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Clinical Characteristics and Angiographic Findings of Acute Myocardial Infarction Associated With Marijuana Use: Consecutive Case Series

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Abstract

Background—Marijuana use has been increasingly legalized in the United States resulting in substantial rise in the number of users especially in the younger populations. While our group and others had described various metabolic effects of this drug, little is known about its association with acute myocardial infarction.

Objective—To present a series of 8 patients with 10 events of ST-elevation MI (STEMI) associated with marijuana use; highlighting their demographic, clinical presentation, laboratory results and angiographic characteristics.

Methods—Retrospective chart review of patients with STEMI presenting to our inner city hospital Coronary Care Unit over a period of 4 years (December 2013–April 2017).

Results—Of the 10 case subjects studied who presented with chest pain, EKG evidence of STEMI with cannabis use, mean age at presentation was 40.1 ± 9.7 (years) SD, ranging from 26 to 59 years old. There were 9 males and one female, of them, 8 were Black, 2 Hispanic and 1 White. Of the 10 cases, 3 (30%) had no known cardiovascular disease (CVD) risk factors (RF) on admission, 1 patient had 3 RF, 4 patients had 2 RF and 2 had 1 CVD RF, which included age, diabetes mellitus type 2 (DM2), hypertension, dyslipidemia, smoking, and family history of premature coronary heart disease. Troponin I (cTnI) peak mean level was 93.5 ± 34.35 ng/ml, range 7.86 – 358.0 ng/ml. All patients had angiographic evidence of obstructive coronary angiography.

Conclusion—In our study, marijuana use is associated with ST-elevation MI in largely minority population, occurring at a relatively younger age with half of the cases either low risk or CVD risk free. Additional studies are needed to further characterize this population given the increase in marijuana use.

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Introduction

As of January 1, 2017, the use of both recreational and medical cannabis has been legalized in 8 states (Alaska, California, Colorado, Maine, Massachusetts, Nevada, Oregon and Washington) and the District of Columbia in the United States [1]. With the increasing legalization of the drug, the use of marijuana has also been on the rise. A recent study has suggested that longer-term moderate/heavy marijuana use during early and late 20s is associated with negative health outcomes at age 50 [2]. Recreational use of marijuana is also associated with ethnic identity amongst minority youth population, adding complexity to the extent of drug usage in communities with diverse backgrounds [3]. With the rising use and demand for marijuana, commercial preparations containing synthetic cannabinoids have also rapidly emerged in the recent past. A recent study found that although it is often assumed to be a safe and legal alternative to marijuana, due to its enhanced metabolic toxicity, it should not be considered a safe alternative [4]. Due to the recent trend towards legalization of marijuana it is imperative to understand the impact of marijuana use on health outcomes. The scientific evidence on the effect of marijuana use on health outcomes is limited and is an area of active research.

Cardiovascular disease (CVD) is the number one cause of death in the United States with 1 in every 4 death is attributed to CVD [5]. It includes coronary artery disease (CAD), including myocardial infarction (MI), hypertension, congestive heart failure (CHF), arrhythmias, peripheral vascular disease (PVD) and strokes. Majority (70%) of CVD risk are attributable to modifiable risk factors, such as obesity and cigarette smoking [6]. The effect of marijuana use on CVD is largely unknown.

It should be noted that racial and ethnic differences have been observed in CVD. The prevalence of CVD and its many risk factors is disproportionately higher in black population compared to other ethnic groups [7]. There are many proposed hypotheses as to why these discrepancies may exist, including poor access to health care services, non-adherence to treatment recommendations, inadequate training and environmental and genetic variations [7,8]. It is also interesting to note that marijuana use was significantly higher amongst black Caribbean adolescents, compared to other ethnicities in a study conducted in an urban setting in UK [9].

In this article, we report a case series of acute myocardial infarction (MI) associated with the use of marijuana in an urban population with large black Caribbean representation.

Methods & Materials

Retrospective review of the electronic medical record was performed within the study period from 12/1/2013 to 04/05/2017. Patients were identified through their name, medical record number and primary diagnosis of ST elevation myocardial infarction (STEMI).

