Abstract

Background: Marijuana is the most commonly used illicit drug in the United States. Current research has yet to come to a consensus on its association with acute coronary syndrome (ACS). Herein, we aimed to analyze how marijuana use relates to acute ST elevation myocardial infarction (STEMI) and non-STEMI (NSTE-MI).

Methods: Using a retrospective study design, we gathered data from August 2014 to September 2020 on all percutaneous coronary interventions (PCIs) done at Brookdale University Hospital Medical Center (BUHMC) in patients with NSTEMI and STEMI. To compare marijuana users (MUs) with non-users, t-tests and Chi-square tests were used. A total of 195 patients were included, with mean age at presentation of 47 years old; 59 were females (30.3%) and 136 were males (69.7%). We identified 37 patients who were MUs. MUs were younger than non-users (P < 0.01), had higher rates of alcohol (P = 0.025), opiate (P = 0.004) and cigarette (P ≤ 0.001) use. On admission, MUs had lower creatinine (P = 0.031), blood urea nitrogen (BUN) (P = 0.031), pro-B-type natriuretic peptide (BNP) (P = 0.052), BMI (P = 0.014) and lower right coronary artery (RCA) disease (P = 0.026).

Results: After logistic regression analyses, results showed that the severity of coronary artery disease (CAD) and admission diagnosis of STEMI or NSTEMI were not found to be significantly related to marijuana use. Age, alcohol, cigarette, creatinine, BUN, BNP, BMI and RCA disease were significantly related to marijuana use. There was a negative correlation between marijuana use and RCA disease (MUs = 29.7% vs. non-users = 50%, P = 0.026). There was no significant association with STEMI, NSTEMI or the severity of CAD.

Conclusion: As daily cannabis use is on the rise, more researches are needed to further determine the effects of marijuana use on CAD.

Keywords: Marijuana; STEMI; NSTEMI; ACS

Introduction

Approximately 80 years ago, prohibition of marijuana use began when the federal government banned the sale, cultivation and use of the cannabis plant. In fact, up until today, it is illegal under federal law for any purpose under the Controlled Substances Act (CSA) of 1970 [1]. Today, marijuana has become the most commonly used psychoactive illicit drug in the United States [2]. The use of recreational marijuana is legalized in 16 states and three territories, and the use of medical marijuana is legalized in 36 states and four territories [3]. There is a concern about the cardiovascular effects of both marijuana and synthetic cannabinoids, most commonly called K2 or 52 spice. There is increased use of K2 due to its non-detectability in the urine drug screen and increased availability on the internet and in special shops [4]. The main culprit for both marijuana and K2’s cardiovascular effects is Δ9-tetrahydrocannabinol (THC) which has been shown to be a major stimulant of the sympathetic nervous system through the release of norepinephrine [4]. THC causes vasoconstriction, increased heart rate, blood pressure and cardiac output, all of which increase the oxygen demand of the myocardium [4]. Also, the cannabinoid receptors, CB1 and CB2, are well known to have an important impact on cardiovascular diseases such as atherosclerosis and acute myocardial infarction (MI) because of their impact on inflammatory processes in the pericardial adipose tissue [5]. In the early 1990s, the average THC content was about 3.7% and today, marijuana extract contains over 50-80% [6]. Their thrombotic effect, which remains controversial, was described as their potential to increase platelet aggregation and platelet expression of glycoprotein IIb-IIIa and P-selectin, rendering them pro-coagulant factors [7]. Also, the platelet membrane was found to be positive with CB1 and CB2 receptors. THC is known to stimulate the sympathetic nervous system, inhibit the parasympathetic nervous system and lead to an inflammatory response in the arterial wall which causes erosion and thrombus formation [8, 9]. Despite the growing body of evidence on marijuana use and its cardiovascular effects, the current data are conflicting and contradictory. Also, while most research studies describe cases of MI due to acute coronary vasos-
Materials and Methods

We reviewed all cardiac catheterizations cases at Brookdale University Hospital Medical Center (BUHMC) between August 2014 and September 2019. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. After obtaining approval from the Institutional Review Board (IRB), we collected our data from centricity and EPIC using search criteria, including dates of procedure and indications for the procedure. Patients with missing and incomplete data were excluded from the study. From this list, we excluded patients older than 60 years old as the elderly population is particularly susceptible to cardiovascular disease and age is a known independent factor. We then divided them into two groups: 1) Patients who were positive for marijuana use based on self-reported use and/or positive urine toxicology for cannabinoids; and 2) Patients who did not report any marijuana use and were negative for cannabinoids in their urine toxicology test.

