

Marijuana and Microcirculation: A Review

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Abstract Marijuana is the most widely used recreational drug across the United States. Ongoing efforts to legalize marijuana, as well as the drug's increasing popularity contribute to the marijuana's reputation as having a low risk profile. Marijuana's association with adverse cardiovascular events, such as arrhythmia and vasospasm is well-documented. We synthesized what is known about how marijuana use pertains to and is implicated endothelial cell damage and its effects on microcirculation. THC exerts effects through the cannabinoid receptors, CB1 and CB2. The downstream effects of CB1 activation point to a role for this receptor in atherogenesis and vasospasm, likely by precipitating oxidative stress. Endothelial cells, when exposed to reactive oxygen species, provide a stimulus for vasoconstriction with a diminished ability for vasodilation. This phenomenon has manifested itself in cases of coronary vasospastic angina, and coronary slow and no flow that have resulted from marijuana use, as confirmed by cardiac catheterization reports that showed no evidence of obstructive lesions that could otherwise be responsible for the patients' symptoms. Marijuana users suffer from acute ischemic stroke at higher rates than non-users. Several theories have been proposed to support this observation, namely marijuana induced reversible cerebral vasoconstriction syndrome, and mitochondrial damage caused by oxidative stress that disproportionately affects cerebral vasculature. As marijuana use continues to grow, so does the importance of elucidating the drug's effect on endothelial cells and microcirculation. Further studies should investigate the temporal association between marijuana and endothelial damage, as well as the possibility of recovery from such injury, and whether there is therapeutic potential in cannabinoid receptors.

Keywords: *marijuana, microcirculation, endothelium, myocardial infarction, stroke, coronary vasospasm*

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1. Introduction

Though recently legalized in several states, and slated for legalization in a handful of others, marijuana remains the most commonly used recreational drug in the United States. "Vaping" is a household term, as stories of its pitfalls have been covered widely in both medical communities and mainstream media. As the list of indications for medical marijuana grows, national use continues to increase. The widespread use of marijuana has contributed to its perception as a drug with a low-risk profile - public support has reached a peak, with over half of US citizens in favor of legalization [1].

Cannabidiol (CBD) is responsible for marijuana's properties as an anticonvulsant, anxiolytic, antipsychotic, and antioxidant [2]. Tetrahydrocannabinol (THC) modulates the drug's psychoactive element. The effect of marijuana on various cardiac parameters is well-documented in a number of review articles and case reports, which describe phenomena from marijuana induced vasospasm, to

arrhythmia, the most commonly occurring abnormal rhythms being atrial fibrillation and ventricular fibrillation [3,31,32]. A database study that was conducted using the National Health and Nutrition Examination Survey estimates that 2.3% of the 89.6 million adults who admitted to marijuana use suffer from concomitant cardiovascular disease (CVD), representing a population of approximately 2 million adults [3].

In the acute setting, marijuana use is associated with an increase in sympathetic activation, and subsequently, an increase in heart rate and systolic blood pressure [4]. Evidence suggests that marijuana increases the risk of acute myocardial infarction and ischemic stroke, even in young and otherwise healthy users, in the acute setting [5]. See Figure 1. Previous studies implicate the cannabinoid receptors in a number of pathologic processes, such as endothelial dysfunction and atherogenesis that could put marijuana users at risk for the development of cardiovascular disease, or cause progression of existing CVD [5]. Here, we describe what is currently known about marijuana as it relates to endothelial dysfunction and the drug's effect on microcirculation.

