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RHYTHM DISORDERS

CLINICAL CASE

Cocaine-Induced Sudden Cardiac Death Unravelling a *SCN5A*-Related Disease

Raffaello Ditaranto, MD, PhD,[a,b,c] Guido Pelletti, MD, PhD,[d] Cesare Rossi, MD,[e] Mauro Biffi, MD,[a,b] Arthur A.M. Wilde, MD, PhD,[b,f] Elena Biagini, MD, PhD,[a,b] Antonietta D'Errico, MD,[g,*] Maddalena Graziosi, MD, PhD[a,b,*]

ABSTRACT

Cocaine consumption is a significant global problem, with an estimated 20 million users worldwide. Sudden cardiac death is frequently reported in this population, particularly among individuals <40 years of age. The role of underlying inherited heart disorders in these cases remains largely unexplored. We report the case of a patient who suffered a cocaine-induced sudden death, where a dedicated program investigating unexplained deaths in the young identified a *SCN5A*-related disease. We hypothesize that inherited heart diseases may contribute to cocaine-induced sudden cardiac death and that a multidisciplinary program systematically evaluating sudden deaths in young individuals is essential to uncover this association and reveal hidden risk factors. Integrating clinical data with traditional pathological examination and molecular autopsy is crucial for determining the cause of death and enabling cascade screening in relatives. (JACC Case Rep. 2025;30:103174) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 42-year-old man experienced a generalized tonic-clonic seizure at home consequent to cocaine overdose. Upon the arrival of the medical emergency team, the patient was agitated, confused and diaphoretic. Electrocardiogram showed a sustained ventricular tachycardia (VT) at 360 ms cycle length (**Figure 1A**) without hemodynamic compromise (blood pressure, 146/105 mm Hg). Intravenous 300 mg amiodarone was administered, successfully restoring sinus rhythm. Electrocardiogram after cardioversion revealed border-line PR interval, prolonged QRS, coved-type ST-segment elevation in V_{1-2} (Brugada pattern type 1), prolonged QTc, and slightly rightward axis (**Figure 1B**). The patient was admitted to the cardiac intensive care unit for further examinations; transthoracic echocardiogram and coronary

TAKE-HOME MESSAGES

- Inherited heart diseases may contribute to the risk of sudden death among cocaine users.
- Establishing a multidisciplinary network for the systematic investigation of sudden death in young individuals is crucial to avoid missed diagnoses and enable family screening.

From the [a]Cardiology Unit, Cardiac Thoracic and Vascular Department, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy; [b]European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart-ERN GUARD-Heart; [c]Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy; [d]Unit of Legal Medicine, Department of Medical and Surgical Sciences, University of Bologna, Italy; [e]Medical Genetics Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [f]Heart Center, Department of Clinical and Experimental Cardiology, Academic Medical Center, University of Amsterdam, the Netherlands; and the [g]Department of Pathology. IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy. *These authors share joint senior authorship.

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ABBREVIATIONS AND ACRONYMS

BrS = Brugada syndrome

VT = ventricular tachycardia

angiography were normal. Laboratory tests showed a mild troponin increase, not suggestive of acute coronary syndrome (high-sensitivity cardiac troponin T: 34 → 40 ng/mL; reference value, <15 ng/mL for males) and the chemical-toxicological screening revealed high urine cocaine levels (>5,000 ng/mL; cutoff, 300 by kinetic interaction of microparticles in solution immunoassay). Serial electrocardiograms documented ST-segment elevation normalization within 4 hours. The patient remained stable with no tachyarrhythmia or bradyarrhythmia documented during monitoring. Flecainide challenge test (2 mg/kg, over 10 minutes), 3 days after admission, was not diagnostic (**Figure 1C**). The patient was discharged 6 days later and offered close follow-up, which he declined.

Four years later, he died suddenly while driving alone: the car hit the guardrail without the driver sustaining any visible injuries. Emergency services arrived at the scene of the accident at 1:00 PM: neither traces of drugs were found in the vehicle nor signs of venipuncture on the body. He had left home approximately 20 minutes earlier, leading to the presumption that he had inhaled at least that long before his death.

DIFFERENTIAL DIAGNOSIS

Owing to the known cocaine use, all possible causes related to sudden death from cocaine intoxication were considered in the differential diagnosis: cardiac arrhythmias, acute myocardial infarction, myocarditis, aortic dissection, ischemic or hemorrhagic stroke, acute pulmonary edema, and seizures.

