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Drugs of Misuse: Focus on Vascular Dysfunction

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Abstract

Common drugs of misuse, including cannabis, opioids, stimulants, alcohol, and anabolic steroids, have strikingly disparate acute and chronic vascular effects, leading to a wide range of clinical cardiovascular presentations. Acute cannabis smoking has been associated with increased risk for myocardial infarction and ischemic stroke in otherwise healthy young people. However, it remains uncertain if people who exclusively smoke cannabis have increased risk for accelerated atherosclerosis similar to that found in people who exclusively smoke tobacco cigarettes. Cocaine and methamphetamines, both stimulants, increase risk for stroke, myocardial infarction, aortic dissection, and accelerated atherosclerosis, but only methamphetamine use is strongly linked to pulmonary hypertension. Chronic alcohol use is strongly associated with chronic hypertension and hemorrhagic stroke, but perhaps confers a lower risk for myocardial infarction. Finally, anabolic steroid use, presumably through adverse effects on circulating lipids and the hematopoietic system, is associated with increased risk for accelerated atherosclerosis and myocardial infarction. Physicians, especially cardiologists, emergency medicine and internal medicine physicians, should be familiar with the short- and long-term vascular consequences of use of these substances, thereby ensuring appropriate, specific, and informed counseling and treatment.

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Brief Summary

Common drugs of misuse, including cannabis, opioids, stimulants, alcohol, and anabolic steroids, have strikingly disparate acute and chronic vascular effects, leading to a wide range of clinical cardiovascular presentations. Physicians, especially cardiologists, emergency medicine and internal medicine physicians, should be familiar with their short and long term health consequences, potentially including stroke, myocardial infarction, pulmonary hypertension, aortic dissection, and others, thereby ensuring appropriate, specific, and informed counseling and treatment.

Common drugs of misuse, including cannabis, opioids, stimulants, alcohol, and anabolic steroids, have strikingly disparate acute and chronic vascular effects, leading to a wide range of clinical cardiovascular presentations. Even agents within the same category, for example methamphetamine and cocaine, both psychomotor stimulants, present with surprisingly distinct clinical phenotypes. Drug use is widespread, even *epidemic*, mandating that physicians, including cardiologists, emergency medicine and internal medicine physicians, be familiar with their short and long term health consequences, thereby ensuring appropriate, specific, and informed counseling and treatment[1]. Treatment is, of course, complex and requires an intensive multidisciplinary approach. Although beyond the scope of this review, the mainstay of treatment is twofold: 1) addressing the underlying pathology, largely using traditional therapeutic approaches but with important deviations (e.g. in the setting of acute cocaine intoxication, avoiding beta-blockade and initiating benzodiazepines, discussed elsewhere in this focus issue), and 2) providing support and resources to address the underlying drug misuse and substance use disorders. In this review, the acute and long-term impact of the above drugs on the vasculature, specifically the coronary, cerebral and pulmonary vasculature, will be discussed and compared. The cardiotoxicity of these drugs, which is significant, will be discussed separately in this focus issue of the *Canadian Journal of Cardiology* (CJC).

CANNABIS

Cannabis sativa comprises over 100 phytocannabinoids, constituents that are unique to the cannabis plant, and hundreds of other compounds including terpenes and flavonoids[2, 3]. Cannabis and cannabis-based products vary with respect to their chemical composition. Many phytocannabinoids interact with the endogenous endocannabinoid system, including the most well-studied phytocannabinoid, delta-9-tetrahydrocannabinol (THC). The endocannabinoid system consists of cannabinoid 1 (CB1) receptors present throughout the body, including the vasculature, heart, and brain, and cannabinoid 2 (CB2) receptors which are highly concentrated on immune cells[2, 4]. CB1 receptors are responsible for many of the adverse effects of cannabis including intoxication, abuse liability, and physiological dependence that can accompany chronic, frequent use. This receptor is also important for many of therapeutic effects of cannabis including appetite stimulation, anti-nausea, and analgesia. The CB1 receptor is known to mediate the pro-inflammatory and pro-oxidative effects of cannabis, whereas CB2 receptors possess anti-inflammatory and antioxidant properties. THC, the primary psychoactive component of cannabis, is a partial agonist at both CB1 and CB2 receptors and is largely responsible for the adverse effects

and many of the identified therapeutic effects of cannabis. THC has also been identified to contribute to the adverse cardiovascular sequelae of cannabis use[2, 4]. Importantly, over the past decade, the average THC content in cannabis has markedly increased from 2–3% to over 20%, and, high potency inhalable cannabis concentrates are available (dabs, wax and shatter), which contain 65 – >90% THC[5, 6]. Synthetic cannabinoid products (e.g. K2 and spice) are also available; many compounds in these products are CB1 receptor agonists that with are characterized as having 10 to 100 fold greater potency and efficacy at the CB1 receptor than THC[2, 7, 8]. Compared to oral, sublingual or topical formulations, inhalation of cannabis with THC leads to faster and potentially greater CB1 receptor activity, increasing the likelihood of adverse cardiovascular sequelae[4]. Cannabis and cannabis-based products are widely available with very low concentrations of THC (<0.3% THC), and their therapeutic potential continues to be investigated. The effects described herein are related to THC-dominant cannabis and cannabis-based products.

Cannabis has been legalized for medical and/or adult-use purposes in Canada since 2018, and in 37 states in the United States. Legalization and recognition of its medicinal role has contributed to the reduced perception of cannabis' harms, which may play a role in increased use. After alcohol and tobacco, cannabis is the most frequently used psychoactive drug in the world[9]. The surge in cannabis use has been accompanied by a marked increase in case reports of acute myocardial infarction and stroke, temporally-related to cannabis use, often occurring in otherwise healthy young people without cardiac risk factors[10]. Adverse effects of cannabis on the vasculature are thought to be major contributors to these acute cardiovascular and cerebrovascular events[4, 10, 11](Box 1). These acute effects will be reviewed below. Additionally, evidence that these acute vascular events may signal permanent vascular damage, portending future cardiovascular and cerebrovascular disease, will be reviewed.

Cannabis–related myocardial infarction

Case reports of myocardial infarctions related to cannabinoids, including both cannabis and synthetic cannabinoid products, are increasing[10]. As previously summarized in this journal[10], patients with cannabinoid-related myocardial infarctions were young, mean age 31 years (range 15–56 years), male (94%), without other coronary risk factors (75%), and 71% presented with a ST-segment myocardial infarction (STEMI) within 6 hours of cannabinoid use (80%). Although the majority or patients reported inhaling combusted or vaporized cannabis, a subset reported only using edibles. The number of case reports of patients using synthetic cannabinoids (i.e., Spice, K2), with its markedly increased CB1 receptor activity, accounted for a third of the reports of cannabinoid-related myocardial infarctions in this review[10]. Although the majority of cannabinoid-related myocardial infarctions occur in people who use cannabis and synthetic cannabinoids regularly, 31% of patients were not regular users. The increasing frequency with which STEMIs, temporally-related to cannabinoid use in otherwise healthy young people without cardiac risk factors, have been reported implicates cannabis and synthetic cannabinoids as a trigger these events[10].

