[Original article]

Is recent cannabis use associated with acute coronary syndromes? An illustrative case series

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Abstract Cannabis is a frequently used recreational drug that potentially imposes serious health problems.

We report three cases where recent and/or chronic use of marijuana led to severe cardiac dysfunction. All three patients collapsed at home and required cardiopulmonary resuscitation (CPR) with initial restoration of spontaneous circulation (ROSC).

The mechanism of the cardiovascular collapse was different in each case. The first case presented with asystole and was found to have diffuse coronary vasospasm on coronary angiography in the hours after acute cannabis abuse. In the second case, an acute anterior infarction with occlusion of both the right coronary artery (RCA) and the left anterior descendens (LAD) was observed in a young patient without known cardiovascular risks but with chronic cannabis abuse. The third case presented at home with ventricular fibrillation presumably caused by an acute coronary syndrome due to left anterior descending (LAD) artery occlusion. The hetero-anamnesis of the family reported that all three patients had recently used cannabis. Toxicological screening also showed no other substance abuse than cannabis.

Using these three cases, we would like to illustrate that the widespread use of cannabis is not as innocent as is believed. Cannabis use can lead to severe cardiovascular problems and sudden death, not only in people at increased cardiovascular risk, but also in young people without any medical history or risk factors.

Keywords *Cannabis – marijuana – cardiac arrhythmia – sudden death*

INTRODUCTION

Cannabis is one of the most popular illicit drugs worldwide. Seventy-eight million European people between 15 and 64 years of age, corresponding to 23.2% of this population, report having used cannabis at least once in their life[1]. In Belgium, the use of cannabis is also popular and, based on epidemiological data, 14.3% of the Belgian population aged between 15 and 64 years has been estimated to have used cannabis [1].

Despite the frequent use of cannabis in a large proportion of the population, the risks of cannabis use are not well known. Sporadic and chronic cannabis use is certainly associated with psychiatric disorders and respiratory effects. However, cardiovascular complications have also been suggested. Indeed, marijuana has been described as a trigger of cardiovascular events such as myocardial infarction and cardiac arrhythmias in a dose-dependent manner [2-4].

We report three illustrative cases of patients who suddenly collapsed at home and in whom recent and/or chronic cannabis use could be an important contributing factor to this acute coronary event.

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Received 18 October 2013; accepted for publication 18 November 2013.

CASE REPORT 1

A 52-year-old man with a history of alcohol and nicotine abuse, arterial hypertension and peripheral vascular disease collapsed at home. Upon arrival of the medical team, asystole was found. After twelve minutes of CPR, ROSC was achieved. Post resuscitation, the ECG revealed ST-segment elevation in the anterior and inferior region.

A coronary angiogram showed poor left ventricular function with hypo- to akinesia of the anterior, lateral and apical walls. Pronounced vasospasm, mainly of the LAD, was present. After intracoronary nitrates, substantial vasodilatation was obtained (figure 1A and B). Toxicological screening of the urine revealed cannabis. No other drugs, including cocaine, could be detected.

The patient was admitted to the intensive care unit (ICU): an intravenous vasodilator (isosorbide dinitrate) was started for the vasospasm, and an inotropic agent was added to maintain adequate systemic blood pressure. Troponin levels only rose 6.35 μg/L (ULN < 0.045 μg/L). Initially, the patient's haemodynamic status recovered. However, at the third day of admission, he developed sustained ventricular tachycardia from which he could not be resuscitated despite defibrillation, CPR and anti-arrhythmic drugs.

At autopsy only non-flow limiting coronary atherosclerosis was found. The family reconfirmed the recent and chronic cannabis use, including smoking a joint two hours before the collapse. A new coronary vasospasm was assumed as the most likely reason of the recurrent ventricular tachycardia.

CASE REPORT 2

A young man, age 23, without known medical history was transferred to our hospital after a short resuscitation at home. On ECG ST-segment elevation in the inferoposterior and anterolateral leads was seen (figure 2).