INVESTIGATIONS

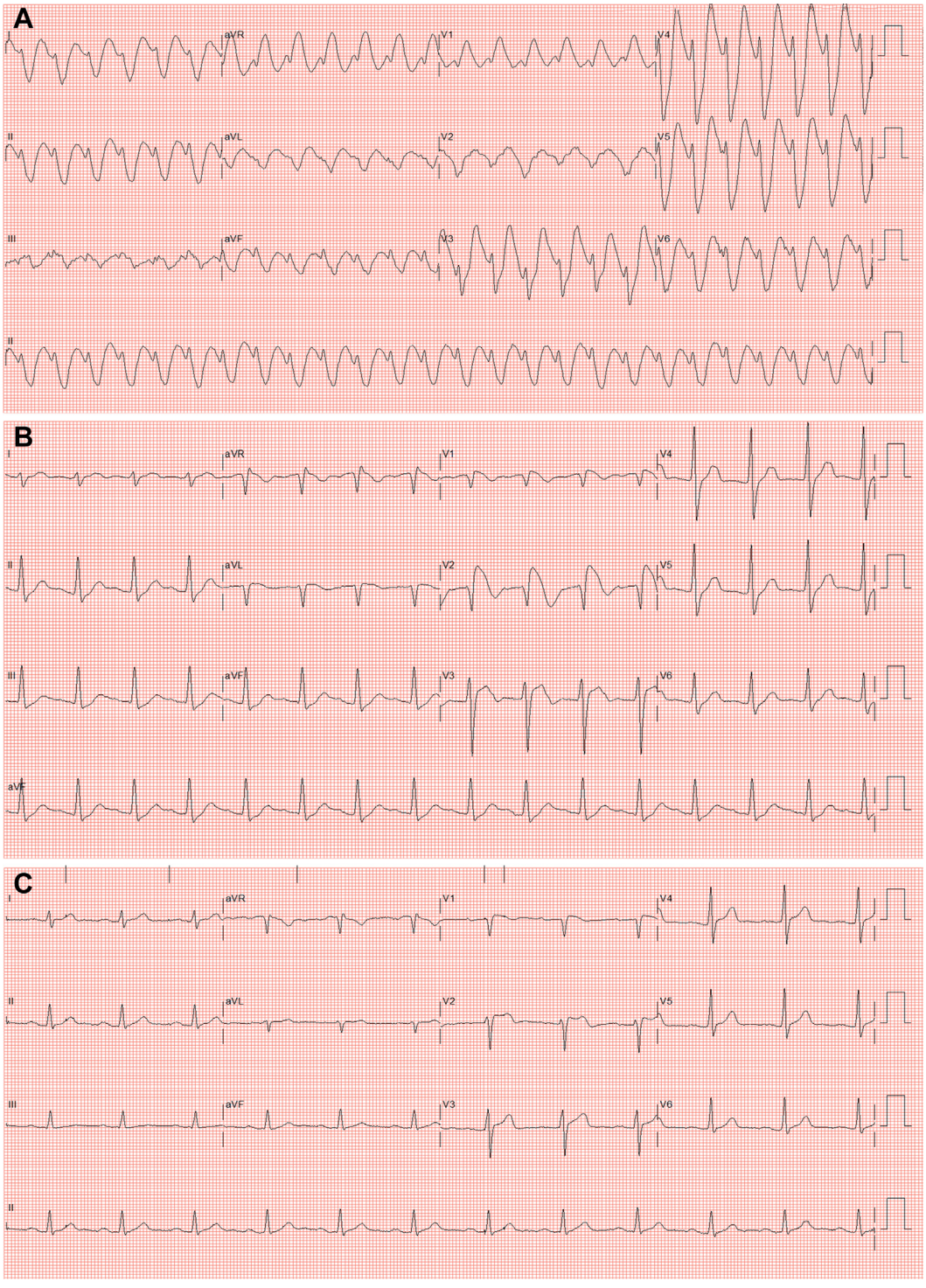
The autopsy, requested by the public prosecutor to assess the cause and the manner of death, was performed by a forensic pathologist. External examination and autopsy excluded a traumatic death. Postmortem toxicology tests revealed very high blood cocaine levels, exceeding the upper limit of detection (>1 mg/L) as determined by gas chromatography coupled with mass spectrometry. Considering the previous VT and the cocaine-induced Brugada pattern type 1, the case was referred to the cardiopathology unit of St. Orsola Hospital (Bologna), hub center of the Emilia-Romagna (Italy) network for sudden death in the young program.[1] Macroscopic examination of the heart (weight, 340 g) revealed mild biventricular dilatation, especially the right ventricular outflow tract. Coronary arteries had mild atherosclerosis. By histology, the right ventricle showed mild interstitial myocardial fibrosis and focal fibrofatty infiltration, with little fibrous component. Fibrous/fibrofatty replacement of the myocardium and degenerative changes of the myocytes were absent (**Figure 2**). No intramyocardial inflammatory infiltrates were identified, although mild inflammation was present in the subepicardium. No relevant abnormalities were found in the rest of the body, except for those related to the circulatory arrest. Genetic testing (next-generation sequencing, 40-gene panel for channelopathies/cardiomyopathies) was performed on DNA from the cardiac samples, revealed a variant in exon 25 of *SCN5A* gene (NM_198056.3, c.4370G>A p.Gly1457Glu), which encodes the pore-forming ion-conducting α-subunit of the cardiac sodium channel ($Na_V1.5$) (OMIM: *600163). This variant is not reported in ClinVar and absent in gnomAD v4.0: moderate evidence of pathogenicity (PM2), according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology criteria for classifying pathogenic variants. It falls within a critical transmembrane domain of *SCN5A*, specifically a mutational hot spot region of 17 amino acids (moderate evidence of pathogenicity; PM1). The pathogenicity prediction model MetaRNN computes a score of 0.983 (strong pathogenicity): supporting evidence of pathogenicity PP3.[2] Accordingly, the combined American College of Medical Genetics and Genomics/Association for Molecular Pathology criteria classify the variant as likely pathogenic (class 4). Family history was negative for sudden cardiac death and cardiac diseases: screening was then proposed but declined.