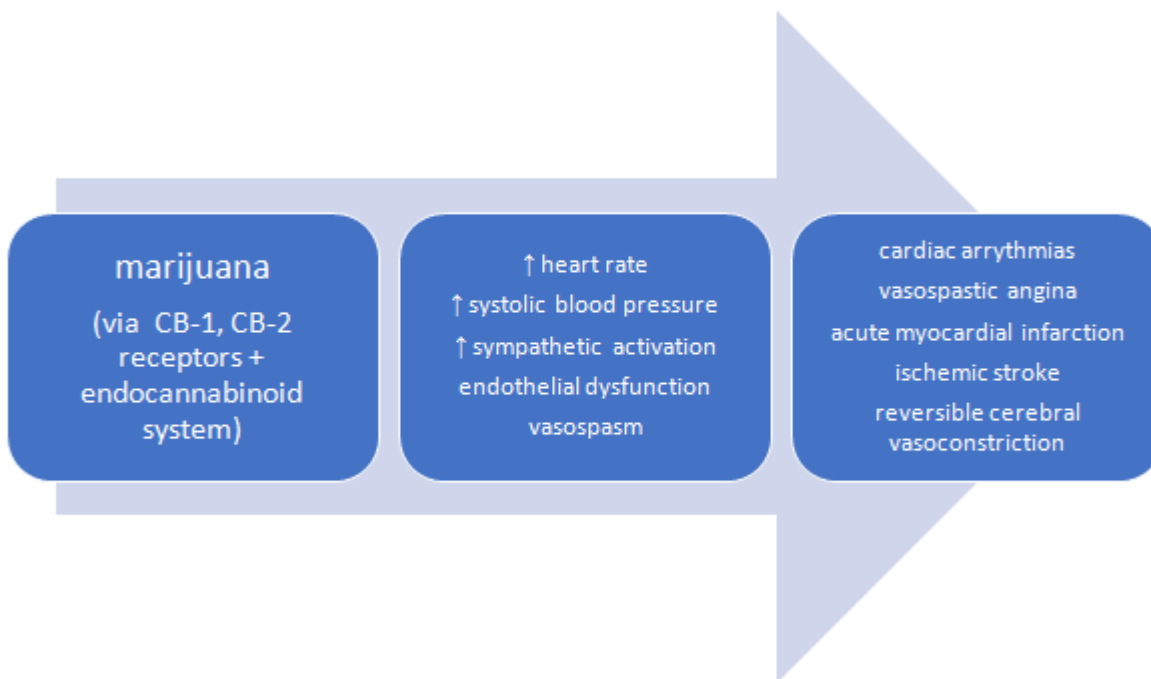


Figure 1. Marijuana effects on the cardiovascular system (CB1 cannabinoid receptor 1, CB2 cannabinoid receptor 2)

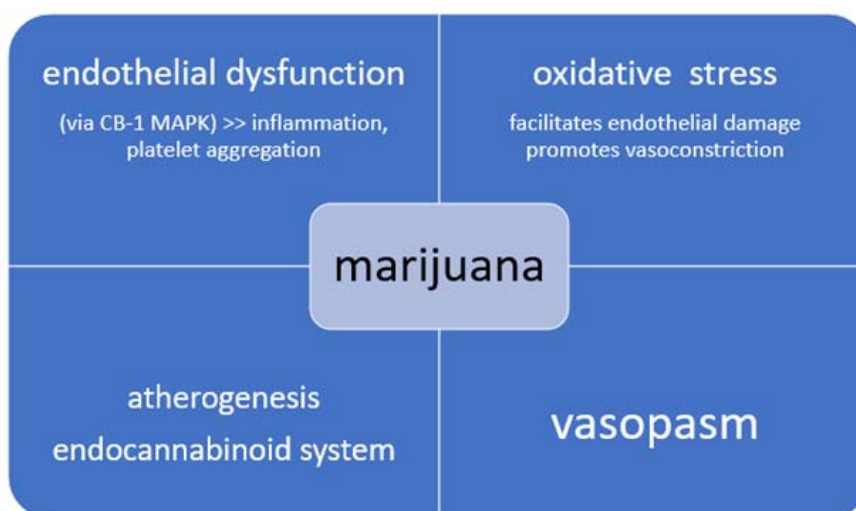


Figure 2. Proposed pathophysiologic mechanisms for marijuana cardiovascular effects

2. Pathophysiology

THC is the active ingredient in marijuana, responsible for producing the cognitive and neurologic effects that drive its use. The physiologic effects of marijuana are modulated through two receptors that are activated by THC - cannabinoid receptor type 1 (CB-1) and cannabinoid receptor type 2 (CB-2) [5] (Figure 2).

CB-1 is the predominant receptor type in the brain, though it is also expressed at a much lower concentration in the peripheral nervous system, heart, lung, thymus, spleen, and reproductive organs. CB2R is predominantly expressed in the immune system mediating the immunosuppressive effects of THC [6]. Expression of CB2R by non-immunogenic cells is generally low, however, it has been observed in cardiomyocytes, fibroblasts, endothelial cells, and vascular smooth muscle cells [7].