Inclusion criteria for STEMI was defined as ST elevation of 2mm or more on minimum of two contiguous leads. In addition, all study subjects in our study required a positive toxicology screen for cannabis at the time of admission. Cases included also had negative toxicology for stimulants. Baseline characteristics for each subject were collected from the

electronic medical record for age, sex, race, vital signs, laboratory values and medical co-morbidities at the time of presentation. Medical management provided during hospitalization prior to cardiac catheterization was recorded. Angiographic findings including anatomic and flow characteristics were also obtained after percutaneous interventions were performed appropriately.

Data was analyzed using SPSS version 21 and presented as mean ± SD. Chronicity of cannabinoid use was not considered as one of the variables for the study, as that information was not available through retrospective chart review.

We have identified 10 cases of STEMI with concomitant use of marijuana in our study period. Details on characteristics of each case are presented in the results section.

Results

Baseline characteristics

In this study, the average age in years for our case subjects was 40.1 ± 9.7 SD, ranging from 26 to 59 years old. Among the 10 STEMI cases in our study, 9 out of the 10 cases were male. It is important to mention that 2 male patients presented twice with 1 year or more in between their initial STEMI diagnosis; given the difference in time and treatment received, they will be counted as different case subjects unless stated otherwise. In terms of categorization, 2 cases were Hispanic, 1 white, and 7 black. Black patients tended to be younger than Hispanics at presentation (average age 38.1 vs 45.5 years old). In addition the black population had increased comorbidities, including HTN, HLD, and obesity when compared to non-black participants in the study. Although the majority of case subjects presented with elevated glucose levels, only 1 patient had a concurrent diagnosis of diabetes mellitus (DM) type 2, rest of subjects had A1C levels less than 7.0% and no known history of DM. Baseline kidney function estimates did not revealed chronic kidney disease (CKD) on any of the subjects as presentation. At admission, all of our case subjects denied family history of CAD and 8 out of 10 admitted to current tobacco smoking at the time of admission.

Baseline characteristics of case subjects	**Total**
	Values are mean ± SD or n (percentage %)
Number of cases	10
Median age in years	40.1 ± 9.7
Sex	
Male	9 (90)
Female	1 (10)
Race	
White	1 (10)
Black	6 (60)
Hispanic	2 (20)

Baseline characteristics of case subjects	Total
Comorbidities	
Hypertension	3 (30.0)
Hyperlipidemia	6 (60)
Diabetes Mellitus (uncomplicated)	1 (10)
Depression	2 (20)
obesity BMI>30	1 (10)
tobacco smoker	8 (80)
family history CAD	0
Blood pressure at presentation to ED	
Systolic blood pressure	127 ± 22
Diastolic blood pressure	83 ± 14

Risk for Coronary Heart Disease (CHD)	Column1
Atherosclerotic Cardiovascular Disease (ASCVD) 10- year risk	11.94% ± 0.12
Framingham 10- year risk	9.11% ± 0.09

Risk for Coronary Heart Disease (CAD)

Age criteria for calculating the 10- year risk score known as Framingham “Hard” Coronary Heart Disease was met by 8 out of the 10 subjects. Calculated scores range from 1.70% to 21.30%, with a mean risk score equivalent to 9.11% ± 9% SD. We also calculated the Atherosclerotic cardiovascular disease (ASCVD) 10-year risk score in patients that met age criteria for its calculation. Out of the 6 cases that were eligible for risk score analysis, the score when translated into risk percentage was from 2.70% to 29.20% with a mean average of 11.94% ± 12% SD. High risk CVD individuals are those with 10% 10-year risk for a hard CHD event using the ATP III Framingham Risk calculator, equivalent to 15% ASCVD risk, assuming the risk for stroke represents approximately one third of ASCVD events [10–15]. The threshold of 15% 10-year risk for a hard ASCVD event using the ACC/AHA Pooled Cohort Equations is higher than that recommended by the ACC/AHA for identification of a primary prevention statin benefit group (i.e. 7.5% or higher) [10, 12–15]. Based on these risk classifications, out of the five subject that ASCVD was calculated 2 had ASCVD >15% and of the 7 that we calculated Framingham score only 2 had Framingham score >10%.

Admission labs

Blood samples were collected on all study subjects on arrival to our Emergency Room at the time of triage prior to admission for acute coronary syndrome (ACS). Samples were analyzed for basic serum electrolytes and complete blood panel levels. The following are their average values with their corresponding standard deviation: sodium 136 ± 2 mEq/L, potassium 4 ± 0.4 mEq/L, chloride 103± 3.8mmol/L, bicarbonate 23 ± 3.7 mmol/L, BUN 15 ± 3.5 mg/dL, creatinine 1.0 ± 0.1 mg/dL, and glucose 154 ± 33.6 mg/dL.