DISCUSSION

Cocaine is a global problem with an estimated 20 million users worldwide.[3] These individuals have a significantly increased all-cause mortality and sudden cardiac death is a possible complication.[4] The role of underlying inherited heart disorders on the latter remains unknown. Here, we report a patient who suffered cocaine-induced sudden death, in whom a systematic program investigating unexplained deaths in the young revealed a *SCN5A*-related disease.

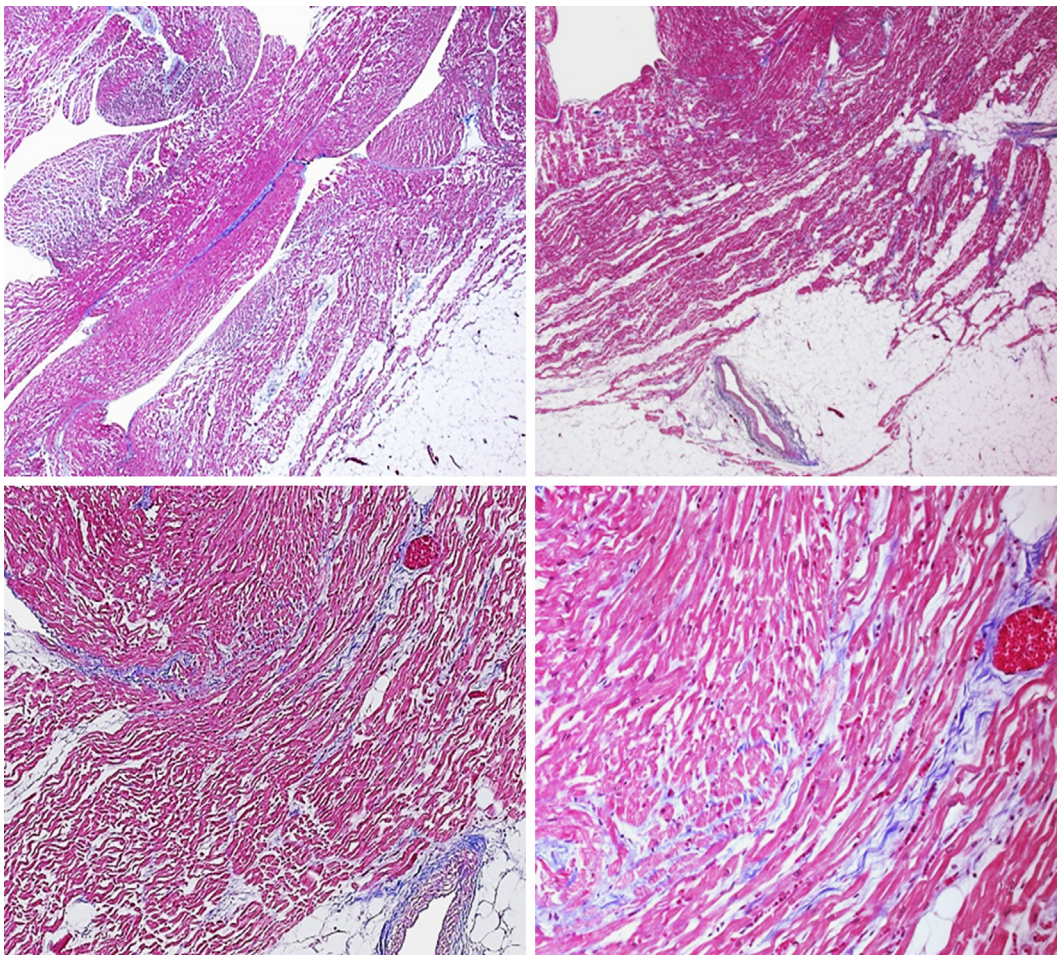
The cardiovascular effects of cocaine are dose dependent. At low doses, it has sympathomimetic actions (increases heart rate and blood pressure) and induces myocardial ischemia by stimulating endothelin-1 (a vasoconstrictor) release from endothelial cells, inhibiting nitric oxide (a vasodilator) production, and promoting thrombosis through

