

CASE REPORT

Sudden unexpected death under acute influence of cannabis.

Benno Hartung¹, Silke Kauferstein², Stefanie Ritz-Timme¹, Thomas Daldrup¹

¹*Institute of Legal Medicine, University Hospital Duesseldorf, Moorenstr. 5, 40225 Duesseldorf, Germany*

²*Institute of Legal Medicine, University Hospital Frankfurt, Kennedyallee 104, 60596 Frankfurt, Germany*

Corresponding author

Benno Hartung

benno.hartung@med.uni-duesseldorf.de

Tel: 0049-211-8119362

Fax: 0049-211-8119366

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Abstract

The acute toxicity of cannabinoids is said to be low and there is little public awareness of the potentially hazardous cardiovascular effects of cannabis, e.g. marked increase in heart rate or supine blood pressure. We describe the cases of two young, putative healthy men who died unexpectedly under the acute influence of cannabinoids. To our knowledge, these are the first cases of suspected fatal cannabis intoxications where full postmortem investigations, including autopsy, toxicological, histological, immunohistochemical and genetical examinations, were carried out. The results of these examinations are presented. After exclusion of other causes of death we assume that the young men experienced fatal cardiovascular complications evoked by smoking cannabis.

Key words

Cannabis; Acute intoxication; Cardiovascular events; Hypertensive crisis.

Introduction

It is estimated that in 2009, between 125 and 203 million people of the world population aged 15-64 corresponding to between 2.8% and 4.5%) had consumed cannabis at least once in the past year¹. Herbal cannabis contains more than 60 cannabinoids, which are only found in the plant genus Cannabis. Δ 9-tetrahydrocannabinol (THC) is considered to be the most potent psychoactive agent². Cannabinoid-related psychological and physiological effects are well reported³⁻⁸. The acute toxicity of cannabinoids is said to be low³ and there is little public awareness of the potentially hazardous cardiovascular effects associated with the consumption of cannabis. Compared to high-nicotine cigarettes, cannabis is considered to induce significantly higher heart rates, cardiac output, blood pressure, and venous carboxy-hemoglobin levels, which significantly reduces exercise time until the onset of anginal symptoms⁹. Several, assumably cannabinoid-triggered arrhythmias and myocardial infarctions have been described¹⁰⁻¹⁸. However, none of these cases mentions blood levels of THC at the time of occurrence of the cardiovascular event. Fatal cannabis intoxications have been described as well^{19,20}; full post-mortem histopathological examinations were not carried out though. Post-mortem toxicological analyses revealed THC-levels in whole blood between

2 and 22 µg/l²⁰. A young soldier who had vainly tried to commit suicide by smoking cannabis spent 4 days in coma and claimed afterwards that others had used this method effectively before²¹. Naturally, diagnoses of death due to cannabis intoxication without autopsy, full histopathological examinations, serum markers of myocardial necrosis and genetic analyses is not assured according to actual standards^{22,23,24} and must leave questions unanswered.

We describe the cases of two young men who died unexpectedly under the acute influence of cannabinoids. To our knowledge, these are the first cases of fatal cannabis smoking where full postmortem investigations were carried out.

Case reports

Postmortem investigations (autopsy, toxicological, histological and immunohistochemical examinations) were performed according to medicolegal standards^{22,23,24}. For the toxicological analyses, a general unknown screening was performed using the immunoassays, GC/MS and HPLC-DAD. THC and its metabolites were determined by GC/MS using deuterated standards. This method was fully validated. Immunohistochemical reactions were performed with the antibody C5b-9 (monoclonal mouse anti-human, Abcam Inc., Cambridge, USA). A targeted mutational analysis of the major concerned ion-channel genes SCN5A (NC_008934), KCNH2 (NC_008916), KCNQ1 (NG_008935), and of the cardiac ryanodine receptor gene RyR2 (NG_008799) including 29 exons (3, 8, 10, 12, 14, 15, 37, 41, 44-47, 49, 50, 83, 88-90, 93-96, 97, 99-103, 105) was performed using polymerase chain reaction (PCR) with published^{25,26} and redesigned primers (primer sequences upon request). Genes with a rare frequency are not completely screened so far. Direct sequencing of the amplicons was performed as described previously²⁵.

