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Coronary thrombosis and marijuana smoking: a case report and narrative review of the literature

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We encountered evidence of myocardial infarction due to coronary thrombosis in an autopsy of an occasional marijuana smoker. These findings prompted us to perform a narrative review of the literature to determine when post-mortem toxicological tests may support a temporal relationship between marijuana smoking and cardiovascular disease. Toxicological examination showed the presence of Δ-9-tetrahydrocannabinol, its main metabolite and cannabinol in blood and urine. Quali-quantitative analysis revealed that Δ-9-tetrahydrocannabinol was taken within 2 h of the onset of cardiovascular symptoms, according to circumstantial data. Post-mortem toxicological results must take into account the degradation and post-mortem redistribution of analytes. However, for any inference about the specific cardiovascular triggering effect of Δ-9-tetrahydrocannabinol intake, we maintain that cannabinoid analysis in blood samples must be considered an essential requirement to estimate the time of last intake and avoid incomplete documentation. The literature, combined with the present case report, highlights an association between marijuana use and negative cardiovascular events, although few authors have supported their conclusions with toxicological results. Thus, additional research is needed. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: forensic sciences; forensic pathology; cardiovascular disease; marijuana smoking; toxicological analysis

Introduction

Cannabis is the most commonly used illicit substance worldwide.[1] Δ-9-tetrahydrocannabinol (THC) is the active compound of *Cannabis sativa*; its highly lipophilic properties (pKa of 10.6) and kinetics are governed by a strong initial binding to serum proteins (approximately 97%). Body fat is the major long-term storage site of THC, resulting in a relatively long terminal half-life with differences in the windows for THC detection in the blood.[2] THC is prominently metabolized to 11-hydroxy-tetrahydrocannabinol (11-OH-THC) and nor-Δ9-tetahydrocannabinol-9-carboxylic acid (THC-COOH). THC and its metabolites also undergo *in vivo* conjugation with glucuronic acid, which facilitates their excretion. It is detectable in the plasma a few seconds after the first puff is smoked, and the peak plasma concentration occurs after several minutes. While the plasma THC concentration decreases rapidly after smoking cannabis, residual quantities of THC (less than 5 ng/mL) as well may be detectable for longer periods, specifically in more habitual consumers. THC-COOH is detected in the blood for longer periods,[3] although free THC-COOH is not excreted in significant concentrations.

The biological effects of THC in humans are mediated by two G-protein-coupled receptors (CB_1 and CB_2).[4] Additionally, THC reportedly has a biphasic effect on the autonomic nervous system with hemodynamic consequences. An increase in sympathetic activity and a reduction in parasympathetic activity, producing tachycardia and an increase in cardiac output, are believed to be useful cannabinoid biomarkers.[5,6] With respect to inter-individual variability, acute cannabis administration increases the heart rate (HR)[7–9] with a peak effect 10 to 15 min after smoking and an increase of 20 to 30 beats per min. Another effect is orthostatic hypotension due to decreased vascular resistance.[10–12] Tolerance to the acute effects of THC develops over several days,[11–13] but this tolerance is rapidly lost when cannabinoid administration is stopped.[14,15] Several cardiovascular diseases (CVDs) are reportedly associated with cannabis intake, although little is known about the exact underlying mechanisms. The association between adverse CVD and cannabis use is usually based on the temporal relationship between intake and the onset of cardiovascular adverse events. Aronow and Cassidy[16,17] demonstrated that the exercise time until the onset of angina was markedly shorter after smoking a single marijuana cigarette than placebo[16] and a high-nicotine cigarette (50% vs 23%, respectively; $p > 0.001$).[17] In 2001, Mittleman *et al.*[18] reported that the risk of myocardial infarction onset in marijuana smokers was 4.8 times greater than the baseline value (95% confidence interval, 2.4–9.5; $p < 0.001$) during the 60 min after marijuana use, then fell to a relative risk of 1.7 times greater than the baseline value (95% confidence interval, 0.6–5.1; $p = 0.34$) in the second hour, after which there was no apparent increased risk. Additionally, review articles refer to the first hour after cannabis smoking as the riskiest hour, with the risk falling rapidly thereafter.[19,20] Several authors have reported cases of CVD in proximity to cannabis use,[21–69] sometimes supported by a positive urinalysis, as reported