Troponin peak

All patients underwent serial troponin I testing on hospital arrival as part of his or her diagnostic workup. Peak troponin levels ranged from 7.86 to 358 between the case subjects with an average peak of 93.5 ± 34.35 SEM ng/ml.

Initial test results at admission	Results
Na	136 ± 2.1
K	4 ± 0.4
Cl	103 ± 3.8
HCO3	23 ± 3.7
BUN	15±3.5
Cr	1 ± 0.1
Glu	154 ± 33.6
WBC	12.5± 5.6
Hgb	14.7 ± 1.8
Plt	280 ±64.5

Management received prior to undergoing cardiac catherization	Total
Statin	2 (20)
Beta Blocker	3 (30)
ACEi	2 (20)
Aldosterone Antagonist	1 (10)
Calcium Channel Blocker	1 (10)
ASA	10 (100)
P2Y12 Inhibitors	10 (100)
Heparin	10 (100)

Management received during hospitalization prior to undergoing cardiac catheterization

All patients in the study received aspirin, heparin and P2Y12 inhibitors after the diagnosis of STEMI was made. 2 of the 10 subjects were already on ACEi and statins at the time of STEMI diagnosis. Only 3 out of the 10 cases received beta- blockers (BB), if adjusted by race, 29% of blacks, 0% white, and 50% Hispanics received BB treatment prior to elective cardiac catheterization. The only female in our study did not received BB, statin, angiotensin converting enzyme inhibitor (ACEi), aldosterone antagonists or calcium channel blockers (CCB) when compared to the male counterpart prior to angiography.

Values are mean ± SD or n (percentage %)

*One case subject had lesions located at mid and distal LAD; they are counted separate for statistics reasons.

Diagnostic testing

All patients received EKG testing after targeted history was obtained on arrival to the ED. Diagnosis of STEMI was made after ST elevations were recorded on EKG tracing with a chief complaint of typical cardiac chest pain. On evaluation, ST elevations for all subjects on precordial or limb leads ranged from 2mm to 6mm with a mean of 3mm ± 1.5 SD. Once STEMI was diagnosed each patient underwent diagnostic and/or therapeutic cardiac catheterization. 8 out of the 10 subjects had thrombus seen on affected arteries, 1 subject had evidence of vasospasm and 1 subject did not revealed either thrombus or vasospasm during the study. The most common vessel involved was the left anterior descending (LAD) artery with 3 cases involving its mid section, 3 involving its distal segment and only 1 involving its proximal region. 1 case revealed occlusion at the first obtuse marginal artery and 1 case subject had a lesion identified in the right coronary artery at its proximal section. Occlusion of all involved arteries averaged 95% ± 9% SD, ranging from 90% to 100% within all cases studied. Left ventricular ejection fraction (EF) as determined by cardiac echocardiogram ranged from 15% to 60%, with a mean of 43%. Four out of the ten cases had a reduced ejection fraction at or below 39%. One of the ten had an EF moderately reduced in the range of 40 to 49%. Five out of the ten cases had preserved ejection fraction ranging above 50 percent. Of the subjects with EF below 39%, only 1 had a severely depressed EF of 15%, this measurement comes from a subject's second infarct 1 year after his first STEMI, both times he tested positive for marijuana. Finally, the presence or absence of angiographic coronary collaterals and the grade as defined by Rentrop classification was determined for all subjects. Two of our subjects revealed grade 1 collaterals with the rest showing grade 0 collateral circulation. Both cases with grade 1 collaterals were in lesions located at LAD artery.

Diagnostic testing results	**Column1**
HDL	44 ± 15.8
Total Cholesterol	210 ± 33.3
Troponin I (peak)	93.5 ± 34.35
Total lesions identified	11
***Lesion site**	
Proximal LAD	3 (27)
Mid LAD	3 (27)
Distal LAD	2 (18)
Tubular LAD	1 (9)
Proximal RCA	1 (9)
Distal RCA	0
OM - 1	1 (9)
Lesion occlusion severity	95% ± 9
Coronary collateral circulation	
Grade	
0	8 (80)

Diagnostic testing results	Column1
1	2 (20)
2	0 (0)
3	0 (0)
LVEF	43.1 % ± 15

Discussion

The average age at which MI occurred in this case series was 40.1 ± 9.7 SD years. It should be noted that only 0.3 percent of the population diagnosed with MI range between the ages of 20 to 39 years old. Though the incidence of MI is higher in the Black population, it still remains a rare occurrence in younger patients. Black males suffer from MI at an incident rate of 2.2 per 1,000 person years [16]. This could potentially highlight the early onset of cardiovascular harm of marijuana use.