Case 1

A 23-year-old male without known relevant illnesses suddenly collapsed while using public transport and died after 40 min of unsuccessful cardiopulmonary resuscitation with a clinical picture of ventricular fibrillation. A small amount of marijuana was found in his pockets.

Autopsy revealed a young man of slim build (BMI 21.3, 77.7 kg, >0.6 of the body weight). Macromorphological findings did not identify the cause of death. The interior organs were highly congested with blood. Beginning arteriosclerotic changes of the abdominal aorta and all three major coronary vessels were seen as well as a remarkable hypertrophy of the cardiac muscle (480 g). There was no significant thickening of the heart ventricles (right chamber: 3 mm, left chamber: 13 mm). The lungs exhibited oedema (right lung, 0.74 kg/ left lung, 0.72 kg).

Histopathological examinations showed different signs of a cardiac hypertrophy and a thrombus formation in a small cardiac vessel (Fig. 1). Immunohistochemical reaction of the cardiac muscle with C5b-9 antibody showed negative results. There were no signs of an infectious disease, however signs of hypertrophy (enlarged myocyte nuclei, interstitial fibrosis) could be revealed. Both lungs showed protein-rich oedema with several iron-negative macrophages, severe blood-congestion with microscopic bleedings and a cholesterol granuloma (Fig.2).

Toxicological examinations proved the acute influence of cannabis (femoral blood: THC 5.2 ng/ml, 11-OH-THC 1.8 ng/ml, THC-COOH 12.9 ng/ml; brain tissue: THC 13.4 ng/g, 11-OH-THC 7.0 ng/g, THC-COOH 4.3 ng/g). Screening tests for other common drugs showed negative results.

Postmortem genetic analysis of the most common genes, associated with potentially lethal channelopathies²⁷, such as long QT syndromes (LQTS; genes KCNQ1, KCNH2, SCN5A), the Brugada syndrome (BrS; gene SCN5A), or catecholaminergic polymorphic ventricular tachycardia (CPVT; gene RyR2) detected polymorphisms in relevant genes (KCNQ1, KCNH2, SCN5A, RyR2). These polymorphisms do not change the amino-acid formation of the genes.

As there is no known medical history and as both cardiac chambers showed normal thicknesses, we assume a dilatative cardiomyopathy as explanation for the hypertrophy of the cardiac muscle. We concluded that death occurred most possibly due to cardiac arrhythmia with cardiac hypertrophy and consecutive stasis-associated thrombus formation of a small cardiac vessel under the acute influence of cannabis.

Case 2

A 28-year-old male with a history of substance abuse (alcohol, amphetamines and cocaine until about 2 years before death; occasionally cannabis), but without known cardiovascular diseases was found dead at home by his girlfriend. Next to the body an ashtray, rolling paper and a sealable plastic bag containing remnants of marijuana were found.

The autopsy showed a young man of athletic build (BMI 25.5, 91 kg). No macromorphologically visible cause of death could be found. The interior organs were highly congested with remarkably fluid blood. Neither the cardiac muscle (430 g; <0.5 of the body weight) nor the great and coronary artery vessels revealed pathological findings. Both lungs exhibited oedema (right lung, 0.88 kg/ left lung, 0.77 kg). The urinary bladder contained 400 ml of urine.

Histopathological examinations of the heart showed several foci of single cell necrosis (Figure 3) and a negative immunohistochemical reaction with C5b-9 antibody. There were no

signs of an infectious disease. Furthermore, protein-rich oedema of the lungs with severe blood-congestion, microscopic bleedings and several iron-negative macrophages similar to Case 1 were seen.

Toxicological examinations proved the acute influence of cannabis (femoral blood: THC 1.9 ng/ml, 11-OH-THC 0.8 ng/ml, THC-COOH 10.1 ng/ml; brain tissue: THC 6.3 ng/g, 11-OH-THC 2.3 ng/g, THC-COOH 2.3 ng/g). General unknown screening for other common drugs was negative with the exception of nicotine and caffeine levels.