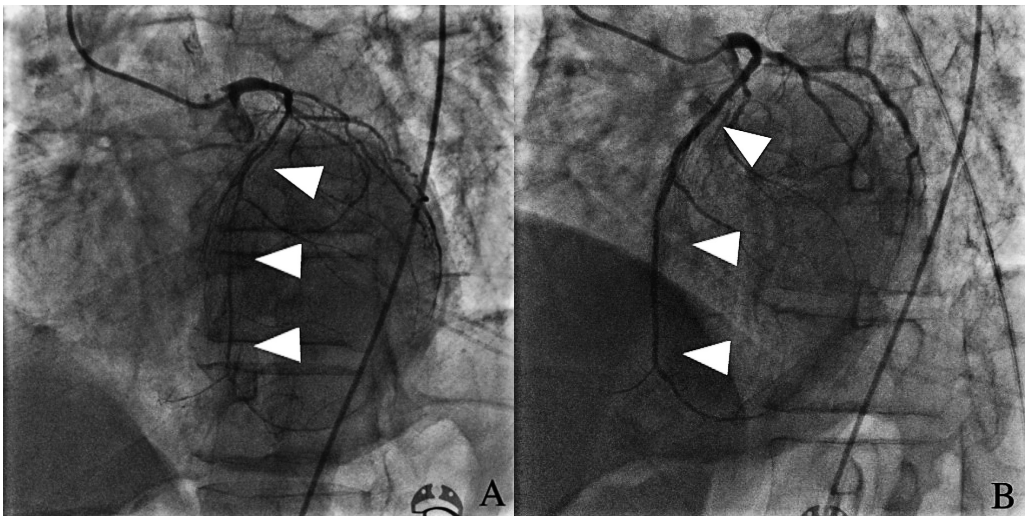

Fig. 1 Coronary angiography of case 1. A diffuse spasm, most notably in the LAD is present **(A)**. After intracoronary nitrates marked coronary vasodilatation is observed **(B)**.

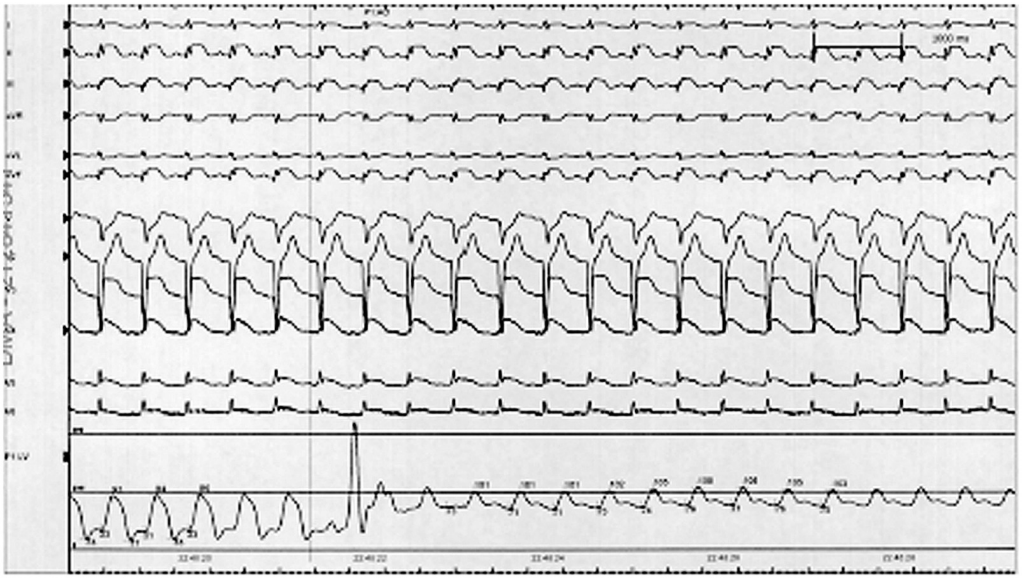

Fig. 2 The ECG in case 2 reveals an acute coronary syndrome with ST elevations.

A coronary angiogram showed a total occlusion of both the ostial LAD and the proximal RCA (figure 3A and C). Desobstruction was easy and both lesions were stented (figure 3B and D). Because of low ejection fraction (12%) and refractory cardiogenic shock, an intra-aortic balloon pump (IABP) was inserted. The patient was known to be a chronic cannabis user, and toxicological screening was also positive for cannabis. However, no other illicit drugs were detected. The troponin level peaked at 1,177 μg/L (ULN < 0.045 μg/L).

