

# Marihuana, Myocardial Infarction, Physicians and Public Policy

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## Abstract

The epidemiologic data that established the link between tobacco smoke and myocardial infarction unleashed a multipronged effort to dissuade cigarette smokers from tobacco usage, prevent individuals from starting smoking, governmental action to warn its citizens of the dangers and in some cases the initiation of law suits against tobacco manufactures for the health care costs that the State or Province had to assume. Physicians and Governments should assess the cardiovascular evidence and consider some similar approaches and programs for marihuana.

**Keywords:** Marihuana; Myocardial infarction; Physicians; Public policy

Marihuana is currently available by physician prescription and will soon be available for 'recreational' use in Canada and will be distributed under guidelines of Provincial governments [1]. In the US, marihuana is available in a few states and is being considered by others [2]. Other countries are no doubt watching these undertakings. The potential adverse effects of marihuana on neurocognitive function and development as well as its impact on traffic accidents are well recognized. The question arises whether physicians, public health authorities and Governments consider the risks of marihuana-induced myocardial infarction and provide cautions to its use, plan programs to alert the public to its dangers and have agreed to assume responsibility for myocardial infarction. To begin to answer these questions, the data that link marihuana (an extracted from the resin of *Cannabis sativa*) or cannabis to myocardial infarction requires examination.

Epidemiologic 'proof of causation' has relied on different kinds of evidence that have been instrumental in establishing the link between various risk factors and myocardial infarction. These include association, temporality of exposure, gradient of risk, biological plausibility and the effect of prevention/treatment interventions [3].

The data on the association between marihuana or other cannabis products and myocardial infarction includes a sufficiently large number of cases of myocardial infarction to suggest an association. Most of the reports are from young individuals who have a low probability of atherosclerotic coronary artery disease [4-29]. As myocardial infarction can be associated with fatal cardiac arrhythmias, the reports of sudden death after cannabis use [29-34] support the contention that cannabis consumption is associated with myocardial infarction. Some investigators have suggested that 'fatal falls from heights' attributed to suicide might be induced in part by cannabis use [35] that might be associated with cannabis-induced sudden cardiac death. The number of case reports declines once 'enough' have been published to confirm the association so that the number of case reports cannot be used to assess the magnitude of the problem.

Cannabis has been implicated in inducing myocardial infarction because the myocardial infarction often occurred in temporal proximity

to the use of marihuana. In addition, other causes of myocardial infarction were often excluded by the absence of significant coronary stenosis on coronary angiogram suggesting marihuana-induced coronary spasm or the presence of a coronary thrombus with minimal atherosclerosis suggesting marihuana-induced thrombosis.

The temporal relation of cannabis use and the development of myocardial infarction has been established. The risk of myocardial infarction is increased 4.8 times over baseline (95% confidence interval, 2.4 to 9.5) in the 60 minutes after marijuana use [36]. A gradient of risk was also reported for death after myocardial infarction with a hazard ratio of 2.5 for those using marihuana less than weekly to a hazard ratio of 4.5 for those who used it once or more per week [37]. Registry data suggest that patients with exposure to cocaine plus marihuana are more likely to have a ST elevation anterior wall myocardial infarction indicating a larger myocardial infarction than persons who have not consumed both of these drugs [38].

It is difficult to define the prevalence and incidence of cannabis-induced myocardial infarction in large part because cannabis has been illegal and acknowledgement of its use would be an admission of guilt that some individuals may not wish to report. There is likely a low marihuana usage rates in persons in the older age group. If marihuana usage in this age group increases with legalization, one should anticipate more cases of myocardial infarction because of the presence of clinical or subclinical coronary artery disease or the presence of multiple risk factors for coronary artery disease in older compared to younger individuals. The prevalence of cardiovascular events requiring hospitalization, of which myocardial infarction was the most common event, was estimated at approximately 2/1000 marihuana consumers in France [39]. It is reasonable to believe that the incidence of myocardial infarction is currently not high but it is also reasonable to believe that the prevalence of myocardial infarction will increase as marihuana consumption increases in the population once it has become legalized. The more widespread use of marihuana in older persons who have occult coronary artery disease or silent myocardial ischemia would be anticipated to increase risk of myocardial infarction.