Chemical examinations showed an elevation of myoglobin (femoral blood: 5050 ng/ml, reference range < 90 ng/ml) and gave a normal result for troponin T (femoral blood: 13 ng/l, reference range < 14 ng/l).

Postmortem genetic analysis of the most common genes, associated with potentially lethal channelopathies²⁷, such as LQTS (genes KCNQ1, KCNH2, SCN5A), BrS (gene SCN5A), or CPVT (gene RyR2) detected polymorphisms in relevant genes (KCNQ1, KCNH2, SCN5A, RyR2). However, these polymorphisms do not change the amino-acid formation of the genes.

We concluded that death occurred due to acute global cardiac failure under the acute influence of cannabis.

Discussion

After exclusion of other causes of death we assume that the young men died from cardiovascular complications evoked by smoking cannabis. In Case 1 signs of an underlying dilatative cardiomyopathy were found which makes a sudden cardiac death highly probable²⁴. In Case 2 no distinct underlying cardiovascular diseases could be revealed which leaves space for interpretation; the elevation of myoglobin could be explained by long-lasting resuscitation efforts. Both men showed protein-rich pulmonary oedema and severe blood-congestion with microscopic bleedings. Numerous iron-negative macrophages were found. Microscopic bleedings in the lung tissue might be the result of drug-induced hypoxia²⁸. Alveolar macrophage exudation is considered to be a major pulmonary effect of smoking cannabis²⁹; cholesterol granulomas (as seen in Case 1, Fig. 2) surrounded by multinucleated giant cells could also be found in rats exposed to marijuana smoke³⁰.

The assumption of fatal heart failure in both cases is corroborated by the acute effects of marijuana, including a marked increase in heart rate that may result in cardiac ischemia in susceptible individuals, lesser increases in cardiac output, supine blood pressure and postural hypotension^{9,15}. We assume the deaths of these two young men occurred due to

arrhythmias evoked by smoking cannabis; however this assumption does not rule out the presence of predisposing cardiovascular factors.

The thrombus formation in a small cardiac vessel would (Case 1) fits to other described vascular complications of marijuana like venous thrombosis or Raynaud's phenomenon⁸. This could fit with the finding that cannabis induces ischemic ST-segment depression due to increased myocardial oxygen demand and decreased myocardial oxygen delivery at the onset of exercise-induced angina pectoris⁶.

One could also consider a significant but subclinical arterial hypertonia that might have been worsened by smoking cannabis⁹, potentially leading to a hypertensive crisis. However both cases do not show specific macromorphological signs and direction-giving medical findings (e.g. from general practitioners) do not exist.

The absolute risk of cannabis-related cardiovascular effects can be considered to be low, as the baseline risk for most cannabis smokers is low and cannabis-induced changes are transient^{8,18}. The risk of myocardial infarction is elevated almost 5-fold in the hour after smoking cannabis and declines rapidly afterwards¹⁴. Consequently, the relative risk for cardiovascular effects is most probably increased within this period. Persons who are at high risk for cardiovascular diseases are even recommended to avoid the use of cannabis¹⁵. The intravenous LD₅₀ for THC in rats is considered to be 28.6 mg (27.4 – 29.85 mg) per kilogram³¹, corresponding to an estimated intravenous lethal dose in humans of around 2000 mg in total or 30 mg per kilogram³. Nevertheless, it is impossible to predict how certain individuals respond to cannabis smoke, as underlying illnesses and complicating factors²⁰ may be unknown.

The presented cases highlight the potentially hazardous cardiovascular effects of cannabis in putative healthy young persons.

Figures

Figure 1 Part of a thrombus within a small artery located within the epicardial fat tissue (Elastica van Gieson staining, bar = 100 µm).

Figure 2 Granulomatous inflammation with acicular cholesterol-like spaces surrounded by multinucleated giant cells (H&E staining, bar = 200 µm).

