

# The Potential for Clinical Use of Cannabinoids in Treatment of Cardiovascular Diseases

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## SUMMARY

Cannabinoids, the constituents of the marijuana plant and their analogs, have not only neurobehavioral but also cardiovascular effects. Great advances in the last couple of decades have led to better understanding of the physiological effects of the cannabinoids and of their role in various cardiovascular pathologies. The potential therapeutic use of cannabinoids in various cardiac diseases, such as ischemic injury, heart failure, and cardiac arrhythmias, has been studied in animal models. The purpose of this article is to review the physiological cardiovascular properties of cannabinoids and to summarize the knowledge related to their potential therapeutic use.

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## Background

The medical use of Cannabis was known for centuries, be it by the use of cannabis resins in India and Near East, or the hedonistic use of the middle-eastern hashish among bohemian circles in Paris at the beginning of the 20th century [1]. Gaoni and Mechoulam were the first to isolate the major psychoactive component of the plant *Cannabis sativa*,  $\Delta^9$ -tetrahydrocannabinol (THC) [2]. In 1988, Devane et al. reported the presence of a specific cannabinoid receptor in the rat brain using a labeled cannabinoid [3]. This receptor is now known as cannabinoid receptor 1 (CB1) after it has been cloned [4]. A second receptor was identified only in immune cells and is known as CB2 [5]. Following the identification of cannabinoid receptors, several groups have searched and isolated endogenous ligands that mimic the action of cannabis. These are now called the endocannabinoids [6,7]. The two most widely studied endocannabinoids are arachidonoyl ethanolamide or anandamide and 2-arachidonoylglycerol (2-AG) [8]. Several other endogenous substances have been identified [9,10]. The signaling mechanism of cannabinoids via inhibition of adenylate cyclase and cAMP production has been described [11]. At first it was assumed that CB1 receptors exist only in the central nervous system. However, after identification of peripheral CB1 receptor in other tissues and in particular in the cardiovascular system [4,12] it became clear

that the endocannabinoid system may have a physiological role in peripheral tissues. In recent years, research has focused on understanding the physiological role of the endocannabinoids in the cardiovascular system. This review will focus on this system's physiology and its therapeutic potential.

## Physiological Cardiovascular Effects of Cannabinoids

In humans, acute exposure to THC or smoked marijuana in controlled settings causes an increase in heart rate, an increase in cardiac output (as measured by echocardiography and dye dilution techniques), reduced peripheral vascular resistance, and an overall modest increase in blood pressure. At times postural hypotension occurs [13–15]. These changes are mediated centrally by the autonomic nervous system, and peripherally by cannabinoid receptor-mediated vasodilatation [15]. Tolerance of the acute effects of THC develops over a few repeated doses, which attenuates the hemodynamic effects observed with acute exposure [13,15]. It should be mentioned that cannabis usage, particularly if inhaled by smoking marijuana, is associated with adverse cardiovascular outcome. A case-crossover study by Mittleman et al. of 3882 patients who had had a myocardial infarction showed that cannabis use can increase the risk of myocardial infarction 4.8 times in the first hour of

exposure [16]. These findings are supported by laboratory studies that indicate that smoking cannabis provokes angina in patients with heart disease [17].

The hemodynamic effect of cannabinoids in animal models is complex, and is highly dependent on the experimental conditions [18]. Several groups have demonstrated that in anesthetized rodents, THC and anandamide, as well as potent synthetic cannabinoid ligands such as HU-210, evoke a triphasic hemodynamic response that includes an initial vagally-mediated bradycardia with secondary hypotension, a transient pressor effect followed by sustained hypotension [19,20]. These hemodynamic effects are sensitive to CB1 receptor antagonist [18,21]. In animals with baro-receptor denervation, the triphasic effect of anandamide is maintained. This indicates that the triphasic anandamide response is peripherally mediated. It has been shown that anandamide directly activates CB1 receptors on the vascular bed and inhibits adrenaline release from peripheral sympathetic nerves (splanchnic nerves) to induce the vasodilatation [22]. In conscious normotensive animals, the hemodynamic effects of exposure to anandamide and other cannabinoids are less pronounced or even absent [23–25]. Stein et al. demonstrated only two phases, an initial bradycardia-related reduction in blood pressure followed by a prolonged increase in blood pressure [23]. In another study, anandamide elicited transient vagal activation followed by a brief pressor response. However, the prolonged hypotensive component was absent [24]. In another study, the nonselective cannabinoid agonist WIN 55212–2 elicited a pressor effect. A small vasodilator effect was noticed only under high dose of the agonist [25]. Similar hemodynamic effects were found in another study with anandamide instead of WIN 55212–2 [26]. It seems that the hemodynamic response to cannabinoids is dependent on the experimental conditions, and vary depending on sedation, cannabinoid type, and the species. Regardless, it is clear that cannabinoids have hemodynamic effects, and therefore may be used pharmacologically for various cardiovascular diseases.

