



## Case Report

## Acute coronary syndrome after cannabis use: Correlation with quantitative toxicology testing

John R. Richards, MD<sup>a,\*</sup>, Gagan D. Singh, MD, MS<sup>b</sup>, Aman K. Parikh, MD<sup>a</sup>, Sandhya Venugopal, MD, MS<sup>b</sup><sup>a</sup> Department of Emergency Medicine, University of California Davis Medical Center, Sacramento, CA, United States of America<sup>b</sup> Department of Internal Medicine, Division of Cardiovascular Medicine, University of California Davis Medical Center, Sacramento, CA, United States of America

## ARTICLE INFO

## Article history:

Received 29 November 2018

Received in revised form 17 January 2019

Accepted 12 February 2019

## Keywords:

Acute coronary syndrome

Cannabis

Chest pain

Marijuana

Myocardial infarction

STEMI

Toxicology

## ABSTRACT

Excluding ethanol, cannabis is the most commonly used drug in the United States and worldwide. Several published case series and reports have demonstrated an association between cannabis use and acute coronary syndrome (ACS). We report the first ever published case of ACS precipitated by cannabis use that was confirmed with concomitant rising quantitative plasma levels of 11-nor-9-carboxy- $\Delta^9$ -tetrahydrocannabinol, a secondary metabolite of cannabis. A 63-year-old non-tobacco smoking male with no prior medical history presented to the emergency department with chest pain immediately after smoking cannabis, and anterior ST-segment elevation pattern was observed on his electrocardiogram. He was taken to the cardiac catheterization lab for percutaneous coronary intervention (PCI) of his left anterior descending artery, whereupon he developed hemodynamically significant accelerated idioventricular rhythm necessitating intra-aortic balloon pump placement. He underwent two further PCI procedures during his inpatient stay and was discharged in improved condition after eight days. Two sequential quantitative plasma cannabis metabolite assays at time of arrival then 6 h later were 24 ng/mL then 39 ng/mL, an increase of 63%, which implicated the patient's acute cannabis use as a precipitant of ACS. We also discuss the putative pharmacologic mechanisms behind cannabis use and ACS. Clinicians caring for patients using cannabis who have vascular disease and/or risk factors should be aware of this potentially deleterious association, as cessation of cannabis use could be important for their cardiac rehabilitation and long-term health.

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## 1. Introduction

Excluding ethanol, cannabis is the most commonly-used drug in the United States and worldwide, and its rate of use is increasing as legalization for recreational and medical use continues to spread according to the 2018 United Nations World Drug Report [1]. Several case series and reports have suggested a direct association between cannabis use and acute coronary syndrome (ACS) [2–4]. Cannabinoid agonists such as delta 9-tetrahydrocannabinol, the major psychoactive compound in cannabis, interact with the endocannabinoid system via G protein-coupled membrane receptors, CB1 and CB2, which are found throughout the body. CB1 receptors are distributed within the central nervous system and modulate autonomic signaling and allostasis, and these receptors are also located in the myocardium and vascular endothelium [5,6]. Cannabis use most commonly results in tachycardia and hypertension through sympathetic nervous system activation and parasympathetic nervous system inhibition, which is the primary mechanism

thought to be responsible for its provocation of ACS through increased myocardial oxygen demand [7,8]. We present a case of ACS precipitated by acute cannabis use and characterized by rising quantitative cannabis metabolite levels.

