# Recurrent out-of-hospital cardiac arrest related to triple-vessel coronary artery spasm: A case report

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## Introduction

Patients with coronary artery spasm (CAS) typically present with nocturnal or early morning chest pain that is responsive to nitroglycerin. However, it has also been reported as a rare cause of life-threatening arrhythmia or sudden cardiac death, which makes the diagnosis as well as the management challenging.[1] Calcium channel blockers and nitrates are recommended therapies to alleviate symptoms such as chest pain by preventing vasoconstriction and promoting vasodilation.[2] However, the optimal approach to patients with sudden cardiac arrest related to CAS is still unknown, with only limited studies showing favorable outcomes from secondary prevention with implantable cardioverter-defibrillator (ICD) in patients who survive a fatal arrhythmia,[3] although it is ineffective for pulseless electrical activity (PEA).[4] We hereby report a case with recurrent cardiac arrest related to severe triple-vessel CAS.

### KEY TEACHING POINTS

- It is important to consider coronary artery spasm (CAS) in the differential diagnosis when there is an absence of other obvious causes of cardiac arrest.
- Provocation testing can help diagnose CAS, given that spontaneous CAS may not be detected during routine coronary evaluation.
- Medical treatment for CAS with calcium channel blockers and/or nitrates is the cornerstone of care.
- Implantable cardioverter-defibrillator implantation has been shown to reduce mortality from CAS-related ventricular tachyarrhythmia arrest but not pulseless electrical activity.

## Case report

The patient is a 61-year-old man with primary hypertension, hyperlipidemia, insulin-dependent diabetes mellitus, persistent atrial fibrillation, status post pulmonary vein isolation in 2015 and 2017 as well as cavotricuspid isthmus ablation of atrial flutter in 2013 on chronic anticoagulation with apixaban and metoprolol for rate control, obstructive sleep apnea on continuous positive airway pressure, who never smoked or abused any drugs. In June of 2021, he collapsed while walking home after playing pickleball for around 3 hours. Bystander cardiopulmonary resuscitation was started, and an automated external defibrillator was used to defibrillate the patient. When brought to the emergency room the patient was in PEA and received advanced cardiovascular life support for 5 additional minutes. An echocardiogram revealed an ejection fraction of 53% without segmental wall motion abnormalities. Left heart catheterization revealed nonobstructive coronary artery disease with evidence of a mid left anterior descending intramyocardial bridge. The patient received an ICD for secondary prevention. He was also started on metoprolol, dronedarone, and apixaban for persistent atrial fibrillation. In April 2022, the patient was again playing pickleball for a few minutes when he became lightheaded. He lost consciousness and became unresponsive. Bystander cardiopulmonary resuscitation was performed for about 5 minutes. He was found in PEA. The patient regained return of spontaneous circulation after advanced cardiovascular life support.

His Glasgow Coma Scale on arrival was 6 (eye response 3; verbal response 1; motor response 2). Vital signs on admission were as follows: blood pressure 85/46 mm Hg, heart rate 171 beats/min, temperature 36.5°C, oxygen saturation 100% while on mechanical ventilation. Physical examination revealed an irregular heart rhythm but no murmurs or gallops, with fine crackles over the lower lung fields bilaterally. Edema was not noted.

**KEYWORDS** Coronary artery spasm; Cardiac arrest; Pulseless electrical activity; Coronary provocation test; Implantable cardioverter-defibrillator
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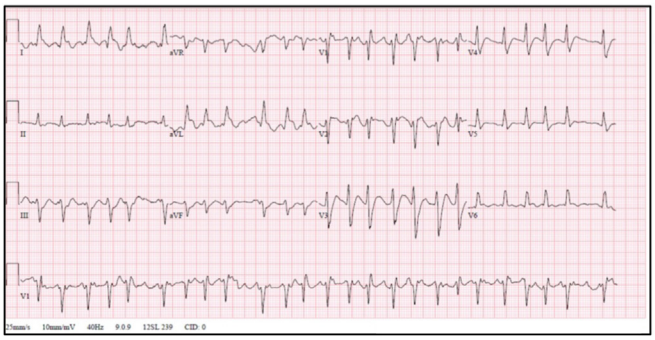