## Potential Therapeutic Values

### Ischemic Reperfusion Injury

Ischemic reperfusion injury is the principal cause of tissue damage occurring during myocardial infarction. Disruption of the normal blood supply, leading to ischemia and necrosis, is the initial trigger of the damage. In most clinical scenarios this initial stage is followed by reperfusion, aimed at stopping ischemia and preventing further cell death. Unfortunately, reperfusion itself inflicts additional tissue damage mediated by reactive oxygen, reactive nitrogen species, and inflammation [27–29].

Preconditioning is a term referring to conditioning of the heart before ischemic–reperfusion injury, to reduce damage. Preconditioning can be achieved by exposing the heart to repeated short ischemic periods, bacterial endotoxins, and heat acclimation [30–36]. Initial suggestions for a role of endocannabinoid in cardioprotection came when blocking of CB2 receptors with the CB2 antagonist SR144528 was shown to abolish bacterial endotoxin or heat-stress-induced preconditioning [37–39]. Another study reported that preconditioning induced by short-term ischemia could be blocked by either CB<sub>1</sub> or CB<sub>2</sub> antagonism [40].

These initial studies were followed by interventional studies in which endocannabinoids and/or synthetic cannabinoids were used in animal models to prevent ischemic damage. In an isolated rat heart model of low-flow induced ischemia and reperfusion, Lépicier et al. demonstrated that palmitoylethanolamide (PEA) or 2-AG, but not anandamide, decreased myocardial damage. CB<sub>2</sub> antagonism with SR144528 totally abolished the beneficial effects of PEA and 2-AG [41]. The CB<sub>1</sub> antagonist SR141716A (rimonabant) only partially blocked the effect of 2-AG. While it may seem that the cardioprotective effect of PEA and 2-AG are mediated by CB<sub>2</sub> receptor, selective CB<sub>1</sub> and CB<sub>2</sub> agonists receptors, ACEA and JWH-015, respectively, reduced infarct size. This indicates that both CB<sub>1</sub> and CB<sub>2</sub> receptors, depending on the particular pharmacologic properties of the compound, may have a cardioprotective role [42,43]. Contrary to the results of the study by Phillippe [39], a subsequent study by Underdown et al. was successful at demonstrating a cardioprotective effect for anandamide in an isolated heart model. The protective effect of anandamide could be blocked by either CB<sub>1</sub> or CB<sub>2</sub> antagonism [44].

Whole animal models also successfully demonstrated a protective effect of cannabinoids against ischemic reperfusion injury. These studies have emphasized the role of CB<sub>2</sub> receptors in cardioprotection. Di Filippo et al. showed that preventive treatment with the nonselective cannabinoid agonist WIN 55212–2 before ischemia significantly reduced the extent of infarct size [45]. The CB<sub>2</sub> antagonist AM630, but not the CB<sub>1</sub> antagonist AM251, abolished the effect of WIN 55212–2. To further strengthen the cardioprotective role of CB<sub>2</sub>, a recent study demonstrated that a single dose of the CB<sub>2</sub> agonist JWH-133 reduced infarct size [46]. Selective CB<sub>2</sub> agonists have antiinflammatory effects in various other models of ischemic–reperfusion injury [47–49]. It is therefore plausible that the protective effect of cannabinoids, at least in part, is related to their antiinflammatory properties mediated by CB<sub>2</sub> receptors.

We published that the nonpsychoactive Cannabis component with potent antiinflammatory properties, cannabidiol (CBD), was protective in an *in vivo* rat model of ischemia–reperfusion [50]. The infarct size was significantly reduced in CBD-treated rats as determined after 7 days, together with reduced myocardial inflammation and improved left ventricular function. The cardioprotective effect was absent in isolated hearts, supporting the crucial role of systemic inflammatory processes, which are modulated by CBD in the *in vivo* model. The underlying mechanisms of CBD signaling are not very clear, but it is not mediated via either CB<sub>1</sub> or CB<sub>2</sub> receptors. One study suggests that the antiinflammatory effects of CBD may be related to enhanced adenosine signaling in immune cells, a signal that has a strong antiinflammatory effect [51].

