Marijuana influence on cardiac modulation and heart rate: novel hypothesis and gaps in evidence.

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Over the last two decades, marijuana consumption for recreational purposes has become ~~more and more diffused~~increasingly common among young adults in the United States of America (USA) [1]. Moreover, legalization of medical and recreational use in different states of the USA and of recreational use in Canada and Uruguay favoured a novel attitude toward this drug so that ~~, on this path,~~ other countries ~~worldwide~~ are taking under consideration ~~legal~~ changes to cannabis legal status.

As a consequence, there has been a growth in the interest of the scientific community ~~put growing interest~~ in the ~~comprehension of the~~ harmful and potential ~~potential~~ beneficial effects of marijuana and its compounds, with greater ~~attention~~ emphasis on~~to~~ the cerebral and the cardiovascular systems (CVS).

Marijuana has been proven beneficial for several medical conditions, including pain, cachexia, epilepsy, multiple sclerosis spasticity, nausea and vomiting, and there is moderate evidence of its potential use for dystonia and glaucoma treatment [2, 3, 4, 5]~~–~~. In opposite, inconclusive and controversial results have been obtained regarding ~~as concerns~~ other pathologies such as anxiety, depression, Alzheimer disease, cancer and cardiovascular (CV) diseases [2, 3, 6]. For instance, a retrospective propensity-matched analysis of 161 000 patients ~~with heart failure~~ showed a reduced risk of death and shorter mean hospital stay in ~~patients used to consume~~ marijuana user hospitalized with acute heart failure ~~–~~in comparison with nonusers [6]. ~~As long~~ While~~as~~ interesting, these data, ~~likewise the majority part of evidence concerning cannabinoids,~~ are retrospective and observational and there is lack of randomized controlled ~~trials~~evidence, as it unfortunately common for the entire medical marijuana field. ~~confirming these findings.~~

In fact, marijuana effects on the CVS are not completely understood, also because~~in reason of~~ of the existing law restrictions that limit ~~limited the~~~~from~~ evaluation~~ing~~ of health implications of cannabis ~~consumption~~ through prospective studies, as underlined by a recently published scientific statement

from the American Heart Association (AHA) ~~recently published online ahead of print on Circulation~~ [7]. This document clarifies that, at the state of the art, available evidence does not support a link between cannabis use and cardiovascular health, and ~~the~~ that ~~potential~~ risks outweigh any potential benefits, with a high potential for abuse and an unacceptable safety profile.

~~The~~ In general, the wide ~~variety~~ spectrum of cannabis CV side effects is explained by the complexity of the endogenous endocannabinoid system (ECS) and by the different mechanisms of action of its compounds [8]. The ECS is composed by two natural cannabinoids (anandamide and 2-arachidonoylglycerol) and two G protein coupled receptors (CB_1R and CB_2R) [9]. In the CV system~~S~~ these receptors are expressed by myocardiocytes, vascular endothelial and smooth muscle cells and circulating blood cells. Moreover, CB_1R has also been detected in ~~neurons of~~ the central and autonomic nervous system, with a potential influence on neurogenic CV modulation [10]. CB_1R activation may lead to vasodilatation/constriction, hypotension, increase or decrease in heart rate while CB_2R stimulation ~~-~~attenuates endothelial activation, chemotaxis, adhesion, transmigration of inflammatory cells [10, 11]. Therefore, cannabis CV effects are strictly ~~tightly~~ dependent on the agonist/antagonist action of its compounds at the receptor level.

Cannabidiol (CBD) and the tetrahydrocannabinolic acid, ~~hepatically~~ decarboxylated in the liver to tetrahydrocannabinol (THC), are the most extensively studied cannabinoids. THC ~~-~~is a partial agonist with equal affinity for both CB receptors, while CBD acts as a CB_1R modulator without binding either to CB_1R or CB_2R [7]. As a consequence, THC has psychotropic effects and stimulates the sympathetic nervous system determining an increase in heart rate, myocardial oxygen demand, platelet activation and systolic blood pressure, being also associated with endothelial dysfunction and oxidative stress [10]. On the other hand, CBD is not a ~~a no~~ psychoactive compound and may reduce heart rate and blood pressure, improves vasodilation in models of endothelial dysfunction, and reduces inflammation and vascular hyperpermeability in diabetic models [12].

Obviously, marijuana pharmacokinetics is also influenced by the route of administration and users ~~physical~~ characteristics [7].

Known acute CV risks ~~side effects~~ of marijuana consumption are coronary artery thrombosis and myocardial infarction, atrial fibrillation, ventricular arrhythmias, stroke, complete atrioventricular block, cardiomyopathies, heart failure, stroke, vasospasm, vascular inflammation, or artery dissection, arrhythmias and sudden death [10].

~~Nonetheless~~However, great part of the evidence comes from the evaluation of patients acceding to the hospital after recent marijuana use, with limited data on chronic effects.