Despite mechanical and inotropic support, the patient remained in cardiogenic shock and the systolic function did not recover. The decision was made to place a biventricular assist device as a bridge to transplantation. Screening for early-onset atherosclerosis revealed no risk factors for atherosclerosis apart from smoking cannabis. Cholesterol, triglycerides and homocysteine levels were within normal range.

After 2 months, the patient left the intensive care unit. Three months later, the patient underwent uneventful cardiac transplantation.

CASE REPORT 3

A 28-year-old man collapsed at home the evening after a night of entertainment. He was athletic and had recently started exercising after a revalidation of 3 months for an arthroscopic hip operation. He smoked cannabis occasionally.

At the arrival of the medical intervention team, the first cardiac rhythm was ventricular fibrillation. After a long period of resuscitation, sinus rhythm was restored, albeit that low blood pressure persisted, for which continuous adrenaline was started.

The ECG showed an ST-elevated myocardial infarction (STEMI) of the anterior and lateral wall. Coronary angiography was performed and showed an occlusion at the ostium of the proximal LAD and at the ostium of the intermediary coronary artery. Additionally, a stenosis in the ostium of the proximal RCA was found. Thrombus aspiration was performed, and a bare metal stent was implanted in the LAD. The ejection fraction was measured at 26%.Toxicological screening was only positive for cannabis.