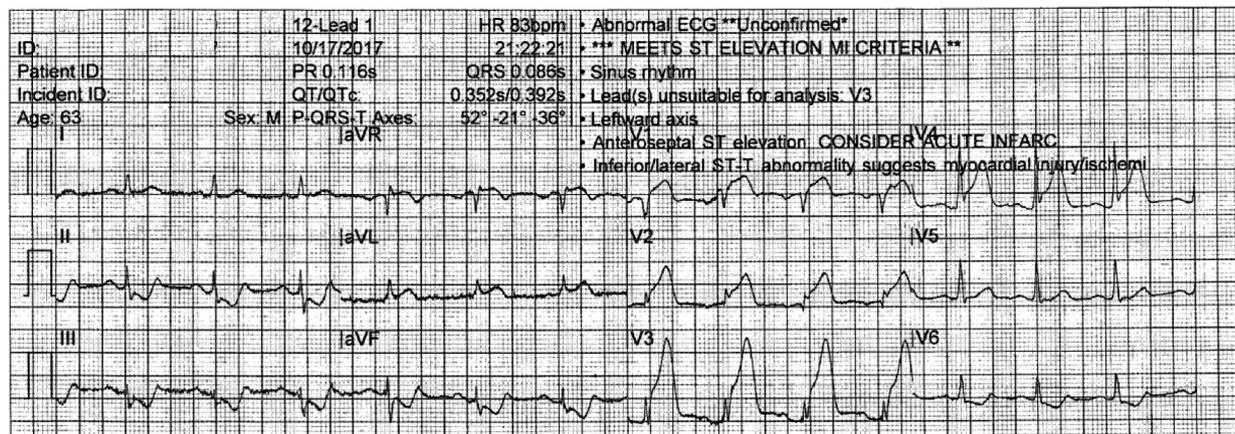
## 2. Case report

A 63-year-old male was brought to the emergency department (ED) by ambulance after developing chest pain for 30 min. The patient stated he had been sitting on a couch watching television and smoking phytogetic cannabis just prior to the onset of chest pain. Prehospital vital signs were: blood pressure 184/114 mmHg, pulse rate 84 beats/min, respiratory rate 18 breaths/min, and pulse oximetry (SpO<sub>2</sub>) 93%. During his 30-min transport time he received 325 mg of chewable aspirin and two doses of 0.4 mg sublingual nitroglycerin, which mitigated his chest pain from a 10/10 subjective pain scale to 7/10. An electrocardiogram was transmitted to the ED prior to arrival and demonstrated ST-segment elevation in precordial leads V1–4 and ST-segment depressions in lead II, III (Fig. 1A). The cardiac catheterization team was then activated. Ten minutes later he arrived in the ED and was immediately triaged to a treatment room and connected to continuous cardiovascular and pulse oximetry monitoring. Initial ED vital signs were: blood

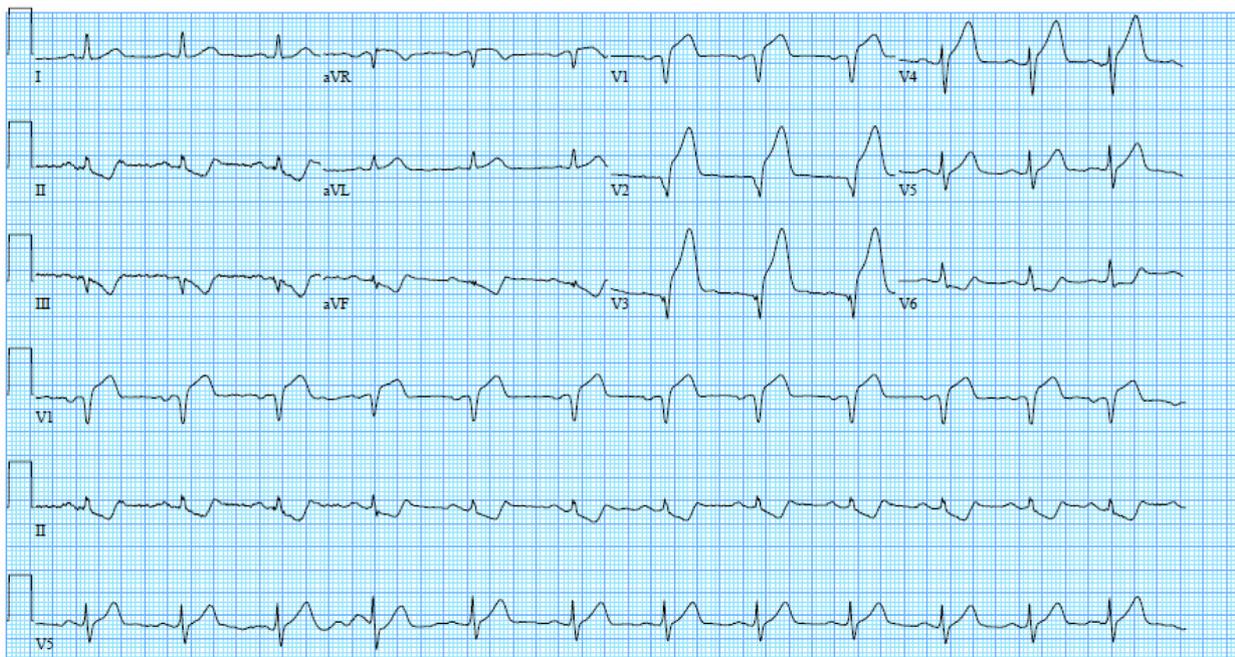
\* Corresponding author at: Department of Emergency Medicine, PSSB 2100, U.C. Davis Medical Center, 2315 Stockton Boulevard, Sacramento, CA 95817, United States of America.

