Marijuana: An Underappreciated Risk Factor for Acute Type A Aortic Dissection?

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ABSTRACT

Background: Stimulants such as cocaine and amphetamines are well-established risk factors for acute aortic dissection. Despite the fact that marijuana is the most commonly used illicit drug in the United States, its relationship to acute aortic syndromes has not been well studied.

Methods: A comprehensive retrospective review was undertaken of all consecutive patients who presented with acute Stanford type A aortic dissection from January 2017 to December 2019. Of 152 patients identified, 51 (33.6%) underwent comprehensive urine toxicology screening at clinical presentation. The characteristics and outcomes of the patients with urine results positive for tetrahydrocannabinol (THC) (n = 9, 17.6%) were compared with the 42 patients who had no evidence of recent marijuana consumption.

Results: Of the 51 dissection patients who underwent broad-spectrum urine toxicology screening upon presentation, 9 (17.6%) returned positive results for THC, a proportion higher than would be expected for the general population. All THC patients were male; 3 concurrently tested positive for cocaine, and 3 others had evidence of recent amphetamine use. The THC patients were significantly younger than the non-THC patients (mean ± standard deviation age 48 ± 11.3 versus 61.4 ± 12.3 years, respectively, P = .004). A greater proportion of the THC cohort had a known diagnosis of aortic aneurysm before the dissection (44.4% versus 4.8%, P = .006). All patients underwent expeditious surgical repair. Thirty-day mortality for the entire cohort of 51 patients was 19.6% (10 deaths); for the THC group, it was 11.1% (1 death). There was no difference in the incidence of major postoperative complications between the 2 groups.

Conclusion: Marijuana is the third most commonly used substance in the United States, after alcohol and tobacco. Although marijuana use is understudied, our results suggest that marijuana may be a contributing risk factor for acute type A aortic dissection, particularly in patients with other predisposing risk factors. Given the recent national trend to legalize marijuana, with the concomitant potential for exponential increases in its consumption, we suggest that the diagnosis of aortic dissection be considered earlier in any younger patient who presents with suggestive symptoms, especially if there is a history of recent marijuana use.

INTRODUCTION

Within the past decade, 33 states in the United States have legalized the appropriation of medicinal marijuana, and 11 states have formally decriminalized the use of tetrahydrocannabinol (THC) for recreational purposes [ProCon.org 2020]. Consequently, and not surprisingly, there has been a steady increase in the national consumption of marijuana, especially among teens and younger adults. According to the 2018 National Survey on Drug Use and Health, 53.2 million people (approximately 19.4% of the US population) ages ≥12 years admitted to some form of illicit drug use in 2018; 3.5 million people used marijuana, confirming it as the most commonly imbibed substance that year (not counting alcohol and tobacco). By comparison, cocaine use was reported by 874,000 people, and methamphetamine by 205,000 [SAMHSA 2018].

Recreational and illicit drug use has been linked to adverse cardiovascular outcomes. The association between cocaine and amphetamine consumption and increased risk for acute aortic dissection has been well described [Shah 2015; Eagle 2002; Wako 2007]. Both agents are sympathomimetic agonists, potentially exacerbating stress on the aortic wall, with a consequent increased risk of dissection or rupture. Although marijuana has been shown to impact the cardiovascular system in a number of ways, including increasing the risk for acute coronary syndromes, as well as being intrinsically arrhythmogenic [DeFilippis 2020; Richards 2019], its relationship to aortic dissection has not been thoroughly explored, a state of affairs that seems a little odd, particularly in light of its prevalent use among the population.

We sought to further examine any potential association between marijuana and acute aortic dissection, in an attempt to better define the risk of an acute aortic syndrome in the large population that consumes this substance.

METHODS

Study Population and Definitions

A comprehensive retrospective review was undertaken of our prospectively collected database to identify all patients who underwent repair for acute Stanford type A aortic dissection from January 2017 to December 2019. Those patients without broad-spectrum urine toxicology screen upon clinical presentation were excluded from analysis. The characteristics of those patients with a urine test positive for THC were compared with those who had no evidence of marijuana consumption (no THC) (Figure 1).

