

# Cardiac Disorders Associated with Cannabis: A Review of Literature

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## Article Info

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## Abstract

The leisure intake of cannabis has shortly amplified in the past years corresponding with its decriminalization and legalization. The natural cannabis has been substituted by synthetic cannabinoids and cannabimimetic in several formulae, which are stronger. In spite of irresistible public insight into the safety of these substances, a growing quantity of grave cardiovascular adverse events are reported in sequential relation to recreational cannabis intake. A multifaceted interface between the active ingredients, the endocannabinoid system, and the autonomic nervous system is responsible in the pathophysiology. Tolerance to the properties of cannabis can develop with repetitive contact due to receptor desensitization. Effects of cannabis may be heightened or transformed by affiliated use of other illicit drugs or drug treatment indicated for the treatment of cardiovascular diseases. Nonetheless, the recent cannabis epidemic would significantly increase global burden of cardiovascular diseases

## Introduction

Marijuana plant known as *Cannabis sativa* was cultivated in Central Asia, and later transported to other parts of the world. Cannabis is a naturally growing plant and can be cultivated inside using hydroponic systems and non-natural lighting<sup>1</sup>. The plant has been used as a medicinal herb or as a mood-altering substance<sup>2</sup>. An increase in the utilization of cannabis has been recently noted due to new rules that have endorsed legalization and tolerated the possession, sales, and cultivation of the cannabis<sup>3</sup>. The estimated users of cannabis are over 183 million in 2014<sup>4</sup>. Cannabis is the most frequently used psychoactive substance after alcohol and tobacco. The recreational cannabis “epidemic” is accompanied by an elevated number of case reports of grave cardiovascular complications. We plan to assess probable cardiovascular adverse events associated with the use of these substances. The probable pathophysiological mechanisms accountable for the most serious cardiovascular events in cannabis users are discussed.

The literature review was performed in searches of EMBASE, PUBMED and MEDLINE databases utilizing the phrases “cannabinoids”, “marijuana”, “cannabis”, “THC”, “cardiovascular disease” and “stroke”. All referenced articles were thoroughly reviewed, the findings were carefully examined for content accuracy. The existing literature was characterized conferring to significance and the clearness of the presented data. Attention was paid to exclude studies with strategies that diverged from normal conducts that cannabis was used recreationally.

## Types Of Cannabis

Cannabis comes in natural and synthetic forms.

### Cannabis: Natural Forms

Cannabis occurs in three naturally growing strains (ruderalis, sativa and indica). Breeding has formed "cross" strains of the plants. These strains diverge in the amount of the two best recognized active ingredients, namely D9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The properties of various cannabis strains may fluctuate based on the variable concentration of terpene resins<sup>5,6</sup>. The sativa strain contains the maximum level of THC, the psychoactive cannabinoid that produces the euphoric effect and has a lower content of CBD, the cannabinoid that may alleviate the ecstatic and effects of THC. The highest content of THC is found in the leaves and buds of the female plants. These are dried for smoking. Other preparations like edibles, oils, waxes, vapor, liquid incense are also manufactured from cannabis. Cannabis is used for refractory nausea and vomiting following chemotherapy and neuropathic pain due to advanced neurologic disorders and cancer<sup>2,7,8</sup>. In the United States of America, cannabis is listed as a Schedule I substance as per section 202 of the Controlled Substances Act of 1970 by the Drug Enforcement Administration. Schedule I drugs have heightened potential for abuse, no currently well-known medical use, and no recognized care for usage with medical guidance. Forty Two states and the District of Columbia have legalized medical uses of cannabis.