That cannabis may be a rare trigger for myocardial infarction was first suggested by Mittleman and colleagues over 20 years ago, when they reported that myocardial infarction risk was increased 5-fold within 1 hour of smoked cannabis use[12]. Their cohort was older, and were more likely to have additional cardiac risk factors compared to those cases included above, so the association may have been less secure. Although significant, the risk of myocardial infarction following cannabis use was much lower than the risk associated with acute cocaine use in a contemporary population, which was estimated to be increased 24-fold[13]. Whether the increased frequency of cannabis-related myocardial infarction in recent years is attributable to more widespread cannabinoid use, or to greater THC potency of the cannabis available today, remains uncertain.

The purported mechanisms underlying acute cannabis-related myocardial infarction are many (Figure 1). First, cannabis increases heart rate and often blood pressure within the first 30 minutes of use[11, 14]. These acute hemodynamic effects are mediated by activation of the sympathetic nervous system, thereby increasing myocardial oxygen demand. In people who use chronically, tolerance soon develops to the sympathomimetic effects of cannabis, and these acute pressor effects may not be seen. It has been observed that people who use cannabis frequently may develop hypotension and bradycardia with use, which could also trigger acute coronary ischemia[15, 16].

Secondly, cannabis smoking is associated with decreased myocardial oxygen supply. Cannabis combustion generates significant carbon monoxide, and smoking cannabis markedly increases carboxyhemoglobin levels. Carboxyhemoglobin levels in cannabis smokers are 5-fold that of tobacco cigarette smokers, perhaps due to differing inhalation topographies[17]. Carboxyhemoglobin reportedly contributes to endothelial dysfunction and accelerated atherosclerosis[18].

Third, cannabis use has a pro-coagulation effect. Platelet membranes express both CB1 and CB2 receptors, and acute cannabis exposure increases glycoprotein IIb/IIIa and P selectin expression on platelet membranes. THC increases ADP-induced platelet aggregation, and factor VII activation, promoting acute coronary thrombosis, even in the absence of coronary atherosclerosis[9, 19]. This pro-coagulant effect is amplified in the setting of endothelial dysfunction, also induced by cannabis[20]. Cannabis, especially - but not exclusively - in its combusted form, increases oxidative stress in endothelial cells, depleting nitric oxide (NO), and leading to endothelial dysfunction[20–22]. This early vasculopathy increases vascular inflammation and further promotes platelet adhesion and aggregation, and vascular thrombosis.

Fourth, cannabis use, due to multiple mechanisms including sympathetic activation, oxidative stress and endothelial dysfunction, is associated with acute vasospasm[22–25]. Vasospasm of the epicardial coronary arteries may occur even in the absence of an unstable plaque[25]. Additionally, vasospasm may occur in the microvasculature, detectable by the phenomenon of slow coronary blood flow in epicardial vessels in the absence of atherosclerosis. Reportedly, this microvascular disease may be reversed with verapamil administration[23]. Finally, under certain circumstances, cannabis may be associated with inflammation of the vasculature, although cannabis has both proinflammatory and anti-

inflammatory effects. Immune cells express anti-inflammatory CB2 receptors, which oppose the pro-inflammatory effects of CB1 receptors[2]. This complexity has implications for accelerated atherosclerosis, discussed below.

Finally, cannabis smoke contains cyanide, raising thiocyanate levels more than tobacco smoke[26]. Thiocyanate is a potent oxidase, resulting in oxidation of LDL, which may further contribute to accelerated atherosclerosis[27]. Thus, adverse vascular effects of thiocyanate associated with smoked cannabis may contribute to long-term increased risk of myocardial infarction and stroke.

Stroke

Similar to cannabis-related myocardial infarction, case reports of cannabis-related stroke have increased in number in recent years[28]. Cannabis use has been linked to strokes, usually ischemic, in otherwise healthy young people without comorbidities. Multifocal intracranial stenoses, most often involving the posterior circulation, have been described[29, 30]. Mechanisms underlying cannabis-related stroke are similar to those proposed for cannabis-related myocardial infarction, and include fluctuating blood pressure, a failure of autoregulation, hyper-coagulability, vasoconstriction and vasospasm. Cardiac emboli, perhaps due to transient arrhythmias triggered by cannabis use, underlie a small proportion of strokes. Of course, many strokes occur in the setting of multi-drug use, including tobacco cigarettes, as well as methamphetamines and cocaine[28, 29]. Synthetic cannabinoid use has also been associated with hemorrhagic stroke[29]. This association has been attributed to the failure of autoregulation in cerebral vessels; synthetic cannabinoids alter release of neurotransmitters, which may produce vasospasm, leading to endothelial dysfunction, rendering the blood vessel walls vulnerable to rupture during acute cannabis-induced fluctuations in blood pressure.

Cannabis arteritis

Cannabis arteritis has been described, but its existence as a discrete entity is controversial. Cannabis arteritis has many similarities to Buerger’s disease, or thromboangiitis obliterans, the accelerated vasculopathy that underlies limb ischemia in young, usually male, tobacco cigarette smokers[9]. Buerger’s disease is characterized by vasospasm and thrombosis, and typically improves with smoking cessation; unfortunately progression to irreversible limb ischemia and amputation in the absence of smoking cessation is the rule. Cannabis arteritis has been described most frequently in the presence of co-use of tobacco and cannabis cigarette smoking. That tobacco cigarette smoking cessation alone does not improve cannabis arteritis argues for a major role for combusted cannabis[31]. Underlying pathophysiology is thought to be similar to that of Buerger’s disease, including vasoconstriction and thrombosis[31]; the role for a contaminant, such as arsenic, in instigating the vasculopathy has also been hypothesized[32].

Accelerated atherosclerosis

It has been suggested that acute cannabis use can trigger an acute myocardial infarction or stroke in a small subset of otherwise healthy cannabis users,[12]. Although of significant interest to public health, it remains unknown whether cannabis smoking, like tobacco

cigarette smoking, will also lead to accelerated atherosclerosis and premature ischemic cardiovascular disease in the larger number of users who do not suffer one of these early events[3]. Epidemiological studies have not been able to definitively answer this question largely due to confounding variables, most commonly, concomitant tobacco smoking[33]. The Nationwide Inpatient Sample (2010–2014) was one of the largest studies to address this question, involving 35,771 patients hospitalized with acute myocardial infarction and cannabis use, and 2,416,162 patients hospitalized with acute myocardial infarction without cannabis use[34]. Lifetime risk of acute myocardial infarction was increased 3–8% in non-medical cannabis users in this retrospective analysis, after controlling for confounding variables. In the Coronary Artery Risk Development in Young Adults (CARDIA) Study, in which adult Black and white men and women between the ages of 18–30 years were enrolled in 1985–86, and followed periodically for the next 25 years, non-medical cannabis use was not associated with coronary calcification in the absence of co-use with tobacco, and was not associated with cardiovascular disease development by middle age[35]. Interestingly, a very recent report found that cannabis use was directly related to an elevated American College of Cardiology/American Heart Association Atherosclerotic Cardiovascular Disease Risk Score[36]. These investigators concluded that at the very least, people who use cannabis should be screened for traditional cardiac risk factors, and risk reduction strategies implemented[36].