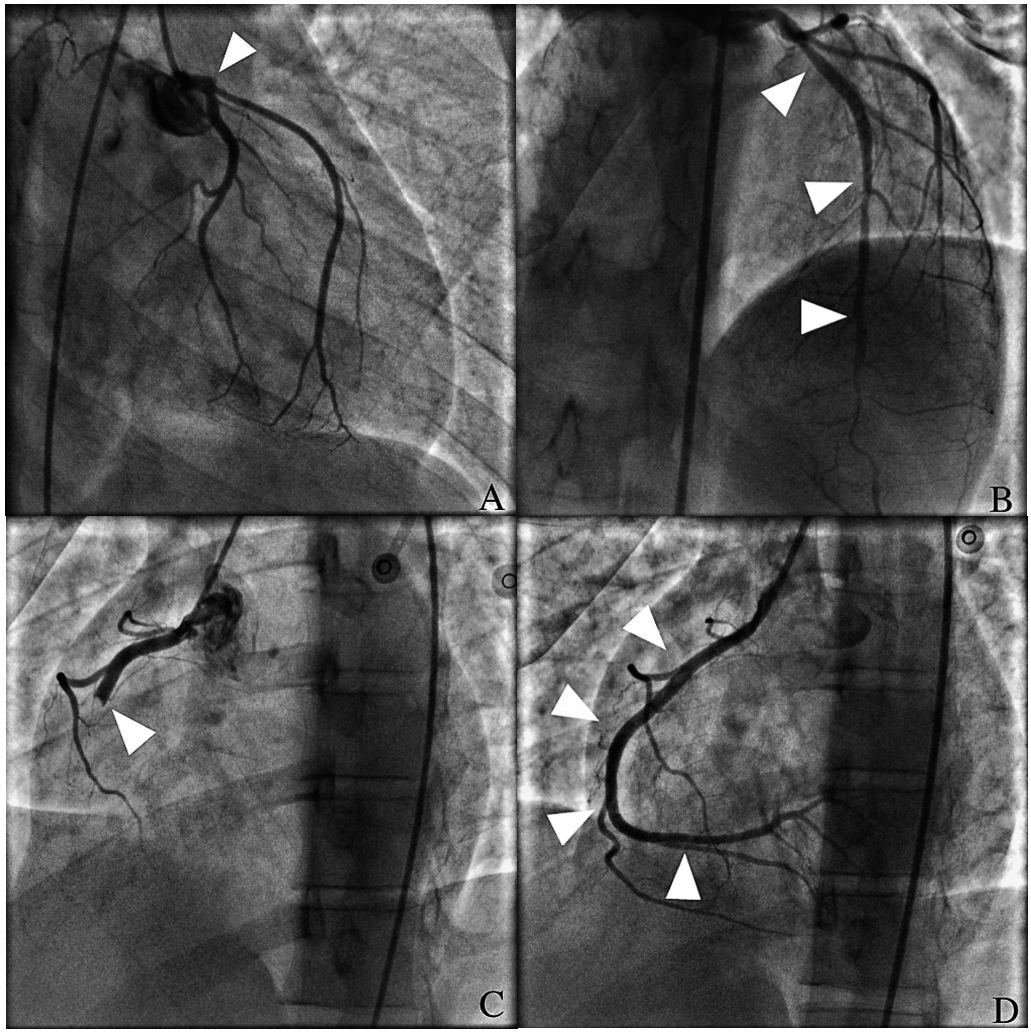

Fig. 3 Coronary angiography of case 2. A total occlusion of the ostial LAD **(A)** and the proximal RCA **(C)**. The lesions of the LAD **(B)** and the RCA **(D)** after desobstruction.

The patient was admitted to the intensive care unit requiring high doses of vasopressors and inotropic agents to achieve an acceptable blood pressure and cardiac output. An IABP was inserted. Troponin serum levels rose above 1,050 μg/L.

Because of worsening haemodynamics, an extracorporeal life support (ECLS) was implanted.

In this patient, screening for coronary risk factors revealed a mildly elevated level of homocysteine (36 μmol/L, ULN < 15 μmol/L), and triglycerides 173 mg/dl (ULN < 150 mg/dl). The high-density lipoprotein level (HDL-cholesterol) was very low (23 mg/dl; the normal value in the Belgian male population correlating with no cardiovascular risk must be above 40 mg/dl.)

After a few days, the patient developed multiple organ failure, which did not resolve despite maximal supportive therapy. After consulting the relatives of the patient, supportive therapy was discontinued and the patient died some hours later.

DISCUSSION

Cannabis is derived from the plant *Cannabis sativa*. Several preparations of this plant (e.g., marijuana, hashish and weed) are either smoked or ingested orally, or are occasionally taken intravenously[5].

Much of what is known about the physiologic effects of cannabis use comes from experiments using delta-tetrahydrocannabinol (THC), the major active cannabinoid in this illicit drug[2]. THC is a mixed agonist for two distinct types of G-protein-coupled receptors: cannabinoid 1 and 2 receptors (CB1 and CB2). CB1 receptors are most abundant in the central nervous system and, to a lesser extent, in some peripheral tissues, such as the heart, adrenal gland, adipose tissue, liver, lung and presynaptic nerve terminals. CB2 receptors are found primarily in the immune tissues[6].

Cannabis has multiple effects on the cardiovascular system.

Cannabis is associated with an acute and dose-dependent increase (20-100%) in the heart rate and blood pressure, particularly in the supine position[7]. These effects are believed to be mediated through sympathetic stimulation and reduced parasympathetic activity, with the maximal increase generally observed within 15 min after a peak THC plasma concentration and lasting for up to 3 h. This rise in norepinephrine increases the myocardial oxygen demand and reduced left ventricular ejection time, thereby lowering the threshold for angina. Moreover, peripheral vascular resistance in skeletal muscles is decreased[2,8].

At high doses, sympathetic activity is even inhibited, and parasympathetic activity is increased, leading to bradycardia and hypotension, particularly postural hypotension, associated with dizziness and syncope or near-syncope[3,9].

Tolerance to the haemodynamic effects of cannabis can occur with frequent use[10]. However, this finding is not universally true.

Cannabis also has the potential to induce cardiac arrhythmias. The user can experience palpitations most often due to dose-related sinus tachycardia. However, sinus bradycardia, atrial fibrillation, second-degree atrioventricular block, and ventricular tachycardia have been reported[11,12]. In our third case report, the initial rhythm was ventricular fibrillation, which has also been sporadically reported in other cases linked to cannabis use. In an autopsy study from Norway, Bachs et al.[13] found that THC was the only drug in post-mortem serum samples of six young adults with sudden death shortly after cannabis use. This observation was among the first to suggest that cannabis may be related to the incidence of ventricular tachy-arrhythmias in certain patients. A possible explanation for the onset of the ventricular arrhythmia is that cannabis may increase the activity in the Purkinje fibres, resulting in an arrhythmia[2].