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| AT/AF | | | | 3255 | 31-Mar-2022 | 19:51 | 13:52:30 | 368/93 | 600/194 | Rest |
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| AT/AF | | | | 3245 | 26-Mar-2022 | 18:52 | 04:31:59 | 397/80 | 600/107 | Rest |
| AT/AF | | | | 3244 | 26-Mar-2022 | 13:32 | 04:38:58 | 387/78 | 600/130 | Rest |
| AT/AF | | | | 3243 | 25-Mar-2022 | 19:00 | 16:53:32 | 385/78 | 600/182 | Rest |
| AT/AF | | | | 3242 | 24-Mar-2022 | 18:42 | 22:20:52 | 387/78 | 600/176 | Rest |

**Figure 1** **a:** Electrocardiogram on admission: atrial fibrillation with rapid ventricular response, ventricular rate 152 beats per minute. Left axis deviation, incomplete right bundle branch block, T-wave inversion on lateral leads. **b:** Implantable cardioverter-defibrillator interrogation after the second arrest without significant ventricular arrhythmia.

An electrocardiogram (ECG) on admission revealed atrial fibrillation with rapid ventricular response and T-wave inversion in the lateral leads (Figure 1a). Sequential ECGs revealed absence of further progression of ischemic changes. His troponin showed a dynamic rise to 44 ng/mL (reference range 0.000–0.034 ng/mL). Urine drug screen was unremarkable. Interrogation of his ICD did not reveal any significant ventricular arrhythmia (Figure 1b). An echocardiogram on the day of admission showed an ejection fraction of 31% with global hypokinesis. He did not have a typical takotsubo cardiomyopathy appearance.

He was managed by our critical care team with respiratory/hemodynamic support (norepinephrine and vasopressin drips) and non-ST-elevation myocardial infarction protocol. Cardiac catheterization once again revealed nonobstructive disease as well as the mid left anterior descending artery intramyocardial bridge. Of note, at the time of the catheterization the patient was still on both intravenous pressors. Upon selective coronary angiography the patient developed severe multivessel coronary vasospasm, which responded to 200 mcg of intracoronary nitroglycerin (Figure 2). On day 5, he was off pressors and was successfully liberated from the ventilator, with full neurological recovery. The patient was then started on calcium channel blockers and nitrates. Follow-up echo 5 days later revealed normalization of left ventricular ejection fraction. He was then discharged home.

Because of uncertainty regarding the etiology of his cardiac arrest, the patient was referred to a major tertiary center. Genetic testing for cardiomyopathy was negative. The patient underwent repeat cardiac catheterization with provocation test with methylergonovine (as he had been on pressors at the time of the initial study), which resulted in severe spasm of the proximal left anterior descending artery with increase in pulmonary artery wedge pressure. This resolved with intracoronary nitroglycerin. The patient was started on high-dose diltiazem. Nitrates were stopped because of headache. He and his family received thorough education regarding the pathophysiology and clinical management regarding coronary artery vasospasm. He was advised to avoid strenuous exercise. He remains symptom free and has completed a course of cardiac rehabilitation.

## Discussion

CAS, previously referred to as Prinzmetal or variant angina, is characterized by unprovoked constriction of the coronary arteries that results mostly in episodes of nocturnal and early morning rest angina and that promptly respond to short-acting nitrates. The electrocardiographic manifestations are either ST depression or elevation. Its prevalence is uncertain, as provocative testing is not widely performed.[2] Among all patients who present with a myocardial infarction, around 10% will not have obstructive coronary lesions; and of these, approximately one-third to two-thirds will have documented coronary vasospasm.[5] There does not appear to be a difference in prevalence between males and females; however, limited studies did reveal less incidence of CAS in women than in men, which may be confounded by higher rates of smoking in males vs in females.[6] CAS does appear to be more prevalent in patients of Asian descent, cigarette smokers, and those with history of recreational drug use such as cocaine and exercise resulting in catecholamine surges.[2,7] The pathogenesis of CAS is complex and heterogeneous, but vascular smooth muscle hyper-reactivity is thought to be the key mechanism. Other mechanisms include autonomic nervous system dysfunction and endothelial dysfunction. The end result is either focal or diffuse coronary vasospasm.[8,9]

Although sudden cardiac death owing to life-threatening arrhythmias is not uncommon, pulseless electrical activity appears to be. In terms of diagnostic criteria, Meune and colleagues[1] postulated that in the absence of another identifiable cause, CAS was to be considered as the cause of cardiac arrest if any of the following occurred: spontaneous spasm during angiography, or transient ST elevation of $>2$ mm in $>2$ contiguous leads that regressed after nitrates or a positive provocation test. Identifying sudden cardiac death as the result of CAS may be challenging, since spontaneous spasm may not be detected during catheterization and provocation testing is not routinely performed.[10] In addition, provocation testing can only be reliably performed in specialized centers that possess the necessary expertise. As a matter of fact, when our patient suffered his first episode of cardiac arrest (ventricular fibrillation and PEA), coronary vasospasm or ECG