Figure 3 Focus of single cell necrosis (H&E staining, bar = 200 μ m).

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Figure 1



Figure 2

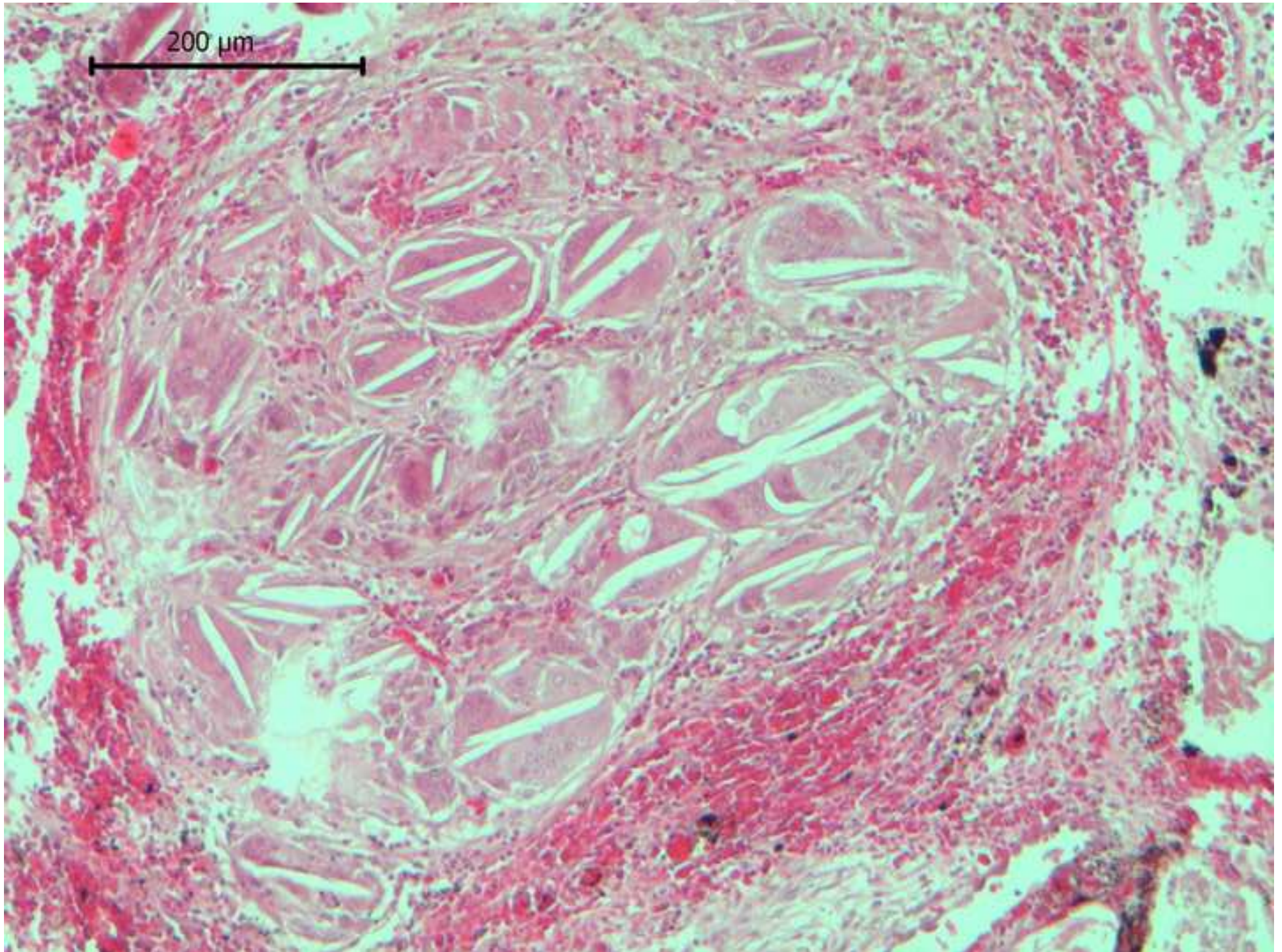


Figure 3