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in Table 1. However, a positive cannabis finding is common up to 5 days after smoking and, in heavy smokers, positivity may be present for weeks or months.[70–73] In fact THC absorption rate differs for occasional versus habitual consumers, thus potentially confounding interpretation in instances where the subject is a more frequent user. Karschner *et al.*[71] acknowledge trace plasma THC levels for upwards of 30 days. Odell *et al.*[72] identify more substantial quantities over a period of 7 days post abstinence. Thus, to attribute cannabis smoking as the proximate cause of CVD based on a positive urinary cannabis analysis result is not scientifically well founded. This is especially true in cases of death. Tormey[74] recently advised coroners not to attribute acute cardiac death to smoking cannabis without relevant Δ-9-tetrahydrocannabinol toxicological data. A case of death in which there was positive circumstantial data of marijuana smoking as well as autopsy evidence of acute myocardial infarction due to coronary thrombosis prompted us to explore the scientific relevance of post-mortem toxicological tests to establish a temporal relationship between marijuana smoking and CVD.

Materials and methods

Case report

A 50-year-old man was found unconscious in his car on his way to work one evening. Cardiac resuscitation was unsuccessfully performed on-site. The medical history of the deceased was negative for hypertension, obesity, diabetes, and heart disease. His wife declared that he had smoked a joint on the day of his death. She confirmed that he was a cigarette smoker (10 cigarettes per day) and occasional marijuana smoker, but that he did not use other illicit drugs.

Autopsy findings

An autopsy performed 24 h after death revealed a slightly enlarged heart (weight, 550 g; longitudinal and transversal diameters, 13 and 15 cm, respectively). Myocardial hyperemia was observed upon gross examination of the septum and posterior myocardial ventricle. Thrombosis of the right coronary artery 2 cm distal to its origin and moderate atherosclerosis of the other coronaries were documented. Diffuse aortic atheromatosis was also observed. Urine and heart whole blood were collected during autopsy and stored at –20°C. The right coronary was sectioned and stained with haematoxylin and eosin. No continuity was seen between the thrombus and the atheromatous component of the plaque, which was separated from the lumen by fibrous tissue and smooth cells; inflammatory cells were also present in the adventitia layer.

Toxicological analysis

Approximately 10 days after the autopsy, a complete toxicological analysis was performed on post-mortem urine and heart whole blood that had been collected during the autopsy and stored at –20°C until use.

THC-COOH, THC, cannabinol (CBN), cannabidiol, and trideuterated analogues of THC and THC-COOH (internal standards) were supplied by LGC Standards (Sesto San Giovanni, Italy). N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) containing 1% trimethylchlorosilane was obtained from Sigma-Aldrich (Milan, Italy). All of the other reagents and solvents were of analytical grade.

The toxicological analyses were performed according to the Systematic Toxicological Analysis guidelines of The International Association of Forensic Toxicologists (www.tiaft.org) while respecting the chain of custody. The blood and urine samples were also tested for THC and metabolites using a validated in-house method that detects THC, cannabidiol, CBN, THC-COOH, and THC-COOH-glucuronide. Briefly, tri-deuterated THC and THC-COOH internal standards were added to the samples to improve identification and quantification. Alkaline hydrolysis with sodium hydroxide was performed to break the bonds between THC-COOH and glucuronic acid. A liquid–liquid solvent extraction after acidification using maleic acid was performed followed by gas chromatography–mass spectrometry (GC-MS) detection of the dried extracts. A derivatization process was necessary to detect THC-COOH. The dry residue was derivatized with 25 μL of BSTFA, incubated for 30 min at 80°C, and then directly analyzed by GC-MS using a Focus gas chromatograph in combination with a mass spectrometer system DSQ (Thermo Electron Corp., Milan Italy) operating in the electron-impact mode at 70 eV. An HP-1 cross-linked methyl-silicone (0.33-μm film thickness) capillary column (12 m, 0.2 mm i.d.) was used for the chromatographic separation. The MS conditions were set in single-ion monitoring with the ions specified in Table 2 for cannabinoid detection. The limit of quantification was 1 ng/mL for THC and 5 ng/mL for THC-COOH with coefficients of variation across the analytical range of 4% to 12% and 5% to 15%, respectively.