FIGURE 1 **Electrocardiograms**



(A) Monomorphic ventricular tachyarrhythmia with right bundle branch block-like morphology, 380 ms cycle length. (B) Postcardioversion ECG: sinus rhythm (92 bpm), borderline PR interval (190 ms), intraventricular conduction delay (QRS 130 ms) with coved-type ST-segment elevation in $V_{1\text{-}2}$ (type 1 Brudaga pattern), prolonged QTc (490 ms), slight right axis deviation. (C) ECG after flecainide challenge (2 mg/kg intravenous over 10 minutes), right precordial leads positioned in the fourth intercostal space: sinus rhythm (71 beats/min), first-degree atrioventricular block (PR interval = 232 ms), saddle-back ST-segment elevation in V_2 (type 2 Brugada pattern), normal QRS (105 ms). and QTc (426 ms) duration. ECG = electrocardiogram.

FIGURE 2 Histological Sections



Histological sections of the right ventricle (anterolateral wall) stained with Azan-Mallory trichrome (myocytes in red Bordeaux, fibrosis in blue), highlighting mild myocardial interstitial fibrosis without fibrous/fibrofatty replacement of the myocardium or degenerative myocyte changes.

platelet activation. Additionally, chronic use may accelerate atherosclerosis. Although a coronary spasm-triggered arrhythmia cannot be excluded, the absence of coronary thrombosis and ischemic myocardial injury do not support ischemia as cause of death in this case. Cocaine levels detected in the patient were significantly high. At high doses, cocaine acts like a class IC antiarrhythmic agent by blocking the voltage-gated sodium channels, with conduction slowing (ie, PR, QRS, and QTc prolongation) until complete inexcitability and can induce a Brugada pattern type 1.[5] Accordingly, monomorphic VT, torsade de pointes, ventricular fibrillation, and asystole are common causes of death in cocaine users, especially soon after cocaine ingestion. Bauman et al[6] found no definite cause of death at autopsy in 81% of deaths attributable to cocaine, suggesting that these deaths were likely arrhythmic. Our patient had experienced a sustained VT and developed a Brugada pattern type 1. This electrocardiographic finding has been frequently reported in cocaine users, mainly after overdose, with both positive and negative subsequent pharmacological challenge.[7] However, long-term data and genetic information from these reports/series are missing. In our case, these findings prompted further evaluation,

revealing 2 additional elements: the *SCN5A* likely pathogenic variant and the right ventricle structural findings. Loss of function *SCN5A* variants account for 20% to 30% of Brugada syndrome (BrS) cases. Additionally, although BrS was described initially as a pure channelopathy, structural abnormalities have been observed in autopsies, endomyocardial biopsies, and cardiac magnetic resonance. The most common histological findings include lymphomononuclear infiltrates, occasionally accompanied by necrosis of adjacent myocytes, focal fibrofatty replacement nondiagnostic for arrhythmogenic cardiomyopathy, and interstitial or replacement fibrosis. Particularly, the increased collagen content within the BrS right ventricular outflow tract epicardium—although its origin remains unclear—is believed to have a cumulative effect on Na^+-current-related arrhythmic vulnerability.[8] This factor typically causes polymorphic VT and ventricular fibrillation, although monomorphic VT may also occur.[9] Considering all the evidence at hand, our diagnostic hypothesis was sudden death owing to cocaine-induced arrhythmia in a patient affected by *SCN5A*-related disease. In this context, the negative sodium channel blocker test was considered a false negative, reflecting the lower sensitivity of flecainide in unmasking BrS compared with ajmaline.[10]

CONCLUSIONS

Sudden cardiac death among cocaine users is a public health concern, but so far the relevance of genetic disorders in contributing to these deaths remains unknown. This case highlights that inherited heart diseases may play a role and that a dedicated program, based on a multidisciplinary team, systematically evaluating sudden death in young individuals is essential to unveil this association. Integrating clinical information with traditional pathological examination and molecular autopsy is crucial to determine the cause of death and facilitate cascade screening in relatives.

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ADDRESS FOR CORRESPONDENCE: Dr Elena Biagini, Cardiology Unit, Cardiac Thoracic and Vascular Department, IRCCS - Azienda Ospedaliero Universitaria - Policlinico di Sant' Orsola, Via G. Massarenti 9, 40138 Bologna, Italy. E-mail: elena.biagini73@gmail.com.

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