Although large epidemiological studies have been unable to answer the question of cannabis use and future cardiovascular risk with certainty, there is certainly biological plausibility that cannabis use – especially combusted cannabis use – could lead to accelerated atherosclerosis. Cannabis smoke consists of largely the same constituents as tobacco smoke – except of course, it does not contain nicotine, and it does contain cannabinoids[2]. The burden of oxidative stress, a key contributor to the development of inflammatory atherosclerosis, conferred by cannabis smoking, would be expected to be similar to that of tobacco smoking[2]. Even minimal tobacco smoke exposure, that is, 1–3 tobacco cigarettes per day, markedly increases cardiovascular risk, raising concerns that even casual cannabis use could do the same[37]. Supporting this concern is the observation that exposure to secondhand cannabis smoke leads to endothelial dysfunction – and this cannabis smoke-mediated endothelial dysfunction persists longer than that caused by secondhand exposure to tobacco smoke[20]. Endothelial dysfunction is predictive of future atherosclerosis[38]. Yet, despite these points supporting biological plausibility, the epidemiological evidence is unclear.

An explanation for the absence of a clear connection between cannabis use and accelerated atherosclerosis may be the mitigating effects that cannabinoids, absent in tobacco smoke, have on the potential vascular toxicity of cannabis use. CB1 and CB2 receptors mediate largely opposing effects, with CB2 receptors mediating significant anti-oxidative and anti-inflammatory effects. Low dose cannabinoid therapy with predominantly CB2 agonist activity has been shown to have beneficial effects on the development of atherosclerosis in an animal model[39]. In humans, there is evidence that C-reactive protein, a marker for inflammation and inflammatory atherosclerosis, may be lowered by cannabis use[40]. Cannabinoids, specifically with increased CB2-receptor activity, have been tested clinically as anti-inflammatory agents in inflammatory bowel diseases[41].

Importantly, this lack of clarity in establishing a connection between cannabis and atherosclerosis does not mean lack of pathogenesis. Previously reported epidemiological studies were based on relatively small numbers of exclusive cannabis users; further, details describing cannabis use, including frequency and mode of use, and whether the cannabis was CBD-dominant or THC-dominant, are lacking[33–35]. Confounding variables, especially smoking, were more prevalent. Prospective studies conducted in well-defined populations who are using the current cannabis products with higher concentrations of THC are needed in order to be relevant.

COCAINE

Cocaine, an extract from the *Erythroxylon coca* plant from South America, can be snorted, smoked or injected intravenously to produce an intense but transient feeling of euphoria, pleasure, sexual arousal and happiness. It is lipid soluble and thus readily crosses the blood brain barrier, where it blocks reuptake of norepinephrine, leading to increased norepinephrine availability. Cocaine also has a moderate effect on dopamine and serotonin release and reuptake[42]. It is estimated that in 2018, 2.1% of people in North America used cocaine[1]. Euphoria and mood effects are transient, due to cocaine's short half-life of 30 – 60 minutes[42]. This short half-life and duration of action prompts repeated use in short intervals, further amplifying cardiovascular risks. In addition to its stimulant effects on mood, cocaine acutely increases blood pressure, heart rate, acute myocardial infarction, and stroke (Box 2). Recurrent use is associated with an accelerated vasculopathy leading to coronary and cerebral atherosclerosis, aortic dissection, and possibly pulmonary hypertension. Although the half-life of cocaine is <60 minutes, with repeated dosing, cocaine and its metabolites accumulate in the body, and the half-life can be increased to several days[43].

Myocardial Infarction

As reviewed elsewhere in this journal, cocaine is estimated to contribute to 25% of myocardial infarctions in young people between the ages 18–45 years[44]. Acute myocardial infarction that is temporally–related to cocaine use is thought to be caused by increased myocardial oxygen demand due to its acute hemodynamic effects, and decreased myocardial oxygen delivery caused by vasoconstriction and vasospasm, and acute intravascular thrombosis[42, 44] (Figure 2).

Prolonged cocaine use has been associated with accelerated atherosclerosis (Figure 2). As reviewed previously[45], repeated bouts of accelerated hypertension directly damage the endothelium. In addition to acute vasoconstriction attributable to norepinephrine, cocaine use is associated with increased circulating levels of the potent vasoconstrictor, endothelin-1, and decreased availability of the vasodilator, nitric oxide[42]. Cocaine also activates platelets and is pro-inflammatory, additional factors that contribute to accelerated vasculopathy[45, 46]. Cocaine-induced endothelial damage promotes activation of fibrinogen and von Willebrand factor, and leads to platelet aggregation. Elevated circulating levels of pro-inflammatory cytokines, including tumor necrosis factor-alpha and interleukin-1 beta, are found in patients who use cocaine and contribute to the accelerated vasculopathy[47]. All of these mechanisms affect both the larger epicardial coronary vessels as well as the microvasculature[48]. There is

no specific treatment tailored to the accelerated coronary atherosclerosis that is a sequelae of long-term cocaine use; referral by the treating physician to support and resources to help treat the cocaine use disorder is mandatory.

Stroke

Of all misused drugs, cocaine is the most frequently associated with risk of stroke, and ischemic strokes outnumber hemorrhagic strokes[29, 30, 42]. People who use cocaine compared to those who do not have a 6.4 fold risk of suffering a stroke within 24 hours of cocaine use. Stroke may occur after any route of cocaine use, but smoking (“crack cocaine”) may pose the greatest risk, and is associated equally with ischemic and hemorrhagic strokes[29, 30]. The accelerated vasculopathy involving the coronary arteries and the coronary microvasculature described above, also involves the cerebral macro and microvasculature. Ischemic stroke may occur during prolonged vasospasm in areas of accelerated vasculopathy in a person with chronic cocaine use disorder, and is more likely to occur in people who have formerly used cocaine than never users[29, 30]. Hemorrhagic stroke may occur when there is rupture at the site of a weakened vessel wall, or at an actual aneurysm, characteristic of the accelerated vasculopathy associated with prolonged cocaine use. Hemorrhagic strokes are more often triggered by acute cocaine use.

Aortic Dissection

Aortic dissection may be triggered by acute cocaine use, especially smoked cocaine, which may be used repeatedly in a short period with extreme vascular damage[42]. Apoptosis of vascular smooth muscle cells has been described in people who have used cocaine long-term, resulting in cystic medial necrosis, the pathology characteristic of aortic dissection[49, 50]. Similar findings have been detected in coronary and carotid arteries, and is part of the constellation of findings of cocaine-mediated accelerated vasculopathy. Recognition that cocaine use may trigger aortic dissection is important clinically, since not all chest pain in a patient with recent cocaine use is attributable to an acute myocardial infarction.