Definitions of patient characteristics, perioperative variables, and postoperative outcomes were obtained from the New York State Cardiac Surgery Reporting System (https://www.health.ny.gov/forms/cardiac_surgery) and from the Society of Thoracic Surgeons Adult Cardiac Surgery Database, version 2.81 (http://www.sts.org/registries-research-center/sts-national-database/adult-cardiac-surgery-database/data-collection).

The Northwell Health Institutional Review Board approved this study (#17-0078; August 7, 2017); patient consent was waived.

Statistical Analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Lenox Hill Hospital [Harris 2009]. All statistical evaluation was performed using Statistical Package for the Social Sciences (SPSS) for Windows, version 26.0 (IBM Corp., Armonk, NY).

Analysis was undertaken using Fisher exact test or χ^2 test for categorical variables, as appropriate. For continuous variables, Student's t test was used for normally distributed variables, and Mann–Whitney U test was used for those values with skewed distributions. Results were considered statistically significant at $P < .05$.

RESULTS

Patient Population

Of 152 consecutive patients who underwent repair of acute type A aortic dissection over the study period, 51 (33.6%) underwent a full u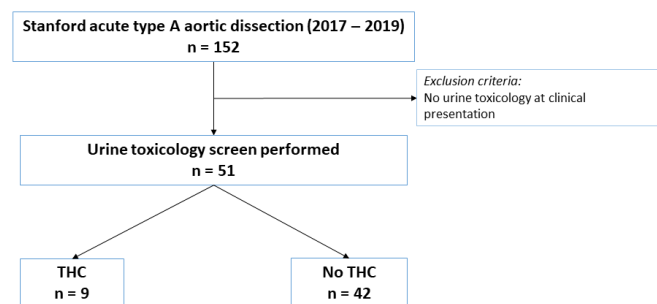rine toxicology screen at presentation and were thus eligible for inclusion in our analysis. Of these 51 patients, 9 (17.6%) tested positive for marijuana, specifically THC (Figure 1). All THC patients were male, age 48 ± 11.3 years (mean ± standard deviation), significantly younger than those who did not test positive for THC ($P = .004$).

A greater proportion of patients in the THC cohort had a preexisting diagnosis of ascending aortic aneurysm compared with the no-THC group (44.4% versus 4.8%, $P = .006$). Three patients in the THC group (33.3%) also tested positive for recent cocaine use, and 3 others had toxicology evidence of amphetamine consumption. Patient demographics are summarized in Table 1.

Dissection Repair

All patients underwent expeditious repair of acute dissection upon diagnosis, the details of which are outlined in Table 2. A detailed description of our surgical technique for type A dissection repair is beyond the scope of this discussion, but has been reported previously [Hemli 2017]. Selective unilateral antegrade cerebral perfusion during hypothermic circulatory arrest via the innominate artery was used in all cases.

Those patients who had negative THC results had longer cross-clamp times than the THC patients (124.7 ± 53.3 versus 86.9 ± 41.0 minutes, $P = .05$), and their perfusion times tended to be longer (205.1 ± 78.8 versus 155.7 ± 41.0 minutes, $P = .09$), although the latter difference was not statistically significant. This finding is interesting, and somewhat difficult to explain, considering there was no significant difference in the types of aortic reconstructions undertaken between the 2 groups. There may have been a slight trend toward a greater proportion of no-THC patients undergoing somewhat more complex aortic procedures.

Clinical Outcomes

Thirty-day mortality for the entire cohort of 51 patients was 19.6% (10 deaths). The majority of patients who died were negative for THC. Of the 9 patients who were positive for THC, there was 1 death (11.1%). This difference in short-term mortality did not reach statistical significance, and its clinical implications remain unclear. The incidence of major postoperative morbidity between the 2 groups was essentially comparable. Postoperative outcomes are outlined in Table 3.