Results

No volatile compounds were detected in the blood. General unknown analysis of the urine revealed nicotine and its main metabolite cotinine. Urine immunochemical screening was positive for cannabinoids. GC/MS analysis confirmed the presence of THC in the blood and urine at concentrations of 5 and 2 ng/mL, respectively. CBN was also qualitatively detected in both the blood and urine. THC-COOH was found in the blood at a concentration of 14 ng/mL as the free component and at 25 ng/mL as the total amount (free THC-COOH plus the glucuronide derivative). THC-COOH in the urine was present at a concentration of 35 ng/mL as the free component and at 69 ng/mL as the total amount.

Discussion

The association between adverse CVD and marijuana use is usually based on the temporal relationship between marijuana intake and the onset of cardiovascular adverse events. However, the proximity to marijuana use is rarely supported by an exhaustive toxicological investigation and, when such an investigation is performed, it is usually limited to a positive urinalysis that is not reliable for estimation of the time of last marijuana intake. In the present case, the autopsy showed a recent myocardial infarction due to coronary thrombosis in a cigarette and occasional marijuana smoker. This finding led us to investigate how post-mortem toxicological tests may support a temporal relationship between marijuana smoking and CVD.

Scientific evidence has already demonstrated the usefulness of the detection of THC, minor cannabinoids, and metabolites in the whole blood and urine to estimate the time of THC use in occasional users. However, some problems need to be addressed. The first issue is the reliability of predicting the last marijuana intake based on the conversion of post-mortem blood concentrations to ante-mortem plasma concentrations. With respect to post-mortem THC degradation and redistribution,[75,76] Gronewold and Skopp[77] found a post-mortem degradation rate of about 50% of THC in the

Table 1. Case reports about THC-related adverse cardiovascular events.