Pulmonary Hypertension

Cocaine use is considered a “possible” risk factor for pulmonary hypertension[51]. This designation is in contrast to the other commonly used stimulant, methamphetamine (discussed below), which is formally and widely recognized as a “likely” risk factor. An association between cocaine use and idiopathic pulmonary hypertension has been reported, and is certainly biologically plausible. Cocaine promotes release of endothelin-1, a known pulmonary vasoconstrictor. Previously discussed mechanisms leading to an accelerated vasculopathy in the systemic circulation, that is, oxidative stress, inflammation, and thrombosis, could certainly impact the pulmonary vasculature as well. A history of stimulant (cocaine or methamphetamine) use was 10 times more likely in a large cohort with idiopathic pulmonary hypertension compared to patients with pulmonary hypertension and an identified risk factor[42]. In another retrospective study, elevated pulmonary pressures were 5 fold more common in patients with a history of cocaine use compared to those without cocaine use history; those with the recent cocaine use (most often smoked) had the highest pulmonary pressures[51].

However, in an experimental setting, acute intravenous cocaine infusion did not acutely raise pulmonary pressures, whereas systemic pressures and heart rate were acutely increased, as expected[52]. In one study, smoked cocaine seemed to be associated with increased risk of pulmonary hypertension[53]. The possibility has been raised that a contaminant in smoked cocaine, not the cocaine itself, is responsible for the pulmonary hypertension[54]. Levamisole, often found in smoked cocaine, is metabolized to aminorex, a compound known to constrict the pulmonary vasculature[54]. The association between cocaine use and pulmonary hypertension remains uncertain.

METHAMPHETAMINE

Amphetamines are psychomotor stimulants, of which methamphetamine, 3,4-methylenedioxymeth-amphetamine (MDMA, Ecstasy or Molly), and nonmedical use of pharmaceutical stimulants (e.g. diet pills, cold remedies, and treatments for attention deficit disorder and narcolepsy), are the most frequently used in North America (2.3 percent of the population in 2018)[1]. In this section, the vascular effects of methamphetamine, about which much is known, will be the focus, but it is likely that these vascular effects may be ascribed to the other derivatives as well. Methamphetamine can be smoked, swallowed in pill form, snorted and/or injected. Like cocaine, methamphetamine crosses the blood brain barrier rapidly, and produces feelings of euphoria, sexual pleasure, empathy, as well as decreased appetite; and like cocaine, the psychostimulant effects are short-lived, promoting repeated or binge use in a short period of time. Methamphetamine increases release and blocks reuptake of catecholamines in neuronal tissue[55], and also increases availability of serotonin[56], an effect with potentially important vascular effects in the pulmonary circulation, discussed below. Compared to cocaine (half-life 30–60 minutes), methamphetamine has a long half-life – with 50% remaining unchanged in the body at 12 hours, depending on dose and route of administration. The vascular effects are similar to those of cocaine, including vasospasm, inflammation and endothelial dysfunction, leading to acute myocardial infarction and stroke, accelerated atherosclerosis, aortic dissection, and with greater certainty than cocaine, pulmonary hypertension[57, 58] (Box 3).

Acute Myocardial Infarction

Cardiovascular disease is the second leading cause of death in people who use methamphetamine[59]. The sympathomimetic effects of methamphetamine increase myocardial oxygen demand, at the same time coronary blood flow is decreased through vasoconstriction and vasospasm. Repeated methamphetamine use increases inflammation, endothlin-1 release, and decreases NO availability, and vascular smooth muscle function[57, 58, 60]. These repeated vascular insults can result in sustained vascular dysfunction, and accelerated atherosclerosis (Figure 3).

Strokes

In contrast to cocaine, methamphetamine use is more commonly associated with hemorrhagic than ischemic stroke; in one series hemorrhagic strokes were five-fold more common than ischemic strokes[29, 30]. Hemorrhagic stroke risk is two-fold greater with methamphetamine compared to cocaine use, and is associated with a 30% mortality[30].

The preponderance of hemorrhagic stroke may be a consequence the long half-life, and prolonged vasoconstrictor effect, of methamphetamine[29, 61]. Strokes of all kinds occur most frequently in young males, reflecting the demographic with the greatest methamphetamine use, and may occur after any route of administration, although are most frequently associated with oral and intravenous use[61].

Hemorrhagic strokes are attributable to both intra-cranial hemorrhage and sub-arachnoid hemorrhage. Acute hypertension in the absence of vasculopathy underlies a subset of hemorrhagic strokes. Acute and repeated bouts of hypertension in conjunction with the accelerated vasculopathy described above likely underlie the majority. Chronic methamphetamine use reportedly leads to “vascular fatigue”, characterized by the generation then rupture of weakened, even aneurysmal cerebral vessels[61]. Subarachnoid hemorrhage has also been attributed to the development of a necrotizing angiitis, potentially reflecting a direct toxic effect of methamphetamine of the vasculature[61].

Aortic Dissection

In a forensic study[62], methamphetamine use was found to be the second most common risk factor, only trailing hypertension, for aortic dissection. Among drugs of misuse, methamphetamine was the most frequent to be associated with aortic dissection, conferring a greater risk than cocaine[58, 63]. The purported mechanism is the surge in blood pressure associated with methamphetamine use; the contribution of the accelerated vasculopathy is likely also significant. Maintaining a high index of suspicion in a young person with chest pain and recent substance use, especially methamphetamines, is critical.

Pulmonary Hypertension

Based on large series of patients, it has been proposed that the World Health Organization upgrade its designation of methamphetamine from “likely” to a “definite” cause of pulmonary hypertension[56, 64, 65]. In these series, large percentages of patients with “idiopathic” pulmonary hypertension have been found to have a history of methamphetamine use[64, 66]. Smoking methamphetamine is the most common route of methamphetamine use associated with pulmonary hypertension[56]. Several mechanisms may underlie this association of methamphetamine with pulmonary hypertension. First, positron emission tomography studies have demonstrated that methamphetamine accumulates in pulmonary tissue – potentially exposing delicate pulmonary tissues to high levels of methamphetamines, thereby increasing risk of methamphetamine-related damage[67]. Second, methamphetamine increases serotonin activity, and in pulmonary tissue serotonin promotes vascular remodeling, vascular smooth muscle growth, and pulmonary hypertension[68]. Third, methamphetamine promotes generation of reactive oxygen species (ROS) in pulmonary endothelial cells, and increased oxidative stress in pulmonary vessels may contribute to vascular remodeling and pulmonary hypertension[57]. Methamphetamines are metabolized by carboxylesterase 1 (CES1). Intriguingly, in one series, a single gene polymorphism in CES1 that would be expected to amplify methamphetamine-ROS generation was detected in almost all patients with presumed methamphetamine-related pulmonary hypertension[57, 68]. Despite treatment, methamphetamine-related pulmonary hypertension portends a poor outcome[66].