The data on the long term effects or risks of marihuana on cardiovascular outcomes are controversial. This may be because cannabis consumption

may peak in youth and taper down over the years so that individuals may not consume the same amount of cannabis over the years making estimates of 'lifetime exposure difficult. In an early study of 1935 adults with myocardial infarction from 45 US hospitals, between 1989 and 1994, with a median follow-up of 3.8 years, marijuana consumption less than weekly was associated with a hazard ratio of 2.5 compared to non-users [37]. Higher consumption was associated with a hazard ratio of 4.5 for total mortality as well as cardiovascular mortality [37]. A second study of 3,886 individuals which included the initial cohort as well as another group of individuals with an 18 years follow-up and evaluated by the same group of investigators did not find a statistically significant association between marijuana use and mortality [40]. A study of lifetime marijuana exposure starting as a youth did not find an increased incidence of coronary artery events in middle age [41]. It would appear that the acute effects of marihuana are the ones linked to myocardial infarction. In studies examining the triggers for acute myocardial infarction, smoking of marijuana was the third most likely precipitating factor [42].

There is abundant data on the biologic plausibility of the association between marihuana or cannabis and myocardial infarction. Marihuana increases myocardial oxygen demand and appears to increase coronary thrombosis and may produce coronary spasm-induced reduction in coronary blood flow. Smoking one marihuana cigarette increased the resting product of systolic blood pressure times heart rate by 54%, increased the venous carboxy hemoglobin level, and decreased the exercise time until angina, in patients with angina pectoris [43]. Smoking one marihuana cigarette significantly decreased the exercise time until the onset of angina, more than smoking one high-nicotine cigarette [43,44]. Marihuana can increase blood coagulation in part through increased platelet aggregation [45,46], enhancing tissue factor expression in activated monocytes resulting in elevated pro-coagulant activity [47] or increase in Factor VII activity [48] although *in vitro* testing data is not strong [48] and some specific cannabinoids may inhibit platelet aggregation [49]. These data suggest an interaction between blood vessel wall and coagulation pathways to account for the presence of, at times, massive coronary artery thrombus formation in young persons with minimal or no coronary atherosclerosis.

A major problem in examining the link between marihuana and myocardial infarction is the multiple types of cannabinoids, although they act mainly on two types of cannabinoid receptors (CB1 and CB2) [50,51]. The complexity of cannabis chemistry is reflected by the currently known existence of over 550 different constituents and their potential interactions [52]. In addition, the complex nature of cannabis metabolism leads to several hundred secondary metabolites of *Cannabis sativa* [53]. Depending on the type of cannabis, there might be beneficial actions of some cannabinoids on the myocardium [54]. Whether this is operative in humans is not established. The other issue is that marihuana may contain mixtures of cannabinoids with different actions on the cardiovascular system [55]. Which ones are present and at what concentration may dictate the cardiovascular response.

### What is the physician responsibility?

In the area of cigarette consumption, guidelines have stated clearly that physicians have a "duty to ask each of their patients whether they smoke and to provide proper information and counseling based on that history" [56]. Physicians have been advised to communicate to "every smoking patient the medical risks associated with smoking and the reduction in risk associated with smoking cessation. Physicians should encourage abstinence and prescribe and follow-up on the use of specific smoking cessation programs and strategies such as self-help, behavioral, or pharmacologic approaches" [56]. If we extrapolate from those recommendations, then a physician should make cannabis consuming patients aware that there is a risk of acute myocardial infarction. The

physician should also alert patients with coronary artery disease and angina pectoris of the risks of exacerbating angina pectoris symptoms which may lead to myocardial ischemia through increasing myocardial oxygen demand and reduction in oxygen supply to the myocardium.

The issue is more complex when the physician is prescribing marihuana or cannabis products for what is presumed as a medical indication. Nevertheless the physician should discuss the benefits and risks of marihuana use. The issue becomes problematic when there are differences in legality regulating cannabis use between Federal and State laws. As George Annas has pointed out [2]; a physician prescribing or encouraging cannabis use, because of a possible medical benefit, may be contravening a Federal statute and risk the consequences of an action which violates Federal law [2].