References	Sex	Age	Adverse Event	Onset	Risk Factors	Clinical Findings	Toxicological Findings	Death
Charles *et al.*, 1979[21]	M	25	MI	30 min	none	normal	n. r.	no
MacInnes and Miller, 1984[22]	M	32	MI	12 h	n. r.	RCA, LCA thrombosis	n. r.	yes
Collins *et al.*, 1985[23]	F	33	MI	0 min	Cigarette	normal	B 5.5 μg/L	no
Choi and Pearl, 1989[24]	M	17	MI	Few days	Cigarette	normal	U pos	no
Podczeck *et al.*, 1991[25]	M	20	MI	0 min	Cigarette /HTN	normal	n. r.	n.r.
Bachs and Mørland, 2001[26]	M	39	MI	n. r.	none	coronary sclerosis	B 22 μg/L; U pos.	yes
Bachs and Mørland, 2001[26]	M	40	MI	n. r.	none	coronary sclerosis	B 4 μg/L; U neg.	yes
Bachs and Mørland, 2001[26]	M	43	MI	n. r.	MI (previous)	coronary sclerosis	B 2 μg/L	yes
Bachs and Mørland, 2001[26]	M	37	MI	n. r.	none	coronary sclerosis	B 5 μg/L; U pos.	yes
McLeod *et al.*, 2002[27]	M	41	MI	12 h	Viagra	n. r.	n. r.	no
Caldicott *et al.*, 2005[28]	M	21	MI	6 h	overweight	LAD thrombosis	n. r.	no
Lindsay *et al.*, 2005[29]	M	22	MI	0 min	Cigarette	LAD thrombosis	U pos	no
Sürder *et al.*, 2006[30]	M	26	MI	1 day	Cigarette	LAD thrombosis	n. r.	no
Taher *et al.*, 2006[31] pos	M no	24	MI	n.r.	Inherited	thrombophilia	LAD thrombosis	U
Tatli *et al.*, 2007[32]	M	24	MI	2 h	Cigarette	LAD thrombosis	n. r.	no
Cappelli *et al.*, 2008[33]	M	30	MI	1 hr	Cigarette/ overweight	LAD thrombosis	n. r.	no
Montisci *et al.*, 2008[34]	M	31	MI	n. r.	none	LAD thrombosis	B e U pos (*)	yes
Dwivedi *et al.*, 2008[35]	M	23	MI	3 days	HTN/ alcohol	n. r.	n. r.	no
Dwivedi *et al.*, 2008[35]	M	50	MI	n. r.	Cigarette	n. r.	n. r.	no
Basnet *et al.*, 2009[36]	M	17	MI	1 day	n. r.	normal	n. r.	no
Kocabay *et al.*, 2009[37]	M	32	MI	3 days	Antipsych./ Cigarette	RCA thrombosis	n. r.	no
Bailly *et al.*, 2010[38]	F	36	MI	Few hours	n. r.	LAD thrombosis	n. r.	no
Karabulut and Cakmak, 2010[39]	M	35	MI	2 h	Cigarette	normal	n. r.	no
Leblanc *et al.*, 2011[40]	M	26	MI	n. r.	Cigarette	normal	U 167,7 μg/L	no
Canga *et al.*, 2011[41]	M	28	MI	2 h	Cigarette	LAD thrombosis	n. r.	no
De Silva and Perera, 2011[42]	M	51	MI	n. r.	Cigarette	LCA thrombosis	n.r.	no
Duchene *et al.*, 2011[43]	F	45	MI	min	None	coronary sclerosis	n. r.	n.r.
Dahdouh *et al.*, 2012[44]	M	20	MI	n. r.	Cigarette	LAD thrombosis	n. r.	yes
Tormey, 2012[45]	M	37	MI	min	Cigarette /DVT	LAD thrombosis	B neg, U pos	yes
Yurtdaş and Aydin, 2012[46]	M	26	MI	3 h	n. r.	RCA thrombosis	n. r.	no
Renard *et al.*, 2012[47]	M	33	MI	n. r.	n. r.	normal	U pos	no
Safaa *et al.*, 2012[48]	M	40	MI	1 h	Alcohol/ HTN	normal	n. r.	no
Arora *et al.*, 2012[49]	M	37	MI	0 min	Viagra, night shift worker, obesity	normal	U pos	no
Casier *et al.*, 2014[50]	M	23	MI	n.r.	(chronic cannabis abuse)	RCA, LAD thrombosis	U pos	no
Hodcroft *et al.*, 2014[51]	M	21	MI	n. r.	Cigarette	LAD thrombosis	n. r.	no
Gunawardena *et al.*, 2014[52]	M	29	MI	4 h	Cigarette/ LSD 2 days before	LAD slow flow	n.r.	no
Velibey *et al.*, 2015[53]	M	27	MI	n.r.	None	LCA thrombosis	n.r.	no
Akins and Awdeh, 1981[54]	M	21	AVB	1 day	None	n. r.	n. r.	no
Singh, 2000[55]	M	14	AF	1 h	None	n. r.	n. r.	no
Kosior *et al.*, 2001[56]	M	32	AF	min	None	n. r.	n. r.	no
Kosior *et al.*, 2001[56]	F	24	AF	min	None	n. r.	n. r.	no
Rezkalla *et al.*, 2003[57]	M	34	VT	3 h	Cigarette	n. r.	n. r.	no
Charbonney *et al.*, 2005[58]	F	22	AF	3 h	OCPs	n. r.	n. r.	no
Fisher *et al.*, 2005[59]	F	35	AT	30 min	Cigarette/ HTN	n. r.	U pos	no

(Continues)

Table 1. (Continued)

References	Sex	Age	Adverse Event	Onset	Risk Factors	Clinical Findings	Toxicological Findings	Death
Lehavi *et al.*, 2005[60]	M	20	AF	Few hours	None	n. r.	n. r.	no
Daccarett *et al.*, 2006[61]	M	19	Arrhythmia	2 min	None	ECG: Brugada-like	U pos; B pos	no
Sànchez Làzaro *et al.*, 2009[62]	M	29	VT	Few hours	Heart transplant, HTN	LAD lesions	U pos	no
Pratap and Korniyenko, 2012[63]	M	19	RBBB	1 h	None	n. r.	U pos	no
Romero-Puche *et al.*, 2012[64]	M	42	Arrhythmia	0 min	n.r.	EGC type I Brugada pattern	n.r.	no
Casier *et al.*, 2014[50]	M	28	VF	Few hours	Occasional cannabis smoker	LAD thrombosis	U pos	Yes
Bachs and Mørland, 2001[26]	M	17	CA	n. r.	Drug abuse	n. r.	B 3 μg/L	yes
Bachs and Mørland, 2001[26]	M	42	CA	n. r.	Drug abuse	coronary sclerosis	B 7 μg/L	yes
Lindsay *et al.*, 2005[29]	M	48	CA	0 min	CABG; angina	n. r.	n. r.	no
Sattout and Nicol, 2009[65]	M	15	CA	0 min	COC, MDMA	n. r.	B neg; U pos	no
Menahem, 2013[66]	M	21	CA	n.r.	Alcohol	Incomplete RBBB	n.r.	no
Casier *et al.*, 2014[50]	M	52	CA	2 h	Alcohol, cigarette, HTN, peripheral vascular disease	Coronary sclerosis	U pos	yes
Ting, 2007[67]	F	31	Cardiac dysfunction		Cigarette, previous drug abuse	LV dysfunction; EF 29%	U pos	no
Kotsalou *et al.*, 2007[68]	M	53	Angina	n. r.	MI (previous)	normal	n. r.	no
Ghannem *et al.*, 2013[69]	M	24	Angina	n. r.	Cigarette	LCA thrombosis	n.r.	no