E-mail address: [jrichards@ucdavis.edu](mailto:jrichards@ucdavis.edu) (J.R. Richards).

A.



B.



**Fig. 1.** Image A: Prehospital electrocardiogram performed en route to the emergency department demonstrates ST-segment elevation in leads V1–4 with reciprocal ST-segment depressions in inferior leads II, III, and V6. Image B: Electrocardiogram performed shortly after arrival in the emergency department confirms earlier findings.

pressure 150/106 mmHg, pulse rate 73 beats/min, respiratory rate 20 breaths/min, temperature 35.1 °C, and SpO<sub>2</sub> 94% on room air. An electrocardiogram was performed at this time (Fig. 1B) with findings similar to the prehospital electrocardiogram.

Further questioning at this time revealed the patient had no past medical or surgical history, and he denied tobacco or synthetic cannabinoid use. He stated he had not seen a physician in 30 years and had never had his lipid profile measured. With regard to other cardiac risk factors, there was no family history of coronary arterial disease, diabetes, or hypertension, although he did admit to a sedentary lifestyle. His height was 182 cm and weight was 113 kg, with a calculated body mass index of 34. He denied lightheadedness, shortness of breath, syncope, palpitations, or lower extremity edema. He admitted to recreationally smoking a large cannabis “joint” just preceding the onset of chest pain, and he described himself as an occasional cannabis user. He obtained his cannabis supply from a well-established legal cannabis dispensary. He denied illicit stimulant or opioid use. He took no prescribed or over-the-counter medications. Physical examination

revealed a slightly overweight, diaphoretic male in mild discomfort. His heart and lung findings on auscultation were normal. He received 180 mg ticagrelor orally and an intravenous (IV) heparin bolus of 5000 units and 1000 units/h infusion was initiated prior to his transfer to the cardiac catheterization suite. During the 20-min period he was in the ED, a complete blood count, chemistry panel, coagulation panel, troponin I, B-type natriuretic peptide (BNP), urinalysis, and qualitative urine toxicology screen for stimulants, benzodiazepines and opioids, were collected. As this qualitative screen did not include cannabis, a quantitative plasma toxicology test for the cannabis metabolite 11-nor-9-carboxy- $\Delta^9$ -tetrahydrocannabinol was also obtained at this time and 6 h later. Initial troponin I was 17 ng/L (normal <40 ng/L) and BNP was 23 pg/mL (normal <100 pg/mL). The other initial lab tests were normal, including the qualitative urine toxicology screen. The quantitative cannabis metabolite test was sent to an outside lab for analysis.

During cardiac catheterization the patient remained hemodynamically stable, and angiography revealed diffuse coronary arterial disease

in the proximal (80% stenosis), mid- (90% stenosis), and distal (70% stenosis) right coronary artery (RCA), and 40% stenosis of the right posterior descending artery (Fig. 2). A large caliber left main artery was encountered that bifurcated into the left anterior descending (LAD) artery with 80% stenosis and left circumflex artery with 50% stenosis. A SYNERGY™ (Boston Scientific, Marlborough, Massachusetts, USA) 3.5 × 38 mm everolimus-eluting stent was placed in the proximal LAD. At this point the patient developed an atypical and sustained accelerated idioventricular ventricular rhythm (AIVR) for 30 min with mild hemodynamic instability. Two sequential doses of adenosine at 12 mg and 18 mg IV were administered without effect. Lidocaine 100 mg IV and amiodarone 300 mg IV were given followed by cardioversion with 150 joules then 200 joules. These measures were unsuccessful, and an intra-aortic balloon pump (IABP) was placed via the right femoral artery for hemodynamic support and increased coronary perfusion. The patient remained hemodynamically stable and just after completion of the IABP placement the patient returned to normal sinus rhythm. A second troponin I sent after the procedure was 24,314 ng/L.