Several case reports have associated cannabis use with kidney, brain, heart and digital infarctions[12]. The vasoconstrictor effect of THC was first described in the 1960s, and the term cannabis arteritis was used in descriptions of peripheral vascular consequences in high-dose cannabis users[14]. Subsequently, a few case reports of patients who developed subacute and progressive ischaemia of the distal upper and lower extremities, leading to tissue necrosis and gangrene, were reported. In some cases, arterial atherosclerotic lesions and venous thrombosis were observed, and others were diagnosed with Raynaud's phenomenon[2].

The vasoconstrictor effect of cannabis has also been postulated to be responsible for cerebral transient ischaemic events and stroke[11].

Our first case presented diffuse coronary vasospasm without any significant lesion. A few case reports of transient cardiac ischaemia secondary to vasospasm have been published[15,16]. Coronary vasospasm after illicit drug use is not unique for cannabis but has also and particularly been reported after the use of cocaine[17]. None of our patients tested positive for cocaine. Slow and no-reflow resulting in STEMI also have been related to cannabis use[18,19].

In our two other cases, myocardial infarction in young patients with a positive cannabis screening was due to total coronary occlusion.

The strongest evidence implicating cannabis as a trigger of myocardial infarction was reported from a large epidemiologic study by Mukamal et al.[20]. The authors found a statistically significant 4.8-fold increase

in the risk of myocardial infarction (95% confidence interval) in the first hour following cannabis use compared with periods of non-use, although less frequent than after the use of cocaine[21]. However, the relative risk in the second hour after use was only 1.7 (95% CI) and statistically non-significant. Therefore, the authors concluded that the elevated risk associated with smoking cannabis appears to be short-lived and vanishes quickly beyond the first hour[2]. We retained cannabis as a trigger for the coronary vasospasm. This was based on both the anamnesis of the family and the toxicological screening which both confirmed cannabis abuse in the hours preceding the angiographically proven vasospasm.

Another proposed mechanism for the triggering of myocardial infarction is that onset occurs when a vulnerable, but not necessarily flow-limiting atherosclerotic plaque is disrupted in response to haemodynamic stress. Thereafter, haemostatic and vasoconstrictive forces determine whether the resultant thrombus becomes occlusive[10]. In our third case, occlusion of the proximal LAD was found on coronary arteriography in a young athletic man with no known coronary risk factors. However, in the laboratory results, we found minimal elevated cholesterol levels, a very low HDL-cholesterol level and a mild elevation of homocysteine levels in the acute setting. Potentially, cannabis use may have triggered plaque rupture leading to thrombosis and total LAD occlusion. Similarly, in our second case both the ostial LAD and the proximal RCA showed an acute thrombogenic occlusion which could be easily wired and stented in a young patient without known coronary risk factors aside from cannabis use.

The effects of acute cannabis use on thrombus formation are thus far not completely elucidated[22]. Moreover, although it is well accepted that platelets synthesize endogenous cannabinoids, available data on the effects of THC on platelet function are presently controversial[7]. On the other hand, elevated concentrations of the endocannabinoid 2-arachidonglycerol levels have been associated with increased cholesterol levels[23], which may have played a role in our third case.

In addition to the haemodynamic effects, smoking cannabis is associated with an increase in carboxyhaemoglobin, higher blood levels of carboxyhaemoglobin than those associated with cigarette smoking, thereby further decreasing oxygen-carrying capacity. Thus, some cannabis-associated infarctions may be caused by insufficient myocardial oxygen supply in relation to the increased oxygen demands that occur as a result of smoking cannabis[10]. These effects can have a particular detrimental impact on patients with known coronary heart disease, in whom cannabis use decreases exercise time until the onset of angina by 50%. However, in all our cases the carboxyhaemoglobin levels measured at the emergency department were within normal values.

CONCLUSION

Our three cases illustrate the potential association between marijuana/cannabis use and acute coronary events, potentially leading to death. Despite the frequent use of cannabis in the young population, public awareness of the risk for potential cardiovascular complications of this drug use is low.