ALCOHOL

Alcohol is the most prevalent psychoactive drug consumed in North America in fact, worldwide. Most adults will have tried alcohol at least one time in their life, and an estimated 7% of Americans have alcohol use disorder, defined as “clinically significant impairment or distress from the use of alcohol”[69, 70]. The effects of alcohol on the cardiovascular system, specifically the vasculature, are complex, and depend on timing, drinking pattern, and chronicity. Alcohol consumption has been most often quantified as low dose <1 drink (12–15 g) per day, medium-dose 1–2 drinks per day, and high-dose ≥ 3 drinks per day, and binge as 5 drinks in men and 4 drinks in women in one setting[71, 72]. Chronic alcohol consumption is associated with hypertension and stroke, particularly hemorrhagic stroke[73]. Conversely, it has been suggested that low dose alcohol has a protective effect on cardiovascular disease, but this assertion has been challenged[72, 74]. The impact of chronic alcohol consumption on the vasculature, and the potential underlying mechanisms, will be discussed (Box 4).

Chronic Alcohol-Related Hypertension

In contrast to acute alcohol consumption, which initially causes a reduction in blood pressure, followed by an increase after 13 hours[71], chronic alcohol consumption has been found to have a dose-related, linear association with hypertension that is consistent across age, race and sex, and which is independent of BMI, smoking status and activity (exercise) level[72, 73, 75–77]. It is uncertain if there is a threshold effect[72, 78].

Many potential mechanisms may underlie the association between chronic alcohol consumption with hypertension, all contributing to a vasoconstrictor, vasodilator imbalance[75, 78] (Figure 4). First, alcohol increases central sympathetic outflow, and the baroreceptors are reset, thereby playing a permissive role in this sympathetic activation[75, 79]. Additionally, withdrawal from alcohol, especially in people who use heavily, may lead to additional episodes of sympathetic activation, contributing to hypertension in the absence of acute consumption[75]. These are acute effects, but the recurrent, repetitive increases in vasoconstrictor sympathetic outflow that accompany alcohol ingestion may have chronic adverse vascular sequelae. Second, sympathetic activity induces release of renin and then generation of angiotensin II, one of the most potent vasoconstrictors in the body[75, 80]. Third, in addition to its direct vasoconstrictor activity, angiotensin II activates NADPH oxidase in the vascular wall, thereby increasing oxidative stress and endothelial dysfunction. In addition to reducing NO via this angiotensin II mechanism, alcohol metabolism leads to free radical generation, further interfering with NO release, and impairing endothelial function. Additionally, alcohol inhibits eNOS, the enzyme responsible for formation of NO. Thus, through many mechanisms, alcohol ingestion decreases nitric oxide activity, a potent vasodilator[75, 78, 81]. Brachial-artery flow mediated dilation (FMD) is mediated by NO release, and abnormal FMD is an early sign of vascular dysfunction; a recent meta-analysis confirmed that long-term, heavy drinking is associated with abnormal FMD[82]. Fourth, the increased oxidative stress related to alcohol use has been shown to promote the generation of 20-hydroxyeicosatetraenoic acid (20-HETE), another vasoconstrictor[80, 82–84]. Fifth, alcohol directly causes release of endothelin-1 and endothelin-2 from vascular endothelial cells,

further contributing to the vasoconstrictor- vasodilator imbalance[85]. Finally, alcohol-induced dysregulation of calcium cycling in vascular smooth muscle cells has been described, thereby impairing vascular relaxation[75].

The treatment of chronic alcohol-related hypertension is, of course, reduction in alcohol use, or preferably, cessation of use[83, 86]. Pharmaceutical approaches that include interference with the renin-angiotensin system and use of calcium channel blockers, both first-line therapies for essential hypertension, are also the drugs of choice here[75].

Stroke

In addition to its association with hypertension, alcohol increases stroke risk, specifically hemorrhagic stroke risk by 14% compared to nondrinkers[87]. This relationship is linear – with greater alcohol consumption leading to greater hemorrhagic stroke risk[85]. It has been suggested that low levels of alcohol consumption may be protective against ischemic stroke, but these studies have been challenged by newer analytical techniques, termed “Mendelian randomization,” that incorporate genetic variants into the model[74].

Mechanisms underlying the increased hemorrhagic stroke risk in people who chronically consume alcohol likely include the vasculopathy attributable to chronic alcohol-induced hypertension, as well as modest changes in hemostatic factors that favor thrombolysis[88].

Myocardial Infarction

Low and moderate levels of alcohol consumption have been associated with decreased atherosclerotic heart disease risk[72, 89, 90]. Again, whether this protective effect will persist when newer analytical approaches are applied is unknown. Although these are population studies that can only demonstrate association, not causation, there are favorable physiologic effects of alcohol that may attenuate atherosclerotic vascular disease, thereby rendering this observation biologically plausible. First of all, as mentioned above, alcohol has favorable effects on the hemostatic system[88]. Secondly, alcohol consumption potentially has anti-inflammatory effects, and of course atherosclerosis has been shown to be an inflammatory process. Alpert and colleagues reported lower C-reactive protein levels in patients who consumed moderate levels of alcohol compared to those who consumed alcohol rarely or not at all[91]. Third, alcohol has been shown to have favorable effects on lipids, including increased levels of high density lipoprotein cholesterol[88], which have been associated with decreased cardiovascular risk. These potentially beneficial effects of alcohol must be understood within the larger picture of alcohol-related disease, especially cancer, infection, and trauma. According to the Global Burden of Disease Study, the level of alcohol consumption that minimized alcohol-related disease was zero[74].

ANABOLIC ANDROGENIC STEROIDS

Anabolic androgenic steroids (AAS) are synthetic androgens derived from testosterone, and are most often used in two settings. First, athletes, especially bodybuilders, may use non-FDA-approved AAS to build lean muscle mass and improve performance. High doses of AAS can be administered orally or through intra-muscular injections, and are commonly used in phases or cycles of 8 to 12 weeks potentially for long periods. AAS in

this setting is associated with increased cardiovascular morbidity and mortality. Secondly, FDA-approved testosterone replacement therapy may be prescribed to treat low testosterone. In older men who may be experiencing erectile dysfunction, fatigue or decreased vigor, this use of testosterone is controversial, and may be associated with increased cardiovascular risk[92, 93]. It should be noted that hypogonadism due to organic causes with documented low testosterone itself is associated with increased cardiovascular risk, and testosterone replacement therapy in this setting is relatively safe. Lifetime prevalence of AAS-use in males is estimated to be 2 to 6%[94, 95].

AAS may increase cardiovascular risk though many mechanisms, including through adverse cardiac remodeling, leading to diastolic dysfunction and sudden arrhythmic death[96, 97]. In this review we will focus on vascular effects that may increase the risk premature atherosclerosis and myocardial infarction[96, 98, 99].