BUHMC is a large metropolitan non-profit hospital that serves residents who are primarily from East and Central Brooklyn, more specifically Brownsville, Canarsie, Flatlands and East New York. Most are African American (AA), Hispanic, foreign-born and most have predominantly low income with 50% receiving government income support. The subjects from this study included 195 patients admitted through the emergency department (ED). Their age ranged from 37 to 60 years old with a mean of 47.68 years (standard deviation (SD) = 6.80). There were 59 (30.3%) female patients and 136 (69.7%) male patients. Of the 195, 125 (64.1%) reported themselves as AA, 38 (19.5%) as Hispanic, 14 (7.2%) as Caucasian, nine (4.6%) as Asian, and nine (4.6%) as others. Our study group were MUs (n = 37) and our control group were non-users (n = 158). All patients had either an acute STEMI or NSTEMI and were found to have positive angiographic findings and required PCI.

Inclusion criteria for STEMI were defined as ST elevation of 1 mm or more on at least two contiguous leads (except for leads V2-V3 which should be at least 1.5 mm depending on age and gender). NSTEMI was defined as an elevation in troponins without any ST segment elevation noted on the electrocardiogram (ECG). The exclusion criteria included 18 patients with missing and incomplete data.

All patients were measured on 30 medical and demographic variables. Each patient’s age, ethnicity, and gender were recorded. The medical variables were the following: troponin on admission, peak troponin level, systolic blood pressure, diastolic blood pressure, low-density lipoprotein (LDL), cholesterol, platelets, creatinine, blood urea nitrogen (BUN), hemoglobin (Hb), potassium, pro-B-type natriuretic peptide (PBNP), A1c, ejection fraction (EF), body mass index (BMI), diagnosis (NSTEMI or STEMI), angiographic findings (which included three categories: left anterior descending artery (LAD), right coronary artery (RCA) and circumflex (Cx)), coronary artery disease (CAD), congestive heart failure (CHF), diabetes (DM), cocaine use, opiate use, cigarette use, alcohol use, marijuana use, severity of disease (one diseased coronary artery = non-severe and ≥ 2 diseased coronary arteries = severe) and white blood cell count (WBC).

The major purpose of the current study was to determine if there was a relationship between marijuana use and cardiac disease. In an attempt to equate groups of variables that might confound this relationship, it was decided to compute propensity scores and use them to control for potential confounding variables. To determine which variables could be used to compute propensity scores, univariate analyses were computed testing the difference between MUs and non-users on each of the cardiac and demographic variables. Alpha for each analysis was set at 0.10 given that this was an exploratory study and we wish to maximize the possibility of finding important covariates.

### Table 1. A Comparison of Marijuana Users With Non-Users on Age, BMI, Cardiac Measures, and Substance Use

| Variable          | Marijuana users (n = 67) | Non-users (n = 158) | Tests results |
|-------------------|-------------------------|---------------------|---------------|
| Age               | M = 42.95; SD = 8.48    | M = 48.73; SD = 5.86 | t = 4.93, df = 193, P < 0.001 |
| PBNP              | M = 690.28; SD = 1,136.80 | M = 2,904.95; SD = 14,031.72 | t = 1.96, df = 165.0360, P < 0.052 |
| BMI               | M = 27.93; SD = 6.03    | M = 30.82; SD = 6.44  | t = 2.49, df = 193, P < 0.014 |
| RCA               | 29.7%                   | 50.0%               | Chi-square (df = 1) = 4.96, P = 0.026 |
| Opiate use        | 48.6%                   | 24.7%               | Chi-square (df = 1) = 8.32, P = 0.004 |
| Cigarette use     | 67.6%                   | 27.8%               | Chi-square (df = 1) = 20.69, P ≤ 0.001 |
| BUN               | M = 13.90; SD = 6.40    | M = 17.00; SD = 12.00 | t = 12.19, df = 103.62, P = 0.031 |
| Creatinine        | M = 1.45; SD = 2.50     | M = 0.98; SD = 0.50  | t = 2.18, df = 191.02, P < 0.031 |
| Alcohol use       | 35.1%                   | 18.4%               | Chi-square (df = 1) = 5.00, P = 0.025 |

*Separate variance t-test was used to compare groups. PBNP: pro-B-type natriuretic peptide; BMI: body mass index; RCA: right coronary artery; BUN: blood urea nitrogen; SD: standard deviation.*
The results of the logistic regression indicated that the overall model was significant (likelihood ratio Chi-square (df = 7) = 71.746, P < 0.001). After examining the results for each covariate, it was found, as with the previous analysis, that only RCA, opiate use, cigarette use, age, and BMI were significantly related to marijuana use controlling for all other covariates in the model.