### What about public policy

A government as it moves to introduce widespread access to marihuana should be considering package labelling warning of the possibility of acute myocardial infarction. It should further consider placing a warning on the use of marihuana for patients with coronary artery disease especially those with angina pectoris. Warnings for patients with multiple risk factors for coronary artery which would place them at risk of myocardial infarction when using marihuana or cannabis should be considered. Government agencies should use best scientific evidence about packaging to select plain unmarked packages except for warnings and content labels or better include pictorial warnings about the dangers of Cannabis use [57,58].

Importantly, the precise composition of cannabinoids in each package will be of considerable value for the scientific medical community investigating the composition of the preparation used by patients that develop myocardial infarction. This kind of labelling will require Governmental agencies to ensure the consistent production of products and ongoing analysis of each batch to define its chemical composition. This is not an inconsequential task considering the large number of cannabis substances [52]. If delivery of marihuana is to be within each State or Provincial mandate, then agreements on product purity and composition should be led by Federal regulation. Detailed information about the composition of marihuana being used will eventually permit clinicians and scientists to understand the relationship between cannabis and myocardial infarction and guide patients away from higher risk preparations.

There will be a need to fund research spanning the areas of improving basic science understanding of the effects of marihuana on the cardiovascular system, the social determinants leading to marihuana use and finding best practices to provide messages to prevent the adverse effects of marihuana consumption. The cardiovascular effects of marihuana should not be neglected in the focus on the neurocognitive and psychiatric effects of marihuana.

Dealing with the social determinants of health has made inroads into improving disease management. Recognizing the social determinants for marihuana consumption, both recreational [59] and for 'medical usage' [60], is a step to preventing adverse outcomes. Lower income areas appear to have higher marihuana consumption rates [59,60]. However if one 'drops the legal barriers' to usage, marijuana will become more widely used by all strata's of society and expose more people to the risks of myocardial infarction.

There is concern that marihuana legalization will lead to the "rise of Big Cannabis similar to Big Tobacco and Big Alcohol" with powerful multinational corporations spending large sums of money to encourage market expansion in order to increase revenue [61]. There is also concern that the potency of illicit cannabis plant material has been consistently increasing over time because the ratio of DELTA(9)-tetrahydrocannabinol

to cannabidiol has increased from 14 fold in 1995 to 80 fold in 2014; a change which increases the likelihood of addiction [62]. Analogous to the argument proposed for cigarettes that there should be differential taxes for differential risks i.e. placing higher taxes on products with higher nicotine content [63], Governments could levy taxes according to the concentration of certain cannabinoids or simply on the ratio of DELTA(9)-tetrahydrocannabinol to cannabidiol in order to reduce the adverse effects of marijuana consumption. This proposal would be consistent with the recommendations of translating scientific evidence into public policy [64].

Government policy makers need to learn from the efforts made to prevent the adverse consequences of cigarette smoking. Reducing tobacco consumption was not easy and required basic, behavioural and population research and changes in the 'system' of incentives and cultural norms that helped perpetuate smoking....." [65]. The question is whether governments, will learn the lessons from tobacco, even though they may benefit financially from the legalization of marijuana, and establish programs and develop 'systems' to deal with this addictive substance and avoid the adverse cardiovascular consequences of marijuana consumption. The annual tax revenue from legalization of marijuana in the State of Colorado, alone, are now approaching \$200 million [66]. A portion of this kind of tax revenue that a Government collects should be spent on reducing risk of harm to its citizens. Furthermore the efforts to limit consumption after it is legalized should not be a single year program but rather must be continuous and regularly updated with newer scientific/medical information on the risks or harms of cannabis while employing newer behavioural and population research methods to inform, educate and improve health behaviour practices of the public.