Myocardial Infarction

Acute myocardial infarction is the most common adverse cardiac event related to AAS use reported in the literature, largely through case reports and case series. Cases of acute myocardial infarction with severe premature atherosclerosis, and acute myocardial infarction without any atherosclerosis, perhaps due to vasospasm or microvascular disease, have both been reported[96]. AAS use induces synthesis of an enzyme in the liver, hepatic triglyceride lipase (HTGL), which metabolizes HDL cholesterol. Within days of initiating AAS use, increased HTGL activity results in decreased circulating HDL levels, which nadir at approximately 52% of baseline levels within a few weeks. LDL levels also increase, but not as dramatically (36%)[100]. Additionally, AAS use is pro thrombotic, through direct AAS effects on platelets, but also by inhibiting vascular cyclooxygenase activity[101, 102]. AAS-use effects on the hemostatic and fibrinolytic systems are more complex, but may also tend to increase thrombotic risk[96]. There is some evidence that AAS use leads to endothelial dysfunction, abnormal vascular reactivity and vascular smooth muscle dysfunction. Endothelial dysfunction portends increased risk for atherosclerosis, and future adverse cardiac events, and increased vasoreactivity may predispose to vasospasm[103]. It is uncertain whether this premature vasculopathy is a direct AAS-related effect or is secondary to the adverse lipid profiles seen in AAS use. Importantly, effects on lipids, the hematologic system, and vascular reactivity are largely reversible soon after stopping AAS[96].

OPIOIDS

In 2017, recognizing the widespread misuse of both prescription and non-prescription opioids, the FDA declared a public health emergency to combat the opioid epidemic[104]. In the U.S., there were more than 100,000 overdose deaths, the majority from opioids, and 10.1 million Americans misused prescription opioids last year[104–106]. Fentanyl has been declared “the world’s deadliest opioid”[105]. Fentanyl is the culprit in over half of all overdose deaths in 2020[105]. Despite their devastating effects on health, opioids, including fentanyl, do not have direct vascular toxicity[104]. Intravenous administration of opioids, such as heroin,

do have severe, even life-threatening toxicity, related to increased incidence of endocarditis. This important topic is covered elsewhere in this focus issue of the CJC.

SUMMARY

The acute and chronic vascular effects of drugs of misuse are widespread and clinically important. Acute cannabis use, especially smoked cannabis, has been associated with increased risk for acute myocardial infarction and stroke. Whether it also results in increased risk for atherosclerosis, increasing long term risk for myocardial infarction and stroke similar to the risk associated with combustible tobacco cigarettes, is uncertain. Acute cocaine and methamphetamine use increase risk for acute myocardial infarction, stroke, and aortic dissection. Both drugs also increase risk for chronic vasculopathy, and its sequelae. However, methamphetamine is also likely associated with the development of pulmonary hypertension, whereas this association with cocaine is less secure. Chronic alcohol use is associated with a dose-related increased risk for hypertension and hemorrhagic stroke; although alcohol use has been associated with decreased risk of myocardial infarction, this association has been challenged, and remains uncertain. Anabolic androgenic steroids are associated with accelerated atherosclerosis and premature myocardial infarction. Although many of these drugs of misuse are associated with long-term vasculopathy, it is probable that discontinuing drug use will also eliminate the trigger for many premature cardiovascular events. Possessing a high index of knowledge of potential vascular sequelae of commonly used drugs of misuse is critical for the appropriate diagnosis, therapy and ultimately, referral to addiction medicine services. Finally, from the public health perspective, additional research into the long-term cardiovascular effects of cannabis is critical, since non-medical and medicinal cannabis has been legalized in Canada and most states, its use is widespread, yet its long-term health effects remain unknown.

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Box 1

Smoking Cannabis

- Myocardial infarction
  - Temporally-related
    - "Trigger" for acute MI
    - Increased risk 4.8-fold within 1 hour of smoking
  - Young males
  - Absence of atherosclerosis
  - Proposed mechanisms
    - Vasospasm
    - Microvascular disease
    - Coronary thrombosis
    - Supply-demand mismatch
- Atherosclerosis
  - Uncertain association due to confounding variables (e.g. tobacco smoking)
  - Biological plausibility (smoking > edibles)
    - Oxidative stress and inflammation
    - Endothelial dysfunction
- Stroke
  - Uncommon
  - Temporally-related
  - Young males
  - Ischemic stroke
  - Anterior and posterior circulations
  - Proposed mechanisms
    - Vasospasm
    - Intracranial stenosis
    - Cardio-embolic
    - Carotid dissection/atherosclerosis

Box 2

Cocaine

- Myocardial infarction
  - Young males
  - Accelerated hypertension
  - Accelerated atherosclerosis
  - Proposed mechanisms
    - Vasospasm
    - Supply-demand mismatch
    - Enhanced thrombosis
- Atherosclerosis
  - Accelerated
  - Episodic recurrent hypertension with endothelial damage
  - Endothelial damage promotes ↑fibrinogen, ↑Von Willebrand factor, and ↑platelet aggregation
  - Inflammation (elevated Tumor necrosis factor-α, Interleukin-1β)
- Stroke
  - Young males
  - Temporarily-related
  - 6.4-fold risk within 24 h of cocaine use vs non-users
  - Ischemic > hemorrhagic
  - Associated with all routes, but smoking (“crack”) may pose greatest risk
  - Proposed mechanisms of ischemic stroke
    - Vasospasm in areas of accelerated vasculopathy described above
  - Proposed mechanisms of hemorrhagic stroke
    - Rupture of accelerated vasculopathy described above
- Pulmonary Hypertension (PH)
  - Designated as “possible” risk factor for PH
  - Cocaine promotes release of ROS and ET1, implicated in pathogenesis of PH

Box 3

Methamphetamine

- Myocardial infarction
  - Second leading cause of death in meth users (1st is accidental overdose)
  - Young males
  - Accelerated hypertension
  - Accelerated atherosclerosis
  - Proposed mechanisms
    - Vasospasm
    - Supply-demand mismatch
- Atherosclerosis
  - Accelerated
  - Sustained recurrent hypertension leading to vascular “fatigue” due to long Meth half-life
  - Fibrinoid necrosis of intima and media, destruction of vascular smoot muscle
  - “Beaded” appearance and aneurysmal formation
- Stroke
  - Young males
  - Temporarily-related
  - Greatest risk among drugs of misuse (e.g cocaine, cannabis, other)
  - Hemorrhagic (intracranial or subarachnoid hemorrhage) stroke risk five-fold ischemic stroke risk
  - Hemorrhagic stroke risk two-fold greater than cocaine or tobacco
  - Associated with all routes (oral, injection, inhaled)
  - Proposed mechanisms of hemorrhagic stroke
    - Rupture of accelerated vasculopathy described above
  - Proposed mechanisms of ischemic stroke
    - Vasospasm in areas of accelerated vasculopathy described above
- Pulmonary Hypertension (PH)
  - Designated as “likely” risk factor for PH
  - 30% of “idiopathic” PH patients have history of meth use
  - Lungs have most rapid uptake and highest concentration
  - Meth promotes release of serotonin, reactive oxygen species and endothelin-1, implicated in pathogenesis of PH
  - Polymorphism of of genes associated with reduced methamphetamine metabolism highly prevalent in PH
  - Angiomatoid plexiform lesions with slit-like vascular channels, venocclusive disease on lung pathology