The novelty of the study by Keen et al. [13] is that the investigators decided to examine cannabis influence on cardiac modulation, and not to focus only on CV events ~~as the majority part of previous studies~~.

In this cross-se~~l~~ectional study 93 African American/Black college students, with a mean age of 20 years,~~.03 (SD = 2.21)~~ were recruited ~~with the purpose~~ to compare heart rate differences between three different marijuana use groups (never used=63; recent use [in the past 24 hours; subacute] = 13; in the past 7 days, but not in the past 24 hours = 17). Heart rate is an easily detectable parameter with the important characteristic to be both a reliable marker of sympathetic activity and a predictor of cardiac health. A racial videotape was shown to the participants and heart rate was registered over three minutes. ~~The expected result was to detect higher heart rate in the subacute use group compared to the others.~~ Surprisingly, the subacute use group ~~showed~~ demonstrated lowerr ~~values of~~ heart rate~~, and statistical significance~~ persisting~~ed~~ also at the ~~covariance~~ after ~~analysis~~ adjustment~~ed~~ for age, sex, blood pressure, and body mass index.

As honestly discussed by the authors, this study has ~~present~~ several limitations. First of all, marijuana consumption was self-reported by the participants, ~~and, consequently, route of administration, quantity and THC and CBD levels were not reported~~with no quantitative data. Moreover, confounding factors as cigarettes smoking, physical activity and consumption of other sympaticomimetics substances were not registered. Finally, study population included only African American/Black college students, thus ~~meaning that this results may not~~limiting ~~be~~ applicability~~ed~~

to people of other ethnicity, even in consideration of the genetic differences ~~founded~~ present in the ECS [14].

Nonetheless, the scientific value of this study is that it examines marijuana effects on cardiac modulation, ~~which is still~~ an almost unexplored field.

The unexpected finding of lower heart rate in the subacute use group may endorse the ~~novel~~ theory that, ~~-~~shortly ~~few hours~~ after cannabis consumption, a compensatory process may take place leading to opposite sympathetic/patasympathetic responses ~~opposite~~ in comparison with those usually observed in the acute phase~~within the first hour~~. ~~As long as~~While insufficient to confirm this hypothesis, the study by Keen et al. may represent a starting point for more focused and organized studies ~~that could provide further evidence as regards~~on the harmful/beneficial CV effects of cannabis, a matter that deserves an effort ~~by the scientific community~~ to be clarified in reason of the recent huge i~~i~~ncrease in cannabis recreational and medical use ~~and the current legal issues relied~~.

References

1. Substance Abuse and Mental Health Services Administration. The National Survey on Drug Use and Health. 2018. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/Assistant-Secretary-nsduh2018_presentation.pdf. Accessed December 20, 2019.
2. Health Canada. Information for health care professionals: cannabis (marihuana, marijuana) and the cannabinoids. 2018. https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/information-medicalpractitioners/information-health-care-professionals-cannabis-cannabinoids.html. Accessed December 20, 2019.
3. National Academies of Sciences, Engineering, and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations For Research. Washington, DC: National Academies Press; 2017.

4. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014;370:2219–27.
5. Whiting PF, Wolff RF, Deshpande S et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA.* 2015;313(24):2456-73.
6. Wu L, Narasimhan B, Ho KS, Li P. Marijuana use is associated with better hospital outcome in patients with acute heart failure: a propensity match analysis from National Inpatient Database. *J Card Fail.* 2019;25:S158.
7. Page RL 2nd, Allen LA, Kloner RA et al.; American Heart Association Clinical Pharmacology Committee and Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Lifestyle and Cardiometabolic Health; and Council on Quality of Care and Outcomes Research. Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement From the American Heart Association. *Circulation.* 2020 Aug 5:CIR0000000000000883. doi: 10.1161/CIR.0000000000000883. Online ahead of print.
8. Eid BG . Cannabinoids for Treating Cardiovascular Disorders: Putting Together a Complex Puzzle. *J Microsc Ultrastruct.* 2018;6(4):171-6.
9. Mendiguren A, Aostri E, Pineda J. Regulation of noradrenergic and serotonergic systems by cannabinoids: relevance to cannabinoid-induced effects. *Life Sci.* 2018;192:115-27.
10. 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(3):151-66.
11. Fulmer ML, Thewke DP. The Endocannabinoid System and Heart Disease: The Role of Cannabinoid Receptor Type 2. Cardiovasc Hematol Disord Drug Targets. 2018;18(1):34-51.

12. Rajesh, M. et al. Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. *J. Am. Coll. Cardiol.* 2010; 56:2115–25.
13. Keen L, Abbate A, Clark V et al. Differences in Heart Rate Among Recent Marijuana Use Group. *Minerva Cardioangiol.* 2020. In press.
14. Vasileiou I, Fotopoulou G, Matzourani M, Patsouris E, Theocharis S. Evidence for the involvement of cannabinoid receptors' polymorphisms in the pathophysiology of human diseases. *Expert Opin Ther Targets.* 2013;17(4):363-77.