### Arrhythmia

Recent evidence suggests that the endocannabinoid system might have antiarrhythmic properties. In an ischemic-induced arrhythmia model anandamide showed significant antiarrhythmic effect; in this model ischemia was induced by 10 min coronary ligation in rats. During the ischemic period, 76% and 46% of the control animals had multiple ventricular premature beats (VPBs) and ventricular fibrillation (VF), respectively. After anandamide

treatment, only 21% and 7% of animals developed VPBs and VF, respectively. Similar reduction in arrhythmic events was observed after reperfusion [52]. The antiarrhythmic effect of anandamide was abolished by SR 144528, a CB2 receptor blocker, but not by SR 141716A, which is a CB1 receptor blocker [53]. In another model, the synthetic nonselective cannabinoid agonist, HU-210, was able to reduce ischemic-induced VF and ventricular tachycardia (VT) events by as much as 90%. These effects were partially blocked by SR144528, a CB2 blocker, but not by SR141716A, a CB1 blocker [54]. The antiarrhythmic effect of HU-210 was also demonstrated on arrhythmia induced by epinephrine and aconitine [55–57]. Unlike in the ischemic model, the antiarrhythmic effect of anandamide in epinephrine-induced arrhythmia was not abolished by CB2 receptor blocker [56].

Reza Hajrasouliha et al. preconditioned rat hearts by inducing mesenteric ischemia. This type of preconditioning is called “remote preconditioning,” because ischemia is induced on an organ other than the heart. It must be assumed that any protective substance produced in the intestine reaches the heart via circulation. Hajrasouliha et al. demonstrated reduced ischemia-induced arrhythmia, as measured by absolute number of VPB, duration of VT, and duration of VF in the preconditioned animals. The antiarrhythmic effect of mesenteric preconditioning was blocked by the CB2 receptor blocker AM 630 but not by the CB1 blocker AM 251 [58]. These studies suggest that cannabinoids may have antiarrhythmic properties in relation to arrhythmias that are mediated by CB2 receptors.

## Heart Failure

Very few studies were reported on the role of the cardiovascular endocannabinoid system in heart failure models. In one study, Wagner et al. demonstrated in a rat model of acute myocardial infarction that animals treated with SR141716A (rimonabant), a CB1 receptor blocker, had higher blood pressure and heart rates compared with control animals. These changes were associated with reduced survival in the treated animals [59]. More importantly, anandamide and 2-AG were measured on platelets and monocytes isolated 30 min after left coronary artery occlusion. Injection of these isolated monocytes and platelets into rats decreased mean arterial pressure, suggesting the direct contribution of endocannabinoids in post myocardial infarction hypotension. In another study, the same authors reported the effect of the CB<sub>1</sub> antagonist AM-251 and the potent synthetic cannabinoid HU-210 on cardiac function in a chronic myocardial infarction model. HU-210 is known to exert hemodynamic changes via CB1 activation [60,61]. As compared with both AM-251 and vehicle, animals treated with HU-210 demonstrated higher left ventricular end diastolic pressure, higher left ventricular systolic pressure, higher maximal rate of rise of left-ventricular systolic pressure ( $dP/dT_{max}$ ), and higher cardiac index. Total peripheral resistance index decreased with HU-210 treatment. On the other hand, animals treated with AM-251 had accelerated postinfarction left ventricular remodeling, as indicated by an increase of left ventricular diastolic and systolic volumes as well as a shift of the pressure volume curve to the right. These two studies point to the potential of activation of the endocannabinoid system during

development of post myocardial infarction heart failure. Interventions aimed at modulating the cannabinoid activity may have a role in heart failure treatment.

## Unanswered Questions

Cannabinoids can induce hypotension and have been reported to be involved in endotoxin association hypotension [19,21,62]. Part of the vasodilatory effect is mediated by CB1 receptors [63]. The recent Rimonabant In Obesity studies (RIO) gave an opportunity to test whether Rimonabant, a CB1 receptor blocker, has a pleiotropic effect on blood pressure [64]. Ruilope et al. have evaluated the effect of Rimonabant on hypertension in the four RIO studies. They demonstrated that Rimonabant treatment is associated with significant reduction in hypertension, which was more pronounced in *a priori* hypertensive patients. This effect was explained by the concurrent weight reduction [65].