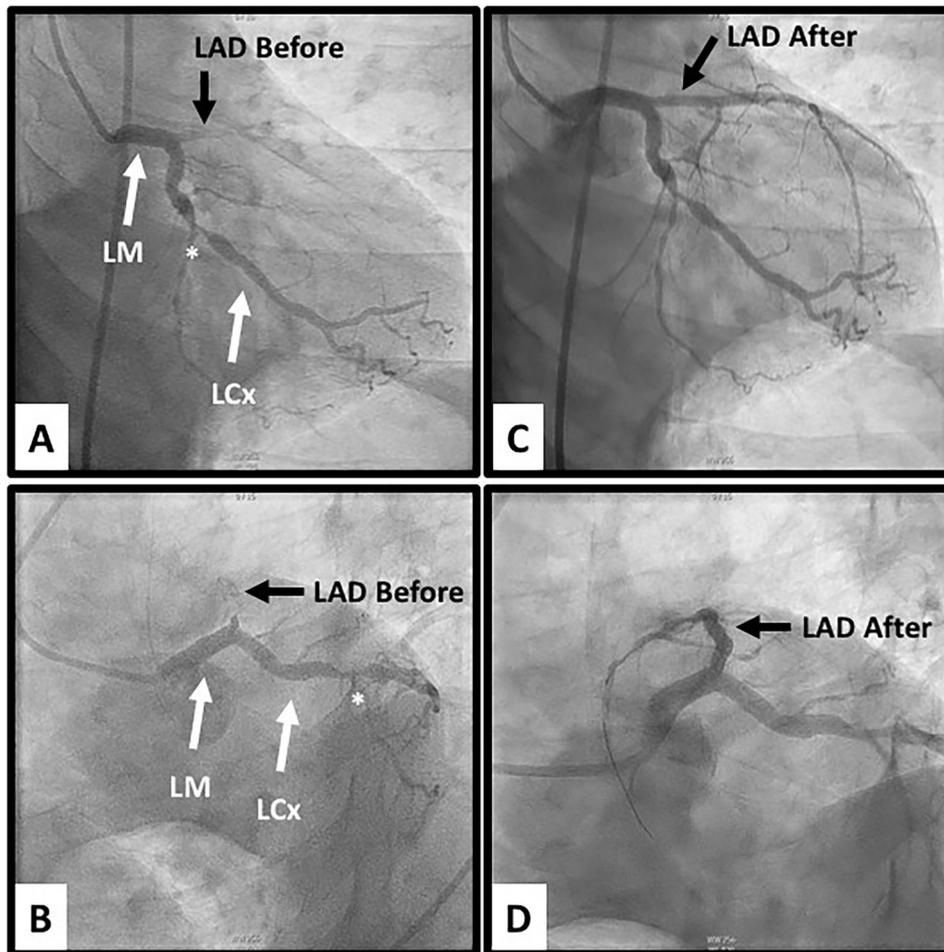
The cardiothoracic surgery team was consulted and deemed the patient was better suited for complex percutaneous coronary intervention (PCI) than bypass graft surgery for the remaining epicardial coronary artery disease. The patient then underwent two subsequent cardiac catheterizations on hospital days two and five for placement of stents in his mid-distal LAD and RCA, respectively. He was discharged in good condition on hospital day eight with prescriptions for carvedilol, lisinopril,

atorvastatin, aspirin, ticagrelor and nitroglycerin. A few days after discharge the quantitative cannabinoid metabolite assay for 11-nor-9-carboxy- $\Delta^9$ -tetrahydrocannabinol returned with the following results: 24 ng/mL then 39 ng/mL 6 h later, an increase of 63%. The patient never returned to his scheduled follow-up appointments.

### 3. Discussion

The association of cannabis use and ACS has been well-documented since the early 1970s [2–8]. Cannabis increases the risk of myocardial infarction nearly five times within 60 min after use and annual risk of an acute cardiovascular event up to 3% [3]. The majority of reported cases of cannabis-associated ACS are younger males without previous history of coronary artery disease and normal coronary angiograms [3,4,9]. As mentioned earlier, the activation of CB1 receptors within the myocardium, vascular endothelium, and autonomic nervous system from cannabis use results in tachycardia and hypertension thus increasing myocardial oxygen demand [4–7]. This may be further worsened if cannabis is smoked, which results in elevated levels of carboxyhemoglobin. Smoking cannabis generates carboxyhemoglobin levels five times higher than measured from smoking tobacco cigarettes [10].