## References

- Hajizadeh M (2016) Legalizing and Regulating Marijuana in Canada: Review of Potential Economic, Social, and Health Impacts. *Int J Health Policy Manag* 5: 453–456.
- Annas GJ (2014) Medical marijuana, physicians, and state law. *N Engl J Med* 371: 983-985.
- Rabkin SW, Sackett DL (1982) Epidemiology of arterial thromboembolism. In Column S, Marker H (eds) *Textbook of Hemostasis and Thrombosis*. JB Lippincott Co. New York, United States 873–888.
- Charles R, Holt S, Kirkham N (1979) Myocardial infarction and marijuana. *Clin Toxicol* 14: 433-438.
- Hodcroft CJ, Rossiter MC, Buch AN (2014) Cannabis-associated myocardial infarction in a young man with normal coronary arteries. *J Emerg Med* 47: 277-281.
- Ayhan H, Aslan AN, Suygun H, Durmaz T (2014) Bonsai induced acute myocardial infarction. *Turk Kardiyol Dem Ars* 42: 560-563.
- Koklu E, Yuksel IO, Bayar N, Ureyen CM, Arslan S (2015) A new cause of silent myocardial infarction: Bonsai. *Anatol J Cardiol* 15: 69–70.
- Renard D, Taieb G, Gras-Combe G, Labauge P (2012) Cannabis-related myocardial infarction and cardioembolic stroke. *J Stroke Cerebrovasc Dis* 21: 82-83.
- Hirapara K, Aggarwal R (2015) Synthetic Cannabis and Myocardial Infarction: A Complication Less Known! *Synthetic Cannabis and Myocardial Infarction: A Complication Less Known! Psychosomatics* 56: 712-713.
- Coutselinis A, Michalodimitrakis M (1981) Myocardial infarction and marijuana. *Clinical toxicology* 18: 389–390.
- Kotsalou I, Georgoulas P, Karydas I, Fourlis S, Sioka C, et al. (2007) A rare case of myocardial infarction and ischemia in a cannabis-addicted patient. *Clin Nucl Med* 32: 130-131.
- Duchene C, Olindo S, Chausson N, Jeannin S, Cohen-Tenoudji P, et al. (2010) Cannabis-induced cerebral and myocardial infarction in a young woman. *Rev Neurol (Paris)* 166: 438-442.
- Karabulut A, Cakmak M (2010) ST segment elevation myocardial infarction due to slow coronary flow occurring after cannabis consumption. *Kardiol Pol* 68: 1266-1268.
- Inci S, Aksan, G, Dogan A (2015) Bonsai-induced Kounis Syndrome in a young male patient. *Anatol J Cardiol* 15: 952–953.
- Velibey Y, Sahin S, Tanik O, Keskin M, Bolca O, et al. (2015) Acute myocardial infarction due to marijuana smoking in a young man: guilty should not be underestimated. *Am J Emerg Med* 33: 1114.e1-1114.e3.
- Yilmaz S, Unal S, Kuyumcu MS, Balci KG, Balci MM (2015) Acute anterior myocardial infarction after "Bonzai" use. *Anatol J Cardiol* 15: 265–266.
- Rickner SS, Cao D, Kleinschmidt K, Fleming S (2017) A little "dab" will do ya' in: a case report of neuro-and cardiotoxicity following use of cannabis concentrates. *Clin Toxicol (Phila)* 55: 1011-1013.
- Shah M, Garg J, Patel B, Guthrie J, Freudenberger RS (2016) Can your heart handle the spice: A case of acute myocardial infarction and left ventricular apical thrombus. *Int J Cardiol* 215: 129-131.
- Surder D, Kucher N, Eberli FR, Roffi M (2006) Intracoronary thrombus in a 26-year-old man. *European Heart Journal* 27: 2631.
- Dahdouh Z, Roule V, Lognone T, Sabatier R, Grollier G (2012) Cannabis and coronary thrombosis: What is the role of platelets? *Platelets* 23: 243–245.
- Bailly C, Merceron O, Hammoudi N, Dorent R, Michel PL (2010) Cannabis induced acute coronary syndrome in a young female. *Int J Cardiol* 143: e4-e6.
- Lindsay AC, Foale RA, Warren O, Henry JA (2005) Cannabis as a precipitant of cardiovascular emergencies. *Int J Cardiol* 104: 230–232.
- Tatli E, Yilmaztepe M, Altun G, Altun A (2007) Cannabis-induced coronary artery thrombosis and acute anterior myocardial infarction in a young man. *Int J Cardiol* 120: 420–422.
- Cappelli F, Lazzeri C, Gensini GF, Valente S (2008) Cannabis: a trigger for acute myocardial infarction? A case report. *J Cardiovasc Med (Hagerstown)* 9: 725–728.
- Dwivedi S, Kumar V, Aggarwal A (2008) Cannabis smoking and acute coronary syndrome: two illustrative cases. *Int J Cardiol* 128: e54-e57.
- Kocabay G, Yildiz M, Duran NE, Ozkan M (2009) Acute inferior myocardial infarction due to cannabis smoking in a young man. *J Cardiovasc Med (Hagerstown)* 10: 669–670.
- Collins JS, Higginson JD, Boyle DM, Webb SW (1985) Myocardial infarction during marijuana smoking in a young female. *Eur Heart J* 6: 637–638.
- McLeod AL, McKenna CJ, Northridge DB (2002) Myocardial infarction following the combined recreational use of Viagra and cannabis. *Clin Cardiol* 25: 133–134.
- MacInnes DC, Miller KM (1984) Fatal coronary artery thrombosis associated with cannabis smoking. *J R Coll Gen Pract* 34: 575–576.
- Gupta BD, Jani CB, Shah PH (2001) Fatal "Bhang" poisoning. *Med Sci Law* 41: 349–352.
- Tormey WP (2012) Cannabis, possible cardiac deaths and the coroner in Ireland. *Ir J Med Sci* 181: 479-482.
- Montisci M, Thiene G, Ferrara SD, Basso C (2008) Cannabis and cocaine: a lethal cocktail triggering coronary sudden death. *Cardiovascular pathology* 17: 344-346.
- Ozen C, Sozen H (1969) The problem of marijuana in Turkey and the Oriental countries (a case of marijuana poisoning that caused death). *Tip Fakültesi Mecmuası* 32: 543-562.