The group of Wagner et al. has indicated another uncloned cannabinoid receptor that may be involved in hemodynamic regulation. In one study they used buffer-perfused rat mesenteric artery preparation precontracted with phenylephrine. Anandamide elicited a dose-dependent vasodilatation that was inhibited by SR141716A, a CB1 blocker. When endothelial cells were removed from the vessel, anandamide maintained its dilator response; this time SR141716A did not prevent the vasodilatory effect. Other potent CB1 ligands, such as HU-210, WIN 55212–2, and the endogenous 2-AG, did not have vasodilatory effects. Moreover, Abn-cbd, which is a cannabinoid that does not bind to CB1 receptor, causes mesenteric vasodilatation in wild-type mice and CB1 knockout mice [60]. These results suggest that the vasodilatory effect of anandamide is mediated by at least another receptor other than the endothelial CB1 receptor. This receptor is yet to be cloned [66]. Abn-cbd may be an agonist of this receptor [60]. While the existence of another, unknown cannabinoid receptor is certainly plausible, other options, such as posttranslational receptor modification or trafficking, may explain the unexpected behavior of the CB receptors in the mesenteric vasculature [67].

## Future Directions

Accumulating animal model data, as presented above, suggest that the endocannabinoid system has a physiological role in the cardiovascular systems. This system is involved in modulating cardiac inflammatory processes, maintaining hemodynamic homeostasis and rhythm control. It is not surprising, therefore, that cannabinoids offers intervention opportunities to alter the course of cardiovascular diseases. Such is the case in ischemic reperfusion injuries, where there is evidence that activating the cannabinoid system may prevent ischemic injuries and arrhythmia. Such is the case in the rhythm control mechanisms, where a few studies indicate potential antiarrhythmic properties for cannabinoids, and such is the case in heart failure (Table 1). However, currently all studies were performed in single animal models and were not reproduced in various species. Furthermore, there are no data to suggest beneficial role of cannabinoids intervention in humans. A search on [clinicaltrials.gov](http://clinicaltrials.gov) using the search terms “cannabinoids”

**Table 1** Mode of action and effect of various cannabinoids in different heart pathologies

Substance	Pharmacologic activity	Cardiac pathology	Observed effect	References
Anandamide	Endogenous cannabinoid	Ischemic reperfusion injury Arrhythmia	Protective effect against ischemic injuries Antiarrhythmic effect in an ischemic model	[44] [50,54]
		Heart failure	Reduces blood pressure in animals after myocardial infarction	[57]
PEA	Endogenous cannabinoid	Ischemic reperfusion injury	Protective effect against ischemic injuries	[41]
2-AG	Endogenous cannabinoid	Ischemic reperfusion injury Heart failure	Protective effect against ischemic injuries Reduces blood pressure in animals after myocardial infarction	[41] [57]
SR144528	CB2 blocker	Ischemic reperfusion injury	Abolishes ischemic, bacterial endotoxin, or heat-stress-induced preconditioning	[37–39, 40]
			Abolishes the protective effect of endogenous cannabinoids against myocardial ischemic injuries	[41]
		Arrhythmia	Abolishes the antiarrhythmic effect of anandamide and HU-210	[50]
AM 630	CB2 blocker	Arrhythmia	Abolishes the antiarrhythmic effect of remote preconditioning	[56]
SR141716A (rimonabant)	CB1 blocker	Ischemic reperfusion injury	Partially abolishes the protective effect of 2-AG against myocardial ischemic injuries.	[41]
		Heart failure	Increases heart rate, blood pressure, and reduces survival in an ischemia-induced heart failure model	[57]
ACEA	CB1 agonist	Ischemic reperfusion injury	Protective effect against ischemic injuries	[42, 43]
JWH-015	CB2 agonist	Ischemic reperfusion injury	Protective effect against ischemic injuries	[42,43]
HU-210	Nonselective cannabinoid agonist	Arrhythmia	Antiarrhythmic effect in an ischemic model	[52,53–55]
		Heart failure	Improves overall systolic function in an ischemic induced heart failure model	[59]
WIN 55212–2	Nonselective cannabinoid agonist	Ischemic reperfusion injury	Protective effect against ischemic injuries	[46]
Cannabidiol (CBD)	Unknown receptor, antiinflammatory effect	Ischemic reperfusion injury	Protective effect against ischemic injuries	[51]

revealed 59 different human studies at various stages of recruitment with cannabinoids, however none are related to the cardiovascular system. Nevertheless, these studies provide evidence for the safety of cannabinoid compounds in humans. CBD, for example, which was shown to reduce infarct size, is currently being tested in inflammatory bowel disease, psychosis, and diabetes. The evidence of a potential role for cannabinoid in various cardiovascular pathologies, together with the safety data gleaned from various human intervention studies, indicate that now is the time to show efficacy across species and continue toward human trials. Given the proven safety of CBD, the leap toward human studies is small. Similarly, HU210 has a proven safety profile in humans and given it's favorable myocardial protection properties should be tested in humans.

## Disclosure

The authors report nothing to disclose.

## Conflict of Interest

The authors have no conflict of interest.

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