Box 4

Chronic Alcohol Consumption

- Hypertension
  - Dose-related
  - Possible threshold effect (Female > 1 drink/day, Male > 2 drinks/day)
  - Linear relationship
  - Across age, race, and sex
  - Independent of BMI, smoking status, exercise
  - Proposed mechanisms
    - Sympathetic activation
    - Activation of the renin-angiotensin-aldosterone system
    - Oxidative stress
    - Vasoconstrictor-vasodilator imbalance (↓NO, ↑AGII, ↑ET1, ↑20-HETE)
    - Increased intracellular Ca2+ VSMC
- Stroke
  - Hemorrhagic
  - Proposed mechanisms of hemorrhagic stroke
    - Vasculopathy associated with hypertension
    - Modest changes in hemostatic factors
- Myocardial infarction
  - Decreased risk in epidemiological studies (low consumption)
  - Proposed mechanisms
    - Modest changes in hemostatic factors
    - Modest favorable changes in lipid profile
    - Possible anti-inflammatory effect

AGII=angiotensin II, Ca2+ VSMC= calcium in vascular smooth muscle cells, ET1=endothelin-1, 20-HETE=20-Hydroxyeicosatetraenoic acid, NO=nitric oxide

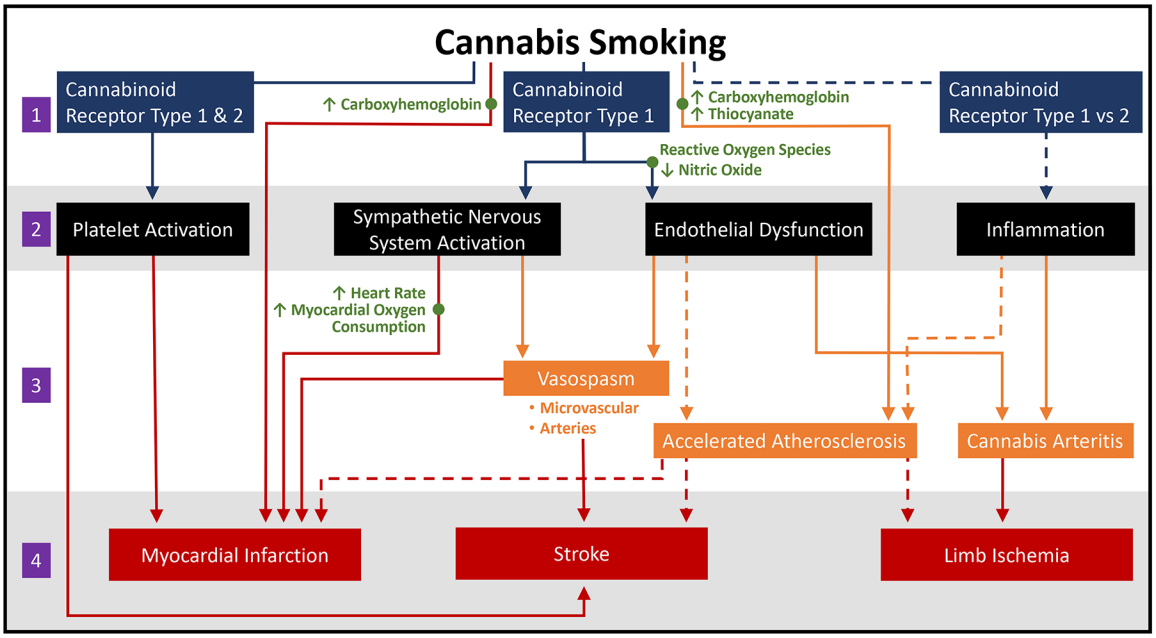

Figure 1.

Cannabis Smoking: Vascular Sequelae and Potential Mechanisms. See text for full discussion. Depending of the frequency and mode of use, acute cannabis has sympathomimetic effects, increasing heart rate and blood pressure. This increase in myocardial oxygen demand is accompanied by decreased oxygen supply due to vasospasm and elevated carbon monoxide levels (combusted cannabis). Cannabinoid 1 (CB1) receptors on platelets and vascular endothelial cells may lead to platelet activation and thrombosis, inflammation and endothelial dysfunction. These factors likely underlie the increased risk for acute myocardial infarction and stroke that occur soon after cannabis use, often in young people without cardiac risk factors. Whether cannabis, especially the cannabis available today with its marked high concentrations of delta-9-tetrahydrocannabinol, increases risk of accelerated atherosclerosis and the entity of cannabis arteritis, remain uncertain, and deserves further study.

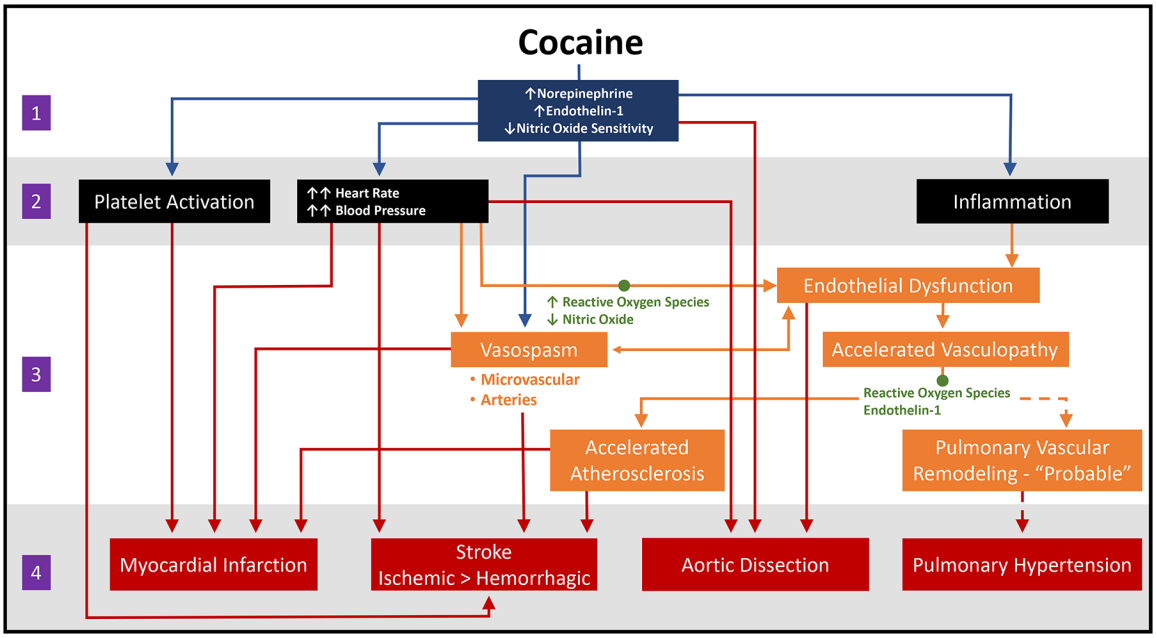

Figure 2.