A significant deliberation in the use of cannabis has been the randomness of the dosage of the active constituents of the artificially prepared forms. Comparable quantities of dried leaves/flowers, waxes/oils, or ingestible systems of cannabis could comprise immensely dissimilar amounts of active mixtures. The method of intake can impact the absorption, bioavailability and blood levels of the active mixtures. The plasma THC concentration and medical effects were alike after smoking and intravenous injection whereas ingestion caused smaller, deferred and lower peak plasma THC concentration in a study of healthy volunteers<sup>9,10</sup>. The possible physiologic effects of THC are also affected by the concomitant use of alcohol intake, nicotine intake and other illicit drugs. It is very essential to regulate the shelf life, bioavailability, dose range of the active compounds comprised of natural derivatives of medical cannabis preparations. A metered dose oral spray [Nabiximols], which has both THC and CBD, has been utilized for management of urinary dysfunction, spasticity and pain, in multiple sclerosis<sup>7</sup>.

### Synthetic Cannabis: Cannabinoids and Cannabimimetics

Synthetic THC compounds, dronabinol and nabilone,

are available in capsule forms for management of weight loss associated with cancer chemotherapy and acquired immunodeficiency syndrome along with symptoms of nausea and vomiting. Illicit production of synthetic cannabinoids and cannabimimetics is utilized for recreational use. Given the advanced strength, it is more appealing to the users, and traditional drug screening tests are unable to categorize them. These constituents include a family of more than 700 synthetic compounds manufactured with chemical alterations of THC to augment the affinity for cannabinoid receptors and intensify the length of action. Synthetic cannabinoids are squirted onto dried leaves and marketed under various names including Spice<sup>11</sup>.

### Effects Of Cannabinoids On The Cardiovascular System

Cannabis acts through the interaction of THC with the endocannabinoid system, an endogenous signaling network involved in a wide range of processes including immunity, endothelial function, inflammation and metabolism<sup>12</sup>. Two G protein-coupled membrane cannabinoid receptors, CBR1 and CBR2 are recognized. CBR1 is widely present in the nervous systems and is the main target of THC. The cardiovascular effects of cannabinoids are due to stimulation of the sympathetic nervous system, and inhibition of the parasympathetic nervous system<sup>12</sup>. Smoking cannabis results in tachycardia<sup>13</sup>. Certain studies have shown that the pretreatment with beta blockers like propranolol; atropine, and medications like rimonabant (reverse agonist of CBR1) prevent the CBR1-mediated modulation of the autonomic nervous system<sup>14-17</sup>. Cannabis also causes elevation of blood pressure<sup>18,19</sup> and atrial fibrillation<sup>20,21</sup>.

Smoking cannabis can decrease the oxygen transport to the heart and other vital organs by an elevation in blood carboxyhemoglobin levels and impaired myocardial oxygen demand to supply ratio<sup>22,23</sup>.

Smoking cannabis results in an instant elevation in heart rate, followed by a extensive rise in serum norepinephrine level. Acute exposure to cannabis causes elevation in systolic blood pressure and can induce various arrhythmias like atrial fibrillation<sup>23</sup>.

Cannabis causes vasodilation by activating the transient receptor potential ankyrin type-1 (TRPA1) ion channels which are located on the perivascular sensory neurons, but the arteriolar vasodilation is not general to all vascular beds. Vasoconstriction is observed in the coronary, cerebral and peripheral arterial systems<sup>24,25</sup>.

### Cardiovascular Complications Of Cannabis

Cannabis users with cardiovascular emergencies are young and frequently have no other risk factors for

cardiovascular disease. The incidence of cardiovascular complication rate has increased 1.1% in 2006 to 3.6% in 2010. The mortality rate from the cardiovascular complications was 25%<sup>26</sup>. Rising fears have led researchers to call for a registry in the United States similar to the efforts of the French Addictovigilance Network<sup>27,28</sup>. Cardiovascular complications of cannabis use include acute myocardial infarction, arrhythmias, stroke, peripheral arteriopathy, stress cardiomyopathy (SC) and sudden death. The adverse events are usually noted in recreational users, but cases have been observed in those using the cannabis for medically approved reasons.