The endocannabinoid system (ECS), which has been implicated in a variety of physiologic processes, consists of the CB receptors as well as endogenous compounds that activate these receptors by mimicking THC-anandamide and 2-AG [5]. Its presence in heart tissue suggests involvement in regulation of blood pressure and heart rate. Previous studies also elucidate a role for CB receptors in atherogenesis, pointing to CB receptor activity as a modifier in the development and progression of atherosclerosis [8].

3. Endothelial Dysfunction

Evidence suggests that even fleeting exposure to marijuana smoke is sufficient to induce endothelial damage. One study exposed rats to marijuana second-hand smoke calibrated to levels meant to replicate second-hand smoke tobacco conditions [9]. Researchers monitored

endothelial function before and after exposure by looking at femoral artery flow-mediated dilation (FMD). FMD permits evaluation of how well arteries can vasodilate in the presence of increased blood flow - poorly responsive arteries predate atherosclerosis and have been implicated in its pathogenesis [10]. They discovered that just one minute of exposure to second hand smoke produced comparable results in terms of FMD for the marijuana and tobacco groups, with impairment of FMD for 90 minutes afterward in the marijuana group - a markedly slower recovery than the tobacco exposed rats, which achieved pre-exposure FMD at 30 minutes. The impairment persisted with marijuana smoke, even in the absence of cannabinoids and rolling papers [9].

With the increasing popularity of “vaping” - using devices that aerosolize marijuana leaf vapor, a small study conducted in rats sought to examine the difference in endothelial function upon exposure to aerosol versus marijuana smoke. Researchers discovered that marijuana leaf aerosol substantially impaired endothelial function to a level comparable to marijuana smoke, controlling for differences in cannabinoid temperature or level of concentration [11]. Their results suggest vaporized marijuana smoke carries similar risks compared to conventional smoking - endothelial damage would therefore be an intrinsic property to marijuana, rather than a consequence of how it is ingested [11]. This contradicts popular perceptions that “vaping” is a cleaner, healthier, or less risky method of using marijuana.

The mechanism by which marijuana smoke actually induces endothelial damage is poorly understood - though there are several working hypotheses. One theory postulates that marijuana precipitates oxidative stress, which contributes to subsequent vasculotoxic effects and platelet aggregation [3]. CB-1 has a well-documented inflammatory role, and its expression on endothelial cells has been confirmed by western blot and flow cytometry [5]. When activated, CB-1 signaling enhances the reactive oxygen species (ROS) mitogen-activated protein kinases (MAPK) [12]. This cascade results in oxidative stress and inflammation, leading to endothelial cell damage - a phenomenon which has been known to occur in human coronary artery endothelial cells [5,8].

4. Cannabinoid Receptors and Atherogenesis

The behavior of endocannabinoids, and therefore, increased CB receptor tone, in the process of atherogenesis offers additional insight about the relationship between marijuana and microcirculation. CB-1 is present in peripheral tissues - the result of activation in areas other than the brain leads to higher circulating levels of inflammatory cytokines, which can incite endothelial damage, an important step in the development of atherosclerosis [8]. Apo-E null mice, when given Rimonabant, a CB-1 antagonist, had lower levels of inflammatory cytokines and oxidative stress, and subsequently showed superior endothelial function and a lower incidence of atherosclerotic plaques [13].

One of the endogenous cannabinoids capable of activating CB-1 receptors is 2-AG, which has been

implicated as a pro-atherosclerotic mediator, suggesting that higher CB-1 tone is a driver of atherogenesis [8]. A positive correlation has been reported between 2-AG levels and markers of increased cardiovascular risk - low HDL, insulin resistance, high triglycerides [14]. Higher levels of both endocannabinoids, anandamide and 2-AG, have been reported in serum of coronary artery disease patients [12]. CB-1 receptors have been found to be abundantly expressed within cells comprising atherosclerotic plaques [15]. CB-1 mRNA is expressed preferentially in plaques found in the vasculature of patients with unstable angina in comparison to those who have stable angina [8]. Anandamide has been found in higher concentrations within culprit lesions of the coronary vessels than in the bloodstream of those same patients, suggesting that CB-1 activators have the potential for release into systemic circulation during cardiac events, furthering atherosclerotic inflammation and advancing progression of existing disease [16].

5. Vasospasm

Endothelial cells - and their reactivity play an integral role in the coronary vascular tone and patency. When damaged, through the mechanism described in the previous section in which ROS are generated via CB-1 signaling, a stimulus for vasoconstriction is provided, leaving the coronary vessels more prone to vasospasm, with a diminished ability to vasodilate [5]. The role of ROS is twofold in these cases, they facilitate endothelial damage on their own, and further contribute to the dysfunction later in the pathway by promoting vasoconstriction [5].