DISCUSSION

Controversy about the potential risks of marijuana use has abounded for decades [Sznitman 2015]. The substance initially gained popularity in the 1960s, when it was considered essentially harmless, although this perception was to completely reverse a decade later, when the agent was deemed "dangerous," first in the court of public opinion, and subsequently through political action [Carliner 2017]. Interestingly, beliefs about the relative safety of THC were to completely change again by >40 years later. California was the first state in the US to legalize medical marijuana [Hasin 2018]. As of January 2020, THC was legal in 11 states for recreational use and 33

Figure 1. Patient flow diagram. THC indicates tetrahydrocannabinol.

Table 1. Patient Demographics

Variable	THC (n = 9)	No THC (n = 42)	*P* Value
Age (y)	48 ± 11.3	61.4 ± 12.3	.004
Female sex	0 (0.0)	13 (31.0)	.09
BMI, kg/m^2	26.2 ± 5.1	28.2 ± 6.1	.35
Diabetes mellitus	0 (0.0)	5 (11.9)	.57
Hypertension	8 (88.9)	30 (71.4)	.42
Hyperlipidemia	3 (33.3)	15 (35.7)	>.99
Peripheral artery disease	2 (22.2)	16 (38.1)	.46
Cerebrovascular disease	1 (11.1)	5 (11.9)	> .99
Dialysis-dependent renal failure	0 (0.0)	1 (2.4)	> .99
Chronic obstructive pulmonary disease	0 (0.0)	3 (7.1)	> .99
Current or prior smoking history	4 (44.4)	15 (35.7)	.71
Prior myocardial infarction	0 (0.0)	3 (7.1)	> .99
Heart failure, NYHA III/IV	0 (0.0)	2 (4.8)	> .99
Left ventricular ejection fraction (%)	57.9 ± 3.0	55.9 ± 11.6	.35
Known diagnosis of aortic aneurysm	4 (44.4)	2 (4.8)	.006
Bicuspid aortic valve	1 (11.1)	1 (2.4)	.33
Marfan syndrome or other aortopathy	1 (11.1)	0 (0.0)	.18
Family history of aortic dissection	1 (11.1)	1 (2.4)	.33
Toxicology positive for cocaine	3 (33.3)	0 (0.0)	.004
Toxicology positive for amphetamines	3 (33.3)	0 (0.0)	.004

Values are mean ± standard deviation or n (%).

BMI indicates body mass index; NYHA, New York Heart Association.

Table 2. Operative Data

Variable	THC (n = 9)	No THC (n = 42)	*P* Value
Cardiopulmonary bypass time, mins	155.7 ± 73.6	205.1 ± 78.8	.09
Aortic cross-clamp time (min)	86.9 ± 41.0	124.7 ± 53.3	.05
Hypothermic circulatory arrest time (min)	29.8 ± 16.9	29.4 ± 18.8	.96
Lowest intraoperative temperature (°C)	24.0 ± 2.9	22.1 ± 4.3	.26
Aortic procedure performed			
Isolated replacement of ascending aorta	7 (77.8)	25 (59.5)	.45
Aortic root replacement	1 (11.1)	15 (35.7)	.24
Total arch replacement	1 (11.1)	2 (4.8)	.45

Values are mean ± standard deviation or n (%).

states for medicinal use [Zvonarev 2019]. State policymakers were forced to develop their own regulatory systems, since marijuana remains illegal under federal law [Kilmer 2017].

The growing consumption of marijuana created a parallel demand for a more potent product [Barry 2018]. On a national level, marijuana potency increased from 1.8% to 10.7% between 1990 and 2010 [Maxwell 2016]. The lack of universal guidelines for the regulation, production, and distribution of commercially legalized marijuana has been poorly addressed [Sevigny 2014]. Although the legalization of marijuana has afforded a number of potential societal economic benefits, such as generating a marketplace for creative enterprise and increasing taxation revenues [Hall 2019], its impacts on public health safety are not yet clearly known.