CONFLICTS OF INTEREST: none.

REFERENCES

1. Health Interview Survey Interactive Analysis: http//www.wiv-isp.be/epidemio/hisia
2. Aryana A, Williams MA. Marijuana as a trigger of cardiovascular events: speculation or scientific certainty? *Int J Cardiol* 2007; **118**: 141-4.
3. Jones RT. Cardiovascular system effects of marijuana. *J Clin Pharmacol* 2002; **42**: 58S-63S.
4. Sidney S. Cardiovascular consequences of marijuana use. *J Clin Pharmacol* 2002; **42**: 64S-70S.
5. Dwivedi S, Kumar V, Aggarwal A. Cannabis smoking and acute coronary syndrome: two illustrative cases. *Int J Cardiol* 2008; **128**: e54-7.
6. Yurtdas M, Aydin MK. Acute myocardial infarction in a young man; fatal blow of the marijuana: a case report. *Korean Circ J* 2012; **42**: 641-5.
7. Cappelli F, Lazzeri C, Gensini GF, Valente S. Cannabis: a trigger for acute myocardial infarction? A case report. *J Cardiovasc Med (Hagerstown)* 2008; **9**: 725-8.
8. Frost L, Mostofsky E, Rosenbloom JI, Mukamal KJ, Mittleman MA. Marijuana use and long-term mortality among survivors of acute myocardial infarction. *Am Heart J* 2013; **165**: 170-5.
9. Fisher BA, Ghuran A, Vadamalai V, Antonios TF. Cardiovascular complications induced by cannabis smoking: a case report and review of the literature. *Emerg Med J* 2005; **22**: 679-80.
10. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. *Circulation* 2001; **103**: 2805-9.
11. Mir A, Obafemi A, Young A, Kane C. Myocardial infarction associated with use of the synthetic cannabinoid K2. *Pediatrics* 2011; **128**: e1622-7.
12. Reece AS. Chronic toxicology of cannabis. *Clin Toxicol (Phila)* 2009; **47**: 517-24.
13. Bachs L, Morland H. Acute cardiovascular fatalities following cannabis use. *Forensic Sci Int* 2001; **124**: 200-3.
14. Nahas GG. Cannabis arteritis. *N Engl J Med* 1971; **284**: 113.
15. Charles R, Holt S, Kirkham N. Myocardial infarction and marijuana. *Clin Toxicol* 1979; **14**: 433-8.
16. Safaa AM, Markham R, Jayasinghe R. Marijuana-induced recurrent acute coronary syndrome with normal coronary angiograms. *Drug Alcohol Rev* 2012; **31**: 91-4.

17. Lenders GD, Jorens PG, De Meyer T, Vandendriessche T, Verbrugghe W, Vrints CJ. Coronary spasm after the topical use of cocaine in nasal surgery. *Am J Case Rep* 2013; **14**: 76-9.
18. Karabulut A, Cakmak M. ST segment elevation myocardial infarction due to slow coronary flow occurring after cannabis consumption. *Kardiol Pol* 2010; **68**: 1266-8.
19. Russmann S, Winkler A, Lovblad KO, Stanga Z, Bassetti C. Lethal ischemic stroke after cisplatin-based chemotherapy for testicular carcinoma and cannabis inhalation. *Eur Neurol* 2002; **48**: 178-80.
20. Mukamal KJ, Maclure M, Muller JE, Mittleman MA. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. *Am Heart J* 2008; **155**: 465-70.
21. Mittleman MA, Mintzer D, Maclure M, Tofler GH, Sherwood JB, Muller JE. Triggering of myocardial infarction by cocaine. *Circulation* 1999; **99**: 2737-41.
22. Heiden D, Rodvien R, Jones R, Mielke CH, Jr. Effect of oral delta-9-tetrahydrocannabinol on coagulation. *Thromb Res* 1980; **17**: 885-9.
23. Cote M, Matias I, Lemieux I, Petrosino S, Almeras N, Despres JP, Di Marzo V. Circulating endocannabinoid levels, abdominal adiposity and related cardiometabolic risk factors in obese men. *Int J Obes (Lond)* 2007; **31**: 692-9.