34. Bachs L, Morland H (2001) Acute cardiovascular fatalities following cannabis use. *Forensic Sci Int* 124: 200-203.
35. Fanton L, Bevalot F, Schoendorff P, Lalliard S, Jdeed K, et al. (2007) Toxicologic aspects of deaths due to falls from height. *Am J Forensic Med Pathol* 28: 262-266.
36. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE (2001) Triggering myocardial infarction by marijuana. *Circulation* 103: 2805-2809.
37. Mukamal KJ, Maclure M, Muller JE, Mittleman MA (2008) An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. *Am Heart J* 155: 465-470.
38. Bartolucci J, Nazzari NC, Verdugo FJ, Prieto JC, Sepulveda P, et al. (2016) Characteristics, management, and outcomes of illicit drug consumers with acute myocardial infarction. *Rev Med Chil* 144: 39-46.
39. Jouanjus E, Leymarie F, Tubery M, Lapeyre-Mestre M (2011) Cannabis-related hospitalizations: unexpected serious events identified through hospital databases. *Br J Clin Pharmacol* 71: 758-765.
40. Frost L, Mostofsky E, Rosenbloom JI, Mukamal KJ, Mittleman MA (2013) Marijuana use and long-term mortality among survivors of acute myocardial infarction. *Am Heart J* 165: 170-175.
41. Reis JP, Auer R, Bancks MP, Goff DC, Lewis CE, et al. (2017) Cumulative Lifetime Marijuana Use and Incident Cardiovascular Disease in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Public Health* 107: 601-606.
42. Nawrot TS, Perez L, Kunzli N, Munters E, Nemery B (2011) Public health importance of triggers of myocardial infarction: a comparative risk assessment. *Lancet* 377: 732-740.
43. Aronow WS, Cassidy J (1974) Effect of marijuana and placebo-marijuana smoking on angina pectoris. *N Engl J Med* 291: 65-67.
44. Prakash R, Aronow WS, Warren M, Laverty W, Gottschalk LA (1975) Effects of marijuana and placebo marijuana smoking on hemodynamics in coronary disease. *Clinical pharmacology and therapeutics* 18: 90-95.
45. Vaziri ND, Thomas R, Sterling M, Seiff K, Pahl MV, et al. (1981) Toxicity with intravenous injection of crude marijuana extract. *Clin Toxicol* 18: 353-366.
46. Deusch E, Kress HG, Kraft B, Kozek-Langenecker SA (2004) The procoagulatory effects of delta-9-tetrahydrocannabinol in human platelets. *Anesth Analg* 99: 1127-1130.
47. Williams J, Klein T, Goldberger B, Sleasman J, Mackman N, et al. (2015)  $\Delta(9)$ -Tetrahydrocannabinol (THC) enhances lipopolysaccharide-stimulated tissue factor in human monocytes and monocyte-derived microvesicles. *J Inflamm (Lond)* 12: 39.
48. Heiden D, Rodvien R, Jones R, Mielke CHJ (1980) Effect of oral delta-9-tetrahydrocannabinol on coagulation. *Thromb Res* 17: 885-889.
49. De Angelis V, Koekman AC, Weeterings C, Roest M, de Groot PG, et al. (2014) Endocannabinoids control platelet activation and limit aggregate formation under flow. *PLoS one* 9: e108282.