In order to determine whether marijuana use was related to cardiac disease, using the propensity scores that were computed dropping, BUN, PBNP and creatinine, two logistic regressions were run, one for each of the measures of cardiac disease, severity of disease and diagnosis which determined the presence of a STEMI. For severity of disease, the logistic regression was significant (likelihood ratio Chi-square (df = 2) = 8.074, P = 0.018). Again, only the propensity score predicted severity of disease significantly, controlling marijuana use. For diagnosis, the logistic regression was not significant (likelihood ratio Chi-square (df = 2) = 1.094, P = 0.579). Neither propensity score nor marijuana use significantly predicted the presence of a STEMI. It appears that dropping PBNP, BUN, and creatinine did not change the results of the analyses and confirms the previous findings that this study does not provide evidence that marijuana use is significantly related to cardiac disease.

### Table 2. Results of the Logistic Regression for Computing Propensity Scores

| Step 1   | B        | SE    | Wald  | df | Sig.    | Exp(B) |
|----------|----------|-------|-------|----|---------|--------|
| Age      | -0.172   | 0.040 | 18.762| 1  | < 0.001 | 0.842  |
| BNP      | 0.000    | 0.000 | 0.349 | 1  | 0.554   | 1.000  |
| BMI      | -0.137   | 0.043 | 10.033| 1  | 0.002   | 0.872  |
| RCA (1)  | -1.312   | 0.508 | 6.657 | 1  | 0.010   | 0.269  |
| Opiate (1)| 2.184    | 0.563 | 15.030| 1  | < 0.001 | 8.883  |
| Cigarette (1) | 2.125 | 0.530 | 16.076| 1  | < 0.001 | 8.370  |
| BUN      | 0.024    | 0.048 | 0.256 | 1  | 0.613   | 1.025  |
| Creatinine | -0.115  | 0.358 | 0.104 | 1  | 0.748   | 0.891  |
| ETOH (1) | 0.131    | 0.542 | 0.059 | 1  | 0.809   | 1.140  |
| Constant | 8.973    | 2.418 | 13.765| 1  | < 0.001 | 7.883.861|

BNP: B-type natriuretic peptide; BMI: body mass index; RCA: right coronary artery; BUN: blood urea nitrogen; ETOH: ethyl alcohol.

### Results

The results for the univariate tests where the P value was 0.10 or less are presented in Table 1.

The results of the univariate analyses indicated that MUs were younger than non-users. They had lower creatinine, BUN, PBNP, BMI scores and RCA disease and higher use of opiates, cigarettes, and alcohol.

In order to determine whether marijuana use was related to cardiac disease, two logistic regressions were run, one for each of the measures of cardiac disease, severity of disease and diagnosis which determined the presence of a STEMI. For severity of disease, the logistic regression was significant (likelihood ratio Chi-square (df = 7) = 71.746, P < 0.001). After examining the results for each covariate, it was found, as with the previous analysis, that only RCA, opiate use, cigarette use, age, and BMI were significantly related to marijuana use controlling for all other covariates in the model.

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### Discussion

The cardiovascular effects of the cannabinoids result mainly from the activation of the sympathetic nervous system by releasing norepinephrine. Norepinephrine was found to rise substantially at 30 min after marijuana consumption and induce tachycardia which may last up to 1 h [10]. It also increases blood pressure, cardiac workload, and myocardial oxygen demand [10, 11]. Shortly after smoking marijuana, patients can develop life-threatening arrhythmias such as ventricular fibrillation [12]. In fact, the risk of acute MI may increase by fivefold within 1 h of cannabis exposure [13]. In our study, no data were available as to the timing of marijuana use prior to arrival to the ED. Rather, our data reflected either recent use, identified as a positive urine toxicology screen for cannabinoid, which can remain positive for approximately 3 - 30 days after its consumption, and/or reported use of marijuana immediately prior to symptom...
onset or symptom onset during active marijuana use.

Our study showed that STEMI, NSTEMI and the severity of cardiac disease were not significantly related to marijuana use. Other studies have found similar results. For example, CARDIA data were used to examine the association between marijuana use and cardiovascular mortality and no association was found [14]. Interestingly, our study revealed a significant correlation between MUs and RCA disease (P = 0.026). MUs were less likely to experience RCA disease. There were no other similar research data found in the literature.

There are mainly case reports describing the possible association of acute MI in the setting of marijuana use. Most of the patients had cardiac catheterization which revealed normal coronary arteries (compared to our study population who had CAD requiring PCI) and most were men with no pre-existing CAD [15, 16]. In many instances, microvascular and epicardial coronary vasospasm in the context of marijuana use rather than atherosclerotic CAD have been outlined. There are limited data on patients who had an acute STEMI, and underwent cardiac catheterization and PCI. A few cases were described in a case report by Wengrofsky et al (2018) where a 30-year-old AA with no prior cardiovascular disease (CVD) experienced recurrent STEMI with recurrent 100% occlusion of the left anterior descending (LAD) artery [17]. Another study conducted by Navneet et al (2017) described 10 cases, with various baseline characteristics, who also had angiographic evidence of obstructive CAD [18]. Our study analyzed 37 MUs who experienced acute coronary syndrome (ACS) associated with coronary thrombosis. There continue to be controversial data regarding the potential risk of MI related to marijuana use and more research is needed regarding their thrombotic potential.