Cocaine Use: Vascular Sequelae and Potential Mechanisms. See text for full discussion. Cocaine blocks norepinephrine re-uptake, leading to marked increases in heart rate and blood pressure. Increased norepinephrine may be accompanied by increased endothlin-1 release and decreased nitric oxide availability, and may promote increased platelet aggregation. These acute effects may precipitate acute myocardial infarction, stroke, and less commonly aortic dissection. Oxidative stress and inflammatory pathways are activated which may lead to endothelial damage, and over time, accelerated vasculopathy. This in turn, may lead to accelerated atherosclerosis and long-term increased risk for myocardial infarction or stroke, and possibly pulmonary hypertension.

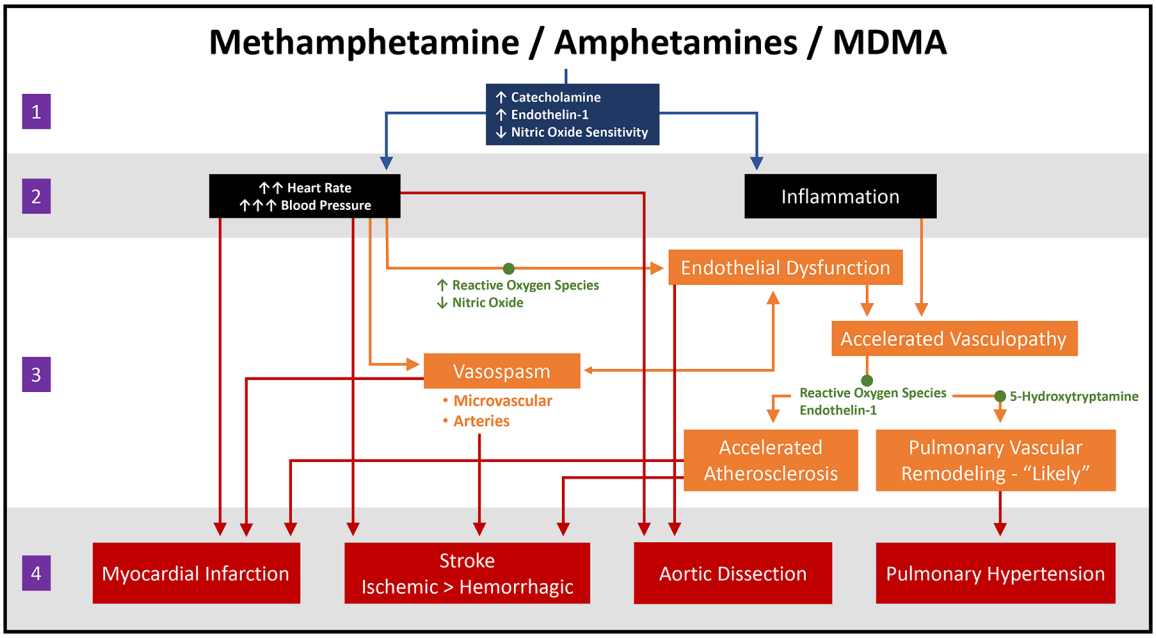

Figure 3.

Methamphetamine Use: Vascular Sequelae and Potential Mechanisms. See text for full discussion. The underlying pathophysiology and vascular sequelae are very similar to those of cocaine use, with some important differences. The half-life of methamphetamine is longer than cocaine, perhaps contributing to the more severe vasculopathy and increased risk for hemorrhagic stroke compared to cocaine. Additionally, methamphetamine use is associated with an increased risk for pulmonary hypertension, which is both irreversible and associated with a worse prognosis (even on therapy) compared to pulmonary hypertension from other causes.

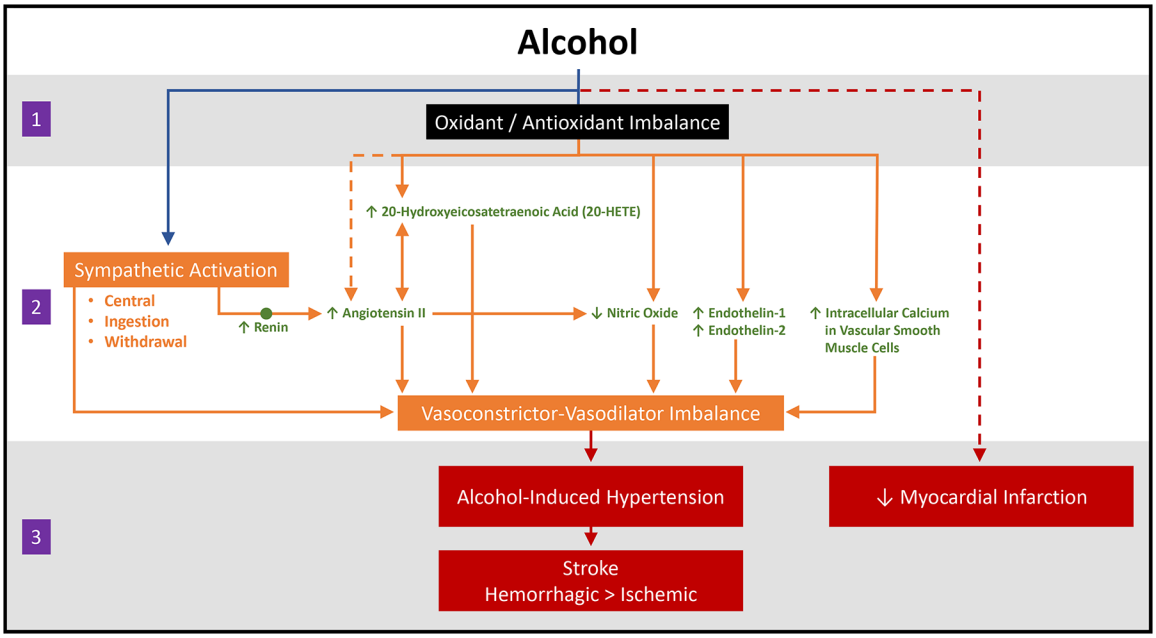

Figure 4.

Alcohol-induced Hypertension: Potential mechanisms. See text for full discussion. Alcohol acutely increases sympathetic nerve activity and increases renin and angiotensin II levels. Through metabolism of alcohol, reactive oxidative species are generated, leading to further increases in angiotensin II, production of 20-hydroxyeicosatetraenoic acid (20-HETE), endothelin 1 and 2, and a reduction in NO availability, creating a vasoconstrictor-vasodilator imbalance. Additionally, alcohol may cause dysregulation of calcium cycling in vascular smooth muscle further increasing vasoconstriction. Alcohol-induced hypertension increases risk of hemorrhagic stroke. Conversely, through antithrombotic, and potentially anti-inflammatory effects, and favorable effects on lipids, alcohol may be associated with a lower risk of myocardial infarction, although this association has been challenged.