The activation of CB1 receptors is pro-atherogenic, with downregulation of Th1 immune response cells in atherosclerotic lesions [11]. Expression of CB1 receptors is higher in macrophages within advanced atheromas of patients with unstable angina compared with those with



**Fig. 2.** Angiographic images from patient with acute thrombotic occlusion of the LAD artery. Images A and B represent pre-intervention angiograms in oblique projections (A: RAO 30 Caudal 30, B: LAO 40 Caudal 30). Both images demonstrate patent LM and LCx arteries. Noted is a high-grade (\*) non-culprit lesion of the mid-LCx vessel. The pre-intervention angiograms also show abrupt interruption in blood flow in the LAD shortly after its origin consistent with acute anterior STEMI. Post intervention angiograms (Images C and D) in the same oblique projections demonstrate a recanalized LAD after treatment with balloon angioplasty and deployment of a single drug eluting stent. (LAD = left anterior descending; LAO = left anterior oblique; LCx = left circumflex; LM = left main; RAD = right anterior oblique; STEMI = ST-elevation myocardial infarction).

stable angina [12]. Other potential mechanisms include the cannabis-induced angiotensin 1 receptor activation, creation of reactive oxygen species, endothelial dysfunction, and regional coronary vasospasm may result in ACS from coronary arterial occlusion and/or thrombosis [6,9,13]. Cannabis-mediated activation of CB1 and CB2 receptors may also lead to procoagulant effects, such as increased platelet membrane glycoprotein IIb-IIIa and P-selectin, lipopolysaccharide-stimulated tissue factor protein expression in activated monocytes, and platelet activation [14–16]. Of note, there is evidence of cardioprotective effects of cannabinoids in several animal studies; however these did not involve smoked phytogenic cannabis, but instead oral and IV synthetic cannabinoids administered at low-doses [17]. Atrial and ventricular dysrhythmias have been directly associated with cannabis use as well [18–20]. In our case, hemodynamically significant AIVR developed during PCI that was refractory to pharmacologic and electrical cardioversion.

A unique aspect of this case was the rising 11-nor-9-carboxy- $\Delta$ 9-tetrahydrocannabinol levels over a span of 6 h. Delta-9-tetrahydrocannabinol undergoes hepatic metabolism by cytochrome P450 complex-mediated microsomal hydroxylation and oxidation, and the majority of cannabis is excreted within five days as hydroxylated and carboxylated metabolites in feces and urine [21]. It is impossible to ascertain acute versus chronic cannabis use from a single quantitative plasma or urine metabolite analysis, and patient history may be subject to recall bias regarding their actual cannabis use. The plasma half-life of 11-nor-9-carboxy- $\Delta$ 9-tetrahydrocannabinol ranges from 4 to 12 h in non-users to up to 4 days in chronic users of cannabis [22]. In a prospective study of non-chronic users of cannabis, smoking an average-size cannabis cigarette containing 3.58% delta-9-tetrahydrocannabinol resulted in an average peak plasma 11-nor-9-carboxy- $\Delta$ 9-tetrahydrocannabinol level of 46.7 ng/mL at 60 min and 28.8 ng/mL at 6 h [20]. In contrast, chronic users may have high levels of 11-nor-9-carboxy- $\Delta$ 9-tetrahydrocannabinol even days after abstinence, but at a declining rate [22]. The acute 63% increase in nor-9-carboxy- $\Delta$ 9-tetrahydrocannabinol level observed in our patient over the time frame of 6 h strongly suggests acute use of cannabis as the primary culprit in precipitation of ACS. Other possibilities include an acute stress response resulting in lipolysis with release of stored cannabinoids from adipose cells in a chronic cannabis user.

#### 4. Conclusion

Clinicians caring for patients using cannabis who have vascular disease and/or risk factors should be aware of the potentially deleterious association between cannabis use and ACS, as cessation could be important for their cardiac rehabilitation and long-term health.

#### Conflict of interest disclosures

The authors have no conflict of interest to report.