Myocardial effects result from alterations in coronary blood flow and heart rate promoting myocardial ischemia and potential infarction [17]. Short-term activation of CB_1 receptor from marijuana smoking has been shown to increase the risk of acute MI by 5-folds in the first hour after smoking and then declined rapidly after the initial hour [18]. Myocardial oxygen supply is also restricted by an increased concentration of carboxyhemoglobin leading to a reduction in oxygen carrying capacity of red blood cells [18]. Further exacerbating the myocardial oxygen supply are elevations in both heart rate and blood pressure, resulting in reduction of diastolic coronary filling and elevated diastolic coronary pressures. Therefore, the reduction in coronary blood flow in combination with reduced oxygen carrying capacity and potential systemic and coronary vasoconstriction lead to an increase in myocardial oxygen supply-demand mismatch, resulting in ischemia and infarction [18].

Additionally, intravascular ultrasounds on patients experiencing THC associated myocardial infarction usually find no evidence of atherosclerotic CAD. Coronary angiography usually confirms coronary vasospasm and platelet thrombus formation without underlying atherosclerosis [19]. Our angiography results showed no evidence of underlying atherosclerotic CAD. 80% of the individuals were found to have thrombus formation as the primary cause of MI. Additionally, the acuity of the MI was exacerbated by lack of collateral circulation. The lack collateral circulation observed could stem from the fact that the individuals did not have underlying chronic CAD as is evident with relatively low Framingham Coronary Heart Disease. The additives effect of acute thrombus formation with poor collateral circulation could explain the high peak troponin levels (93.5 ng/ml ± 34.35 SEM) and acute depression in ejection fraction (43.1 ± 15%) despite minimal underlying CAD.

There is increasing body of literature that supports the observed thrombus formation with marijuana use. Cannabinoids have been found to induce significant amount of arachidonic acid production in human platelets [20]. In addition, studies in ram and sheep models

showed THC as potentiator of cyclooxygenase 1 and 2 (COX-1, COX-2) leading to thromboxane A2 and subsequent prostaglandin production [21]. These findings are significant as both arachidonic acid and COX are pro-inflammatory molecules that can lead to endothelial injury, platelet activation, vasoconstriction and subsequent rise in the risk of cardiovascular event.

THC also induces CB_1 and CB_2 activation that has been shown to activate platelet aggregation via increased platelet Glycoprotein IIa/IIIb and P-selectin expression [22, 23]. Additionally, THC associated increase in inflammation leads to production 2-Arachidonoylglycerol (2AG) that serves as a precursor Arachidonic Acid [22]. Initial effects of 2-AG on platelet aggregation begin with Phosphotidylinositol 3 Kinase/AKT pathway leading to myosin light chain kinase phosphorylation and subsequent actin polymerization that result in conformational changes in platelet structure. Additionally, the conformation changes result in ATP secretion and 2-AG mediated platelet aggregation [24]. One study investigating 2-AG mediated platelet aggregation showed retardation in platelet aggregation in subjects being treated with aspirin and/or Plavix. The same study also showed subjects on Aspirin and/or Plavix had minimal THC induced platelet aggregation, highlighting the potential clinical benefits of antiplatelet therapy in potentially preventing THC induced myocardial ischemia and infarction [25].

The lack of observed CAD in the study can also be supported with the relatively low rates of DM2. Effect of chronic marijuana use on insulin secretion was investigated by Muniyappa et al using C-peptide deconvolution and oral glucose tolerance test modeling, total insulin secretion, β-cell glucose sensitivity, rate sensitivity, and potentiation of insulin secretion. From the study results, chronic marijuana smoking does not appear to affect glucose sensitivity in peripheral tissues and pancreatic β-cell function, leading to normal glucose tolerance in long-term heavy users [26].