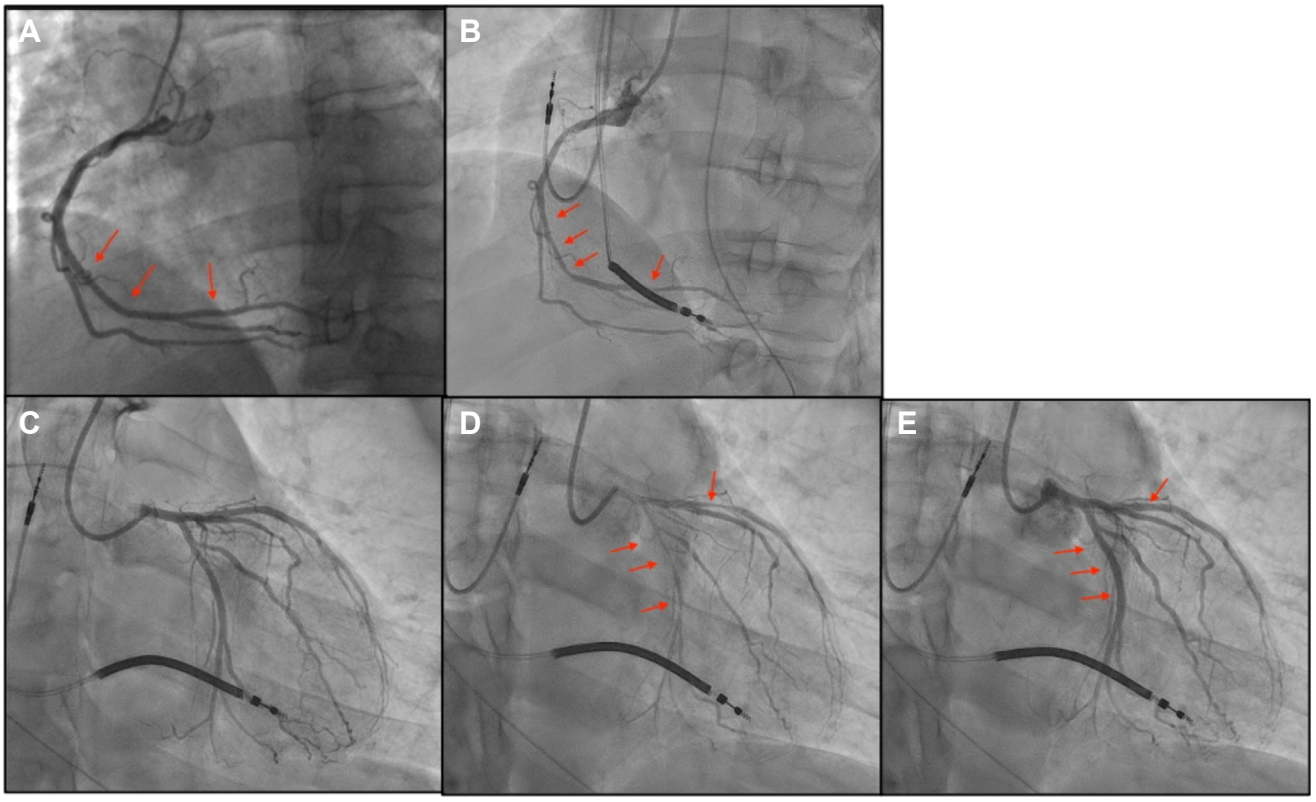


**Figure 2** Cardiac catheterization after cardiac arrest. **a:** Right coronary artery on June 25, 2021. **b:** Diffuse moderate mid right coronary artery spasm. **c:** Initial left coronary angiogram with 50% stenosis at the end of mid left anterior descending artery myocardial bridge. **d:** Developed spontaneous spasm with long 75% stenosis in large diagonal artery, severe diffuse spasm throughout left circumflex artery "strings" as indicated by arrow. **e:** Resolved diffuse coronary artery spasm after intracoronary artery nitroglycerin injection. Time frame: **a**, June 25, 2021; **b–e**, April 12, 2022.

evidence of ST elevation/depression were not identified. He underwent ICD placement for secondary prevention of sudden cardiac death. Even so, he developed another episode of PEA arrest about 10 months later. Cardiac catheterization revealed the presence of severe 3-vessel coronary vasospasm, which led to the conclusion that this was the most likely cause of his recurrent cardiac arrest. Unfortunately, the patient was on vasopressors at the time of testing. Subsequent provocation test with methylergonovine confirmed the presence of coronary artery vasospasm. Thus, performing a provocation test in patients without another identifiable cause of cardiac arrest may be helpful, and CAS must be considered in the differential.