Marijuana-induced vasospasm has been reported in several case reports and series. One such presentation, in which there was a temporal association with marijuana use and cardiac symptoms, involved a patient with chest pain found to have NSTEMI, but with a coronary angiogram lacking any findings of flow limiting stenosis or occlusion [17]. In this case, the authors concluded that a transient vasospasm, likely precipitated by marijuana use, was responsible for the patient's chest pain [17]. Another case report presented a patient with no known CVD, and a cardiac catheterization report that revealed no obstructive lesions or stenosis, with recurrent STEMI [33].

In addition to vasospastic angina, there are multiple reports of coronary slow and no flow phenomenon (CSFP) in association with marijuana use. CSFP is an angiographic finding whereby there is a filling delay in distal coronary vasculature, but no significant occlusion or stenosis can be visualized that might explain the later opacification [18]. Clinical manifestations of slow coronary flow range from acute coronary syndrome to serious arrhythmias [19].

The pathologic findings in patients with CSFP are equally diverse- subendocardial biopsies reveal a wide spectrum of patterns including fibromuscular hyperplasia and mitochondrial abnormalities [20]. The pathogenesis of CSFP is the common denominator among this multitude of causes, of which marijuana is suspected to be part. Drawing from the above literature, it's plausible that regular marijuana use causes recurrent disturbances in

microvascular function that accumulate over time, leading to a syndrome of functional coronary vasculature occlusion, even in the absence of typical occlusive findings on catheterization.

6. Cerebrovascular Effects

Acute ischemic stroke has been shown to afflict marijuana users at a higher rate than non-users [21]. A 2016 study found that recreational marijuana use increased the risk of hospitalization due to ischemic stroke in patients ages 18-54, however the rates could be even higher due to rate underreporting of illicit drug use in this age population [28]. A recent systematic review found a temporal relationship between marijuana use and ischemic stroke; the time-course showed acute ischemic stroke to follow marijuana use [22].

Thanvi and Treadwell propose several possible mechanisms underlying this connection between marijuana and ischemic stroke, including vasculitis, vasospasm, and reversible cerebral vasoconstriction syndrome (RCVS) [23]. RCVS refers to a class of conditions that results in a reversible multifocal narrowing within cerebral circulation [24]. This transient stenosis has common clinical manifestations, such as the typical thunderclap headache, and focal neurologic deficits. Although RCVS generally follows a clinically benign course, it can result in acute ischemic strokes that leave patients with lasting deficits [24]. The fact that the narrowing is reversible implicates a defect in regulating cerebrovascular tone as the underlying pathophysiology, although exact mechanism of RCVS has not been clarified [25].

In a prospective study of 67 patients who had suffered RCVS, 32% were cannabis users [26]. The same authors later conducted a subsequent study of 159 patients hospitalized for acute stroke [27]. They identified 21 patients who experienced reversal of multifocal cerebral artery narrowing by 3-6 months after stroke, without any additional causes of cerebral infarction apparent. They demonstrated that reversible vasoconstriction resulting in acute stroke had been brought on by cannabis use, identifying it as a precipitating vasoactive substance in 14 of their patients [27].

A recent study in rats demonstrated that mitochondrial dysfunction could result from THC exposure, leading to increased promotion of reactive oxygen species, which cause vasculotoxic effects according to the cascade of events described earlier [29]. Given the high oxygen demand of the brain, neurons and glial cells are rich in mitochondria, making the effects of mitochondrial damage and subsequent oxidative stress particularly devastating [30]. As a result, there may be a heavy burden of endothelial dysfunction within the cerebral circulation from THC exposure [29].

7. Conclusion

As marijuana use continues to grow across the US, understanding the drug effects on microcirculation and underlying mechanisms for endothelial damage sheds light on the pathophysiology responsible for the clinic

phenomena that we observed. Future research should of course focus on uncovering the exact mechanism, and should also seek to elucidate the timeframe by which marijuana induces vascular damage. Long-term studies of marijuana users of varying degrees are warranted to observe the accumulation of damage over a longer duration, as well as to track whether recovery is possible, and to what extent it can occur. Given the potential role for cannabinoid receptors in advancing CVD, it is also worth exploring these receptors as potential therapeutic targets of CVD arising from other etiologies.

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