Moreover, it is interesting to note that obesity prevalence in the study population was 10%. This observation is supported by the results from CARDIA and NHANES III studies suggesting the association between marijuana use and lower BMI with lower abdominal fat content [27, 28]. However, upon further investigation of relative amount of abdominal fat distribution, a study conducted by Muniyappa et al. has found that marijuana smokers had significantly higher visceral fat content, as opposed to subcutaneous fat, when compared with nonusers [26]. This finding is significant because the ratio between visceral adipose tissue and subcutaneous adipose tissue is an independent predictor of cardiovascular events, irrespective of presence of risk factors [29].

National statistics show that among non-Hispanic black men and non-Hispanic black women, the age-adjusted prevalence of hypertension was 44.9% and 46.1%, respectively[16]. It was demonstrated that THC binds the PPARγ receptor leading to short term increase in superoxide dismutase activity and bioavailability of nitric oxide, a potent vasodilator [30]. Conversely, long term THC use has been associated with increased peripheral vascular resistance [31]. The proposed mechanism resulting in vasoconstriction with chronic THC exposure is related closely to increase in vasoconstrictive prostanoids and antagoinism of endogenous vasorelaxing endocannabinoid anandamide [30–33].

Vasoconstriction may also be affected by the properties of the vessel itself. In vessels where the predominant vasodilating factor is Endothelium-derived Hyperpolarizing Factor, THC inhibits vasodilation and promotes vasoconstriction. Further, it should be noted that alterations in sympathetic tone may play a role in variable vasoactive effects of THC [34]. THC mediated vasoconstriction was inhibited in the rabbit ear artery with denervation and alpha adrenergic blockade, underscoring the potential sympathetic effects of THC.

Out of the 5 subject that ASCVD was calculated 2 had ASCVD >15% and of the 7 that we calculated Framingham score only 2 had Framingham score >10%. Moderate risk approximately is those with 5% to 15% 10-year risk for an ASCVD event [10]. Majority of our subjects were moderate risk. It has been suggested that in select moderate risk subjects quantitative risk scoring evaluation of one or more additional risk indicators may be performed to identify those who should be reclassified as high risk [10]. Such additional risk factors include cigarette smoking, LDL >190 mg/dL. It remains to be seen whether marijuana use should be considered an independent risk factor. Moreover, It has been suggested that cannabinoid-induced activation of G-protein coupled receptor 55 (GPR55) results in increased IL-12 and TNF-α, which in turn raises endocytic activity in monocytes, potentially leading to foam cell formation and atherosclerosis [35]. It has also been suggested marijuana's action on promoting the release of C-Reactive Protein (CRP). The JUPITER trial highlighted the importance of CRP reduction with statin use in patients with normal metabolic profiles. Statin use in those with elevated CRP, but normal LDL, showed reduction in fatal and non-fatal MIs. Further, those on a statin also had reduced need for coronary interventions. Therefore, it remains to be seen whether those with CRP elevation resulting from marijuana use can benefit similarly from statin use [36, 37].

Some limitations of our study include the relatively small sample size, confounding factor of tobacco smoking, and predominantly unknown family health history in the study population. Furthermore, the last known time of marijuana use could not be ascertained as this was a retrospective analysis, though all subjects had positive urinary toxicology for THC and negative for other stimulants or substances. Additionally, the chronicity of marijuana use could not be established given the retrospective analysis.

In conclusion, acute MI is an increasingly recognized cardiovascular consequence of marijuana use, especially in the urban population. The characteristics of acute MI in this study show that they occur in relatively young individuals, with low or no pre-existing coronary burden and relatively low Framingham risk scores. Most of the individuals suffered from acute thrombus formation in the coronary system. Myocardial damage was likely exacerbated by the lack of collateral circulation, represented by reduced EF and high peak troponin levels. Given the rising use of marijuana with its concurrent steps for its legalization in the US it is imperative to understand the potential harms of marijuana use. Further studies are needed to understand the interaction between THC, metabolic derangements, inflammation, vasoreactivity, platelet aggregation that result in myocardial ischemia and infarction. Efforts to meticulously characterize patients at risk to suffer from myocardial infarction associated with THC are needed. Additionally, understanding the biochemical pathways involved can help guide therapies. The role of antiplatelets, statins, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitor in primary

and secondary prevention remains to be seen. Such measure will allow better understanding of the pathophysiology and potential prevention strategies of THC associated myocardial infarction.

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