n.r.= not reported; LCA= Left Coronary Artery; LV= left ventricle; EF= ejection fraction;. RCA= Right Coronary Artery; LAD= Left Anterior Descending; CABG= Coronary Artery Bypass Grafting;

MI= Myocardial Infarction; AVB= Atrio-Ventricular block; AF= Atrial Fibrillation; AT= Atrial Tachyarrhythmia; CA= Cardiac Arrest; RBBB= Right Bundle Branch Block; VF= Ventricular Fibrillation; VT= Ventricular Tachycardia; DVT= Deep Venous Thrombosis;

B= Whole Blood; U= Urine; HTN= High Blood Pressure;

COC = Cocaine; MDMA = Ecstasy; LSD = Lysergic acid; Antipsych.= Psychiatric Medication; OCPs= Oral Contraceptives.

(*) Whole Blood and Urine positive also for COC and benzodiazepines.

Table 2. Target ion and qualifiers of THC, minor cannabinoids and metabolites in the GC-MS analysis

Compound	Target ion (m/z)	Qualifiers (m/z)	
THC	299	231	314
THC-d3	302	234	317
CBD	231	246	314
CBN	295	296	310
THC-COOH	371	372	473
THC-COOH-d3	374	375	476

THC = Δ-9-tetrahydrocannabinol; THC-d3 = Δ-9-tetrahydrocannabinol-d3; THC-COOH = 11-nor-9-carboxy-Δ-9-THC; CBD = cannabidiol; CBN = cannabinol; THC-COOH-d3 = 11-nor-9-carboxy-Δ-9-THC-d3.

blood during the 2-day interval between death and sampling; they also observed *in vitro* degradation of the glucuronide form of THC-COOH during storage at –20°C. Holland *et al.*[78] found that the THC levels in the central blood were two-fold higher than those in the peripheral blood. Huestis *et al.*[79–82] proposed two mathematical models for converting post-mortem blood concentrations to ante-mortem plasma concentrations in intermittent cannabis consumers, Model I uses linear regression analysis of plasma THC concentrations and the elapsed time after marijuana smoking, whereas Model II is based on linear regression analysis of the plasma THC-COOH/THC concentration ratio versus the elapsed time after marijuana smoking. When applying these models to whole blood concentrations instead of plasma, one must remember that THC and THC-COOH concentrations in whole blood are lower than those in plasma because of restricted distribution of these analytes into erythrocytes.[81] Some authors have estimated the blood-to-plasma ratio at approximately 0.5 for living humans,[82,83] while others[84] have suggested that plasma levels can be calculated from whole blood concentrations by multiplying by 1.6. The possibility of applying the mathematical models directly to blood samples was introduced by Karschner *et al.*;[85] they suggested dividing the blood concentration by 0.5 and then inserting this value into the formula to estimate the time of the last marijuana use.

By applying the above-reported general evidence to our case, we found a higher THC concentration in the post-mortem blood (5 ng/mL) than that reported in the literature after THC abstinence, which is generally less than 2 ng/mL.[2] Furthermore, high blood

concentrations of both THC-COOH-glucuronide and the free form of THC-COOH were also detected despite post-mortem degradation.[77] These results indicate a short interval between THC smoking and death. In addition, CBN was detected in the blood, providing evidence of THC smoking less than 1 h before death.[84,86] We calculated that the THC concentration in the heart whole blood would correspond to approximately 8 to 10 ng/mL in plasma samples. We calculated an interval of approximately 1 h using Model I and an interval of 1 h 39 min using Model II.

