therapies such as PCSK9 inhibitors may have a particular role in reducing cardiovascular risk and potentially even spasm in such patients, although future studies will need to test this hypothesis. Furthermore, a recent large registry study showed that patients with a positive ergonovine provocation test had low 24-month incidences of cardiac death, arrhythmia, and acute coronary syndrome (0.9%, 1.6%, and 1.9%, respectively). A risk score (Japanese Coronary Spasm Association Score) has been proposed for prognostic stratification for future major adverse cardiac events and includes the following risk factors: out-of-hospital cardiac arrest, tobacco use, angina only at rest, coronary artery disease, multivessel vasospasm, ST-segment elevation on ECG, and β-blocker use. The incidence of major adverse cardiac events in the low-, intermediate-, and high-risk groups was 2.5%, 7.0%, and 13.0%, respectively. However, further studies are needed to validate this scoring system and determine how it might affect clinical management.

Regarding ventricular arrhythmias in the setting of coronary artery vasospasm, this rare complication is associated with significant morbidity. A large Japanese registry demonstrated that patients who have coronary artery vasospasm with an out-of-hospital cardiac arrest had a significantly lower major adverse cardiac event–free survival at 5 years (72% versus 92% in those without cardiac arrest). The role of ICD implantation in coronary artery vasospasm is not well established. The current data are limited to small observational studies. A case series of 8 patients, who presented with ventricular fibrillation, experienced recurrent ventricular arrhythmia at a median of 15 months. Furthermore, in an observational study of 23 patients who had vasospasm with ventricular arrhythmia, at a median follow-up of 2.1 years, 5 patients had a cardiac arrest (4 with ventricular fibrillation and 1 with pulseless electric activity). Considering the morbidity associated with long-term intracardiac devices, particularly in this patient population, which tends to be younger, alternatives, such as a subcutaneous ICD or wearable cardioverter-defibrillator, may be considered in the future. For example, a recent communication describes the use of a wearable cardioverter-defibrillator in patients with a high risk of sudden cardiac death, including one with coronary artery vasospasm. This may be a reasonable new strategy for short-term secondary prevention with a permanent ICD reserved for those who demonstrate recurrent ventricular arrhythmia. Certainly, larger, prospective studies are necessary to address this important issue.

Coronary artery vasospasm is a condition with a broad spectrum of manifestations and triggers and should always be considered in patients with signs and symptoms consistent with myocardial ischemia, particularly in the absence of significant angiographic coronary artery disease. Although the long-term prognosis is generally favorable, major complications, such as myocardial infarction and sudden cardiac death, can occur. Further studies will be helpful for identifying high-risk patients and those who would benefit from more aggressive interventions.

Disclosures
Dr Bhatt discloses the following relationships: Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Get With The Guidelines Steering Committee; Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committees), SLACK Publications (Chief Medical Editor, Cardiology Today’s Intervention), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor); Research Funding: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Site Co-Investigator: Biotronik, St Jude Medical; Trustee: American College of Cardiology; Unfunded Research: FlowCo, PLx Pharma, Takeda. The other authors report no conflicts.

References


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