In regards to PBNP, there was a positive correlation found with marijuana use. MUs had lower PBNP (P = 0.052) than non-users. Unfortunately, no research studies have examined the association between marijuana use and PBNP.

Moreover, MUs who experienced MI were found to be younger with a mean age of 42.95 versus 48.73 for non-users and were mostly men. In fact, many victims of cardiovascular events, such as sudden cardiac death and arrhythmias, are young men with few cardiovascular risk factors [19]. For this reason, we expected MUs to have less cardiovascular risk factors and comorbidities. However, when computing the analyses for each of the research variables that we identified as being a risk factor for CVD, our analyses did not show any statistical differences between MUs and non-users.

Our study also analyzed the associated negative consequences of concomitant use of other illicit and prescription drugs. The research analyses demonstrated a higher rate of cigarette, opiate, and alcohol use among MUs. A research study conducted by Golfo et al (2014) found similar results [20]. In a community sample of 1,075 subjects, daily consumption of marijuana use was associated with an increase in opiate, cocaine and tobacco use as well as stimulant, hallucinogen, and inhalant [20]. In 2017, another study included a comprehensive cross-sectional survey of 239 questions that were completed by 2,032 subjects to study the patterns of cannabis use and their use of prescription and illicit drugs, alcohol and tobacco. Of the respondents, 74.6% admitted to daily cannabis use and the most cited substitution was prescription drugs (69.1%), mainly opioid (35.3%), followed by alcohol (44.5%) and then tobacco use (31.1%) [21].

Obesity is a well-established known risk factor for ischemic heart disease [22, 23]. Most of the patients were overweight or obese with a mean BMI of 27.93 in MUs and 30.82 in non-users (normal BMI = 18.5 to 30.0). However, MUs were found to have a lower BMI (P < 0.014), despite the evidence in clinical trials and laboratory studies that cannabis use stimulates appetite. This observation is similar to the research findings from CARDIA and NHANES III where an association between marijuana use and lower BMI with lower abdominal fat content was found [24, 25].

In regards to the renal function, MUs were found to have lower creatinine and BUN levels (P = 0.031). This is contrary to a large-scale cross-sectional study that did not find any relationship. The authors examined the association between marijuana use and serum creatinine, estimated glomerular filtration rate (eGFR) and the risks of having stage 2 chronic kidney disease (CKD) in 13,995 US adults aged 18 to 59 years. The authors did not observe any clinically significant association [26]. MUs were statistically significantly younger than non-users and this may explain the lower BUN and creatinine values as the prevalence of CKD is higher in older people. Nevertheless, the effects of marijuana on the renal function remain largely unexamined and more research studies are needed.

Limitations

Some study limitations may have impacted the results of the study. For example, our study was limited by a small sample size and may have restricted our ability to observe a positive correlation between marijuana use and MI.

Also, there was a high percentage of AA (64.1%) among the subjects which may have influenced the study results. BUHMC serves mainly a low-socioeconomic population who are mainly AA. It is well known that AA have a higher overall mortality from CAD compared to any other ethnicity particularly at a younger age especially when combined with financial constraints and lack of health insurance [27]. Although MUs were found to be mostly AA, marijuana use was not shown to be related to severity of disease and diagnosis of STEMI and NSTEMI on admission. However, being that they were younger (P < 0.001), ethnicity can help explain the earlier occurrence of cardiovascular events in our study sample.

Lastly, as mentioned previously, K2 is well known to be noxious to the cardiovascular system. However, some patients may have been excluded from the control group due to the non-detectability of K2 in the urine toxicity. Although this may have limited the number of participants in the control group, our study did include patients who reported marijuana use even when the urine toxicology was negative.

Conclusion

Our retrospective study analyzed the relationship between marijuana use and acute coronary events. The results showed a significant correlation between marijuana use and age, alco-
hol, cigarette, creatinine, BUN, PBNP, BMI and RCA disease. However, STEMI, NSTEMI and the severity of CAD were not shown to be significantly related to marijuana use. With the continued decriminalization and increased use of both medical and recreational marijuana, there is a need for large-scale randomized studies to determine the associations between marijuana use and cardiovascular events. The research community needs to explore causal or risk factor relationships to adequately inform the public on this subject.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

The manuscript has been sufficiently de-identified to protect the patient.

Author Contributions

The corresponding author FJL wrote the main manuscript and participated in data collection. AMA helped in directing and supervising data collection and analyzing the research results. TAO provided help with data collection and editing of the research article. AK, RC, and HC provided guidance and support in describing the method for data collection, research objectives and helped in reviewing and editing the article. LP helped in statistical data analysis and helped in writing the result section of the research article.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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