The optimal approach to patients with sudden cardiac arrest related to CAS is still unknown. Lifestyle modification with smoking cessation, reduction of stress, and avoidance of vasospastic agents such as alcohol, sympathomimetic agents, nonselective beta-blockers, ergot alkaloids, capecitabine, and 5-fluorouracil is crucial.[3] Medical therapy with calcium channel blockers and/or nitrates is the standard of care. The dose is determined by titration as tolerated and the goal is symptom relief.[1,2] Unfortunately, medical therapy alone sometimes fails to eliminate the recurrence of CAS and subsequent arrhythmic events. In patients with evidence of atherosclerosis on angiography a statin is usually started. Percutaneous intervention is rarely used as a feasible treatment in patients with refractory left main CAS, although it has been reported.[11] And its performance may actually result in potential multivessel spasm and increased risk of stent thrombosis if there is subsequent spasm distal to the stent.[12] Case reports and small-group studies have also demonstrated potential efficacy of sympathectomy as a last-resort strategy for patients with CAS that is refractory to optimal medical therapy. For instance, Lin and colleagues[13] reported decreased major adverse cardiac event incidence in sympathectomy group compared to conventional treatment group in patients with refractory CAS (sympathectomy group n = 37, incidence = 16.22% vs conventional group n = 42, incidence = 61.90%, $P = .0001$).

In patients who survive sudden cardiac death, there is a consensus that an ICD should be implanted, but to date there is limited prospective data on efficacy. However, observational data appears to be favorable.[14] Unfortunately, real-world experience shows that some of these patients may die from PEA arrest despite implantation of an ICD.[4] Such is the case of our patient, who received an ICD after his first episode of ventricular fibrillation arrest, yet still suffered from a PEA arrest. Thankfully, spontaneous and severe 3-vessel coronary artery vasospasm was revealed during cardiac catheterization and confirmed with subsequent methylergonovine provocation testing.

The long-term prognosis of CAS-related cardiac arrest is uncertain, and data are limited given the small sample size. In a retrospective study that included 188 patients with

variant angina and aborted sudden cardiac death, Ahn and colleagues[15] reported that 26 patients (32.4/1000 patient years) suffered from a recurrence of ventricular tachyarrhythmia with a cumulative risk of sudden cardiac death of 16.7% at 10 years of follow-up (16.7% vs 2.5% of healthy subjects, $P < .001$). Patients who received an ICD had a lower rate of sudden cardiac death in comparison with patients without the device.[16] Possible explanations for cardiac arrest recurrence include multivessel spasm, failed medical treatment, medication nonadherence, and myocardial scar resulting from injury at the time of the initial arrest.[16] In other studies, diffuse right coronary artery vasospasm and horizontal/descending ST-segment pattern of early repolarization were predictors of recurrent sudden cardiac death in patients with CAS.[10,16] Patients who have diffuse spasm have an increased incidence of spasm-induced myocardial infarction and intractable spasm refractory to conventional treatment.[17] In our case, the patient suffered from recurrent cardiac arrest (first episode of ventricular fibrillation and PEA, then a second episode of PEA; episodes 10 months apart, both associated with strenuous exercise) and was found to have diffuse 3-vessel coronary spasm. Besides medical treatment with coronary calcium blockers, statin, and avoidance of vasospastic agents, he was advised to avoid strenuous exercise.

## Conclusion

Sudden cardiac death including ventricular tachyarrhythmia and PEA without another identifiable cause may be due to CAS even in patients without complaints of chest discomfort. Our case underscores the importance of considering CAS in the differential diagnosis when there is an absence of other causes of cardiac arrest. Provocation testing should be performed during angiographic evaluation if no spontaneous spasm is identified. Conventional management includes smoking cessation, avoidance of vasospastic agents, and medical treatment with calcium channel blockers and nitrates. Restriction of physical activity should also be recommended in selected patients, especially when it is a proven trigger, as in our case. Diffuse, multivessel spasm has been associated with a high risk of cardiac arrest, and ICD implantation may be helpful as a secondary prevention strategy in patients with ventricular tachyarrhythmias, although there is limited data in this regard. Further studies are necessary to investigate the optimal approach for patients with sudden cardiac death related to CAS and recurring cardiac arrest despite optimized medical treatment and ICD implantation.

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