Thus, in occasional marijuana consumers such as the man herein described, the cannabinoid concentration in post-mortem blood and the application of mathematical models can demonstrate that THC was taken within 2 h of the onset of cardiovascular symptoms, according to the circumstantial data. However, validation of post-mortem analysis to estimate the last intake in comparison to ante-mortem measurements would require further surveys considering that several authors have found that the models by Huestis *et al.*[81,82] are not appropriate for habitual users.[70,71]

How this temporal association is likely to support a relationship with an acute cardiovascular adverse effect is a more complicated issue considering that several mechanisms have been called into question to explain the increased risk of CVD related to marijuana use (increased HR, lability of blood pressure, increased cardiac workload and catecholamines, and procoagulative effects). Among these mechanisms is the reduced oxygen-carrying capacity of blood related to an increased carboxyhemoglobin level, which can also be caused by tobacco smoking. In the case herein reported, the general unknown analysis of the urine detected nicotine and its main metabolite cotinine. Thus, considering that combining tobacco with marijuana is a popular method of smoking in both North America and Europe,[87,88] it may be difficult to separate the specific cardiovascular effects of each substance; this was true in both our case and other similar cases. This corroborates the idea that in terms of a temporal association, post-mortem toxicological results cannot presently be considered conclusive to state that THC is an acute CVD trigger. Furthermore, the scientific literature reports mixed results in terms of the effects of marijuana smoking on platelet function. Levy *et al.*[89] noted that high concentrations of cannabinoids induced irreversible aggregation of human platelets, independent of an added inducer (adenosine diphosphate), most likely due to their lysis and the release of an endogenous inducer. In contrast, others maintained that high THC concentrations inhibit platelet aggregation by direct inhibition of an agonist that was not well described.[90] Deusch *et al.*[91] demonstrated the positivity of the surface of human platelets for both CB1 and CB2 receptors and that THC enhanced glycoprotein IIb-IIIa and P-selectin expression in a concentration-dependent manner *in vitro*, suggesting that human platelets are target cells of cannabinoids. Catani *et al.*[92] demonstrated the ability of endocannabinoids to modulate the activation and aggregation of human platelets by a CB1- and CB2-dependent mechanism and determined that CB1 and, to a lesser extent, CB2 are expressed by highly purified human platelets and are localized inside them. However, both Deusch *et al.*[91] and Catani *et al.*[92] cautioned against inferring any relevance regarding the procoagulatory effects of THC. Keown *et al.*[93] suggested that the effects on platelets are not mediated by CB1 or CB2 activation. They demonstrated that platelet aggregation mediated by endocannabinoid 2-AG is due to the activation of a cyclooxygenase pathway, leading to the formation of thromboxane A2. This effect was completely blocked by aspirin, but not by CB1 or CB2 antagonists. Dahdouh *et al.*[44] indicated that THC might induce an inflammatory response at the arterial walls, leading to endothelial erosion and subsequent thrombus formation. However, there is experimental evidence of a possible protective role of THC in the progression of human atherosclerosis.[94] In addition, preclinical models acknowledge that cannabinoids may be cardioprotective,[95] while a 2013 study[96] reported that habitual cannabis use among a cohort with established coronary disease was not associated with a statistically significant increased mortality risk. This would appear to cast doubt on its risk potential in healthy subjects. Moreover, tolerance is exhibited in more regular subjects in regard to the impact of cannabinoids on blood pressure and HR as indicated by the Federal Drug Administration warning labelling for synthetic oral THC/dronabinol (http://www.fda.gov/ohrms/dockets/dockets/05n0479/05N-0479-emc0004-04.pdf: MARINOL®).

In conclusion, post-mortem THC measurement can be used to estimate the time of last marijuana intake in intermittent consumers to avoid incomplete documentation, although further surveys are needed for a better comparison with ante-mortem analysis. Nevertheless, except in rare cases of a robust temporal relationship together with the exclusion of other causes of CVD, it must be emphasized that separation of the specific cardiovascular effects of each substance is difficult considering the frequent concomitance of other risk factors, such as tobacco smoking. To this regard, it would be interesting to perform a prospective epidemiological study taking into consideration the differences in the tar content, THC content, and effect of the inhalation mode in association with different cannabis preparations. Finally, we believe that our review of the literature and the findings in the present case report highlight the fact that an association between marijuana use and negative cardiovascular events is rarely supported by toxicological results. Thus, additional research is needed.

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