#### References

- [1] United Nations. World drug report 2018. Available from [https://www.unodc.org/wdr2018/prelaunch/WDR18\\_Booklet\\_1\\_EXSUM.pdf](https://www.unodc.org/wdr2018/prelaunch/WDR18_Booklet_1_EXSUM.pdf), Accessed date: 20 November 2018.
- [2] Casier I, Vanduyhoven P, Haine S, Vrints C, Jorens PG. Is recent cannabis use associated with acute coronary syndromes? An illustrative case series. *Acta Cardiol* 2014;69:131–6.
- [3] Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. *Circulation* 2001;103:2805–9.
- [4] Pacher P, Steffens S, Haskó G, Schindler TH, Kunos G. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. *Nat Rev Cardiol* 2018;15:151–66.
- [5] Benowitz NL, Rosenberg J, Rogers W, Bachman J, Jones RT. Cardiovascular effects of intravenous delta-9-tetrahydrocannabinol: autonomic nervous mechanisms. *Clin Pharmacol Ther* 1979;25:440–6.
- [6] Liu J, Gao B, Mirshahi F, Sanyal AJ, Khanolkar AD, Makriyannis A, et al. Functional CB1 cannabinoid receptors in human vascular endothelial cells. *Biochem J* 2000;346(Pt 3):835–40.
- [7] Beaconsfield P, Ginsburg J, Rainsbury R. Marijuana smoking. Cardiovascular effects in man and possible mechanisms. *N Engl J Med* 1972;287:209–12.
- [8] Jouanous E, Raymond V, Lapeyre-Mestre M, Wolff V. What is the current knowledge about the cardiovascular risk for users of cannabis-based products? A systematic review. *Curr Atheroscler Rep* 2017;19:26.
- [9] Lee J, Sharma N, Aponte CS, Zaidi S, Fung D, Marmur JD, et al. Clinical characteristics and angiographic findings of myocardial infarction among marijuana users and non-users. *Scied J Cardiol* 2017;1(2) (pii: 1000008).
- [10] Wu TC, Tashkin DP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. *N Engl J Med* 1988;318:347–51.
- [11] Yuan M, Kiertscher SM, Cheng Q, Zoumalan R, Tashkin DP, Roth MD. Delta 9-tetrahydrocannabinol regulates Th1/Th2 cytokine balance in activated human T cells. *J Neuroimmunol* 2002;133:124–31.
- [12] Sugamura K, Sugiyama S, Nozaki T, et al. Activated endocannabinoid system in coronary artery disease and antiinflammatory effects of cannabinoid 1 receptor blockade on macrophages. *Circulation* 2009;119:28–36.
- [13] Lipina C, Hundal HS. Modulation of cellular redox homeostasis by the endocannabinoid system. *Open Biol* 2016;6:150276.
- [14] Dahdouh Z, Roule V, Lognoné T, Sabatier R, Grollier G. Cannabis and coronary thrombosis: what is the role of platelets? *Platelets* 2012;23:243–5.
- [15] Williams JC, Klein TW, Goldberger BA, Sleasman JW, Mackman N, Goodenow MM.  $\Delta$ (9)-tetrahydrocannabinol (THC) enhances lipopolysaccharide-stimulated tissue factor in human monocytes and monocyte-derived microvesicles. *J Inflamm (Lond)* 2015;12:39.
- [16] Deusch E, Kress HG, Kraft B, Kozek-Langenecker SA. The procoagulatory effects of delta-9-tetrahydrocannabinol in human platelets. *Anesth Analg* 2004;99:1127–30.
- [17] Mendizábal VE, Adler-Graschinsky E. Cannabinoids as therapeutic agents in cardiovascular disease: a tale of passions and illusions. *Br J Pharmacol* 2007;151:427–40.
- [18] Lehari A, Shay M, Gilony C, Even L. Marijuana smoking and paroxysmal atrial fibrillation. *Harefuah* 2005;144(1):2–3 [72].
- [19] Baranchuk A, Johri AM, Simpson CS, Methot M, Redfearn DP. Ventricular fibrillation triggered by marijuana use in a patient with ischemic cardiomyopathy: a case report. *Cases J* 2008;1:373.
- [20] Brancheau D, Blanco J, Gholkar G, Patel B, Machado C. Cannabis induced asystole. *J Electrocardiol* 2016;49:15–7.
- [21] Manno JE, Manno BR, Kemp PM, Alford DD, Abukhalaf IK, McWilliams ME, et al. Temporal indication of marijuana use can be estimated from plasma and urine concentrations of delta9-tetrahydrocannabinol, 11-hydroxy-delta9-tetrahydrocannabinol, and 11-nor-delta9-tetrahydrocannabinol-9-carboxylic acid. *J Anal Toxicol* 2001;25:538–49.
- [22] Karschner EL, Schwilke EW, Lowe RH, Darwin WD, Herning RI, Cadet JL, et al. Implications of plasma Delta9-tetrahydrocannabinol, 11-hydroxy-THC, and 11-nor-9-carboxy-THC concentrations in chronic cannabis smokers. *J Anal Toxicol* 2009;33:469–77.