### **Acute Myocardial Infarction [AMI]**

The incidence of AMI increases within an hour after exposure to cannabis<sup>29</sup>. Frequently cannabis users presenting with AMI have been young men with no preexisting obstructive coronary artery disease<sup>5,30</sup>. In general, AMI in cannabis users is linked with higher short-term mortality as there is a delay in procuring medical care in young with people with diminished judgement due to cannabis use<sup>31,32</sup>.

The drug screen has often been positive for cannabis only, although routine urine toxicology may be negative in those using synthetic cannabinoids<sup>33-35</sup>. This can cause marked underestimation of the AMI in the young cannabis users. Marijuana caused increased myocardial oxygen demand, reduced oxygen supply, and acts as a pro-coagulant<sup>36</sup>. Microvascular coronary artery spasm without atherosclerotic coronary artery disease have been described.

### **Left Ventricular Cardiomyopathy**

The endocannabinoid structure is thought to be responsible in myocardial stunning, takotsubo [stress] cardiomyopathy, sepsis and hemorrhagic shock<sup>36,37</sup>. Cardiomyopathy can be due to tachycardia or atrial fibrillation<sup>39</sup>.

The catecholamine rush may be largely responsible for the association. The presence of pre-existing myocardial dysfunction can predispose to deterioration of left ventricular systolic function particularly with the use of potent synthetic cannabinoids<sup>38</sup>.

### **Arrhythmias and Sudden Cardiac Death**

Rhythm disturbances range from sinus tachycardia to ectopic atrial or ventricular rhythms, and atrial or ventricular fibrillation in cannabis users, the pathophysiology being a hyperadrenergic state<sup>40</sup>. Cardiac ischemia due to microvascular spasm of acute coronary syndrome can cause fatal ventricular arrhythmias. These can cause dizziness, syncope, cardiac arrest or sudden cardiac death. Increased incidence of atrial fibrillation

in the younger (less than 50 years old) individuals and recurrence may occur upon repeated cannabis exposure<sup>41</sup>.

### **Cerebrovascular syndrome**

Neurological indications were the most common reasons (44%) for hospitalization of cannabis users in French healthcare facilities from 2004 to 2007<sup>5,42</sup>.

Patient admitted with stroke and substance abuse, cannabis was linked with ischemic but not hemorrhagic events, while amphetamines were related to predominantly hemorrhagic events<sup>43</sup>. Comparable outcomes were reported from the United States Nationwide Inpatient Sample, cannabis was an independent prognosticator of acute stroke and associated with a threefold increase in hospitalization with acute ischemic stroke<sup>44</sup>.

The ischemic strokes are frequently noted in the posterior cerebral circulation, the principal mechanism of stroke was noted to be reversible cerebrovascular spasm (RCVS). RCVS causes severe headache, photophobia, vomiting, blurred vision and a "string and beads" appearance of cerebral arteries on angiography<sup>45</sup>. Multifocal tightening of cerebral arteries in the posterior circulation was predictive of cannabis use<sup>46</sup>. Reversibility of cerebral vasoconstriction was noted on angiography within days after cessation of cannabis use<sup>47</sup>.

### **Vasculopathy**

Cannabis vasculopathy is clinically inseparable from thromboangiitis obliterans but tends to occur at an earlier age. The angiography shows segmental narrowing of distal arteries with minimal collateralization<sup>48,49</sup>.

Arteritis in the extremities can lead to tissue necrosis and gangrene. Other vascular problems of cannabis use have included migratory thrombophlebitis, renal artery dissection and central retinal vein occlusion<sup>40,50</sup>.

### **Conclusions**

Cannabis use has increased in epidemic proportions; extremely strong and unregulated synthetic cannabinoids and cannabimimetics have made the arena difficult. Cardiovascular symptoms have been occurring at a startling rate in users of cannabis and its related chemicals. Grave illness has occurred in young adults who are profound users of these compounds due to the wrong belief of them being safer, and swift decriminalization and legalization processes in the various states. Studies are greatly required in this expanse.

The current data should make physicians and legislators aware across the globe of the potentially hazardous effects of the unregulated use of cannabis.

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