50. Pertwee RG (2005) Pharmacological actions of cannabinoids. *Handb Exp Pharmacol*: 1-51.
51. Pertwee RG, Howlett AC, Abood ME, Alexander SPH, Di Marzo V, et al. (2010) International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2. *Pharmacol Rev* 62: 588-631.
52. ElSohly MA, Radwan MM, Gul W, Chandra S, Galal A (2017) Phytochemistry of Cannabis sativa L. *Prog Chem Org Nat Prod* 103: 1-36.
53. Appendino G, Chianese G, Tagliatalata-Scafati O (2011) Cannabinoids: occurrence and medicinal chemistry. *Curr Med Chem* 18: 1085-1099.
54. Durst R, Danenberg H, Gallily R, Mechoulam R, Meir K (2007) Cannabidiol, a nonpsychoactive Cannabis constituent, protects against myocardial ischemic reperfusion injury. *Am J Physiol Heart Circ Physiol* 293: H3602-H3607.
55. Jones RT (2002) Cardiovascular system effects of marijuana. *J Clin Pharmacol* 42: 58S-63S.
56. A Statement of the Joint Committee on Smoking and Health (1995) Smoking and Health: Physician Responsibility. *Chest* 108: 1118-1121.
57. Noar SM, Hall MG, Francis DB, Ribisl KM, Pepper JK, et al. (2015) Pictorial cigarette pack warnings: a meta-analysis of experimental studies. *Tob Control* 25: 341-354.
58. Hughes N, Arora M, Grills N (2016) Perceptions and impact of plain packaging of tobacco products in low and middle income countries, middle to upper income countries and low-income settings in high-income countries: a systematic review of the literature. *BMJ open* 6: e010391.
59. Galea S, Ahern J, Tracy M, Vlahov D (2007) Neighborhood income and income distribution and the use of cigarettes, alcohol, and marijuana. *Am J Prev Med* 32(6 Suppl): S195-202.
60. Reinerman C, Nunberg H, Lanthier F, Heddleston T (2011) Who are medical marijuana patients? Population characteristics from nine California assessment clinics. *Journal of Psychoactive Drugs* 43: 128-135.
61. Spithoff S, Emerson B, Spithoff A (2015) Cannabis legalization: adhering to public health best practice. *CMAJ* 187: 1211-1216.
62. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, et al. (2016) Changes in Cannabis Potency Over the Last 2 Decades (1995-2014): Analysis of Current Data in the United States. *Biol Psychiatry* 79: 613-619.
63. Chaloupka FJ, Sweaner D, Warner KE (2015) Differential Taxes for Differential Risks--Toward Reduced Harm from Nicotine-Yielding Products. *N Engl J Med* 373: 594-597.
64. Califf RM, Robb MA, Bindman AB, Briggs JP, Collins FS, et al. (2016) Transforming Evidence Generation to Support Health and Health Care Decisions. *N Engl J Med* 375: 2395-2400.
65. Wolf Dtkoff S, Grindle A (2017) Audacious Philanthropy. *Harvard Business Review* 1-7.
66. State of Colorado (2017) Marijuana Revenue. Colorado, USA.