Marijuana remains classified as a Schedule I drug under the Controlled Substances Act, which defines it as having no medical purpose and a higher potential for abuse [Mead 2019]. It contains the chemicals THC and cannabidiol (CBD). Currently, the Food and Drug Administration (FDA) has approved 3 CBD medications (dronabinol, cannabidiol, and nabilone) for medicinal indications, including nausea but excluding analgesia [Oberbarnscheidt 2020]. Marijuana extracts that contain <0.3% THC are excluded from the Schedule I classification and are readily available throughout the US as over-the-counter products in variable CBD potencies.

Non–FDA-approved marijuana products, such as those found in certain foods and oils, may contain potentially harmful substances, particularly in the form of synthetic marijuana [Chase 2016; Gunderson 2014]. It has been reported that adolescents tend to prefer the synthetic form of THC because it is often cheaper, is associated with a greater sense of euphoria after consumption, is less detectable using standard drug testing, and it may actually be misperceived as being legal, even though it is not [Palamar 2016]. Classifying marijuana as a controlled substance has made it somewhat more difficult

to study the longer-term effects of its use and to formulate evidence-based regulation and policy-making [Martz 2018].

The adverse cardiovascular effects associated with marijuana use have largely been reported only through case reports or smaller observational studies. Based on these findings, clinicians are nevertheless encouraged to consider routine screening for marijuana when young adults present with cardiovascular symptoms [DeFilippis 2020]. Although marijuana is not considered to be a sympathomimetic agent per se, its impact on the cardiovascular system can be synergistic when combined with other stimulants, such as cocaine [Lukas 1994]. This is worth noting, given that 3 of the 9 patients in our series who tested positive for THC also had toxicology consistent with recent cocaine consumption, and 3 others had evidence of amphetamine use. Marijuana has been shown to increase heart rate, blood pressure, and systemic sympathetic tone. Consistent marijuana use has also been shown to increase carboxyhemoglobin levels, resulting in a relatively smaller systemic reservoir of oxygenated hemoglobin. This classic discrepancy between oxygen supply and demand is thought to be one of the mechanisms underlying marijuana-associated cardiac injury [Desbois 2013; Lindsay 2005; Mittlemen 2001].

Given that marijuana can potentiate sympathetic activity, particularly when used in conjunction with other stimulating agents, it would not be surprising to suggest that it may place an individual at higher risk for aortic dissection, particularly in those who may already be predisposed to the pathology for other reasons. Indeed, we found that a greater proportion of patients in the THC group had a preexisting diagnosis of ascending aortic aneurysm than those in the no-THC cohort.

Even though our sample size is quite small, our study nevertheless represents the largest series to date to specifically interrogate dissection patients with respect to marijuana consumption. Of 51 dissection patients, 17.6% tested positive for THC, a positivity rate markedly higher than

Table 3. Short-Term Clinical Outcomes

Variable	THC (n = 9)	No THC (n = 42)	P Value
30-Day mortality	1 (11.1)	9 (21.4)	.67
Stroke	0 (0.0)	12 (28.6)	.09
Reoperation for bleeding	0 (0.0)	2 (4.8)	>.99
Deep sternal wound infection	0 (0.0)	0 (0.0)	>.99
New dialysis-dependent renal failure	1 (11.1)	7 (16.7)	>.99
Sepsis of any cause	1 (11.1)	2 (4.8)	.45
Duration of ICU stay (h)	244.8 ± 236.1	244.2 ± 246.1	>.99
Length of postoperative hospital stay (d)	14.7 ± 9.3	14.7 ± 11.8	.54
Length of postoperative hospital stay (d)	11 (10 to 16)	10 (7 to 21)	
Readmission to hospital with 30 days (for any reason)	0 (0.0)	6 (14.3)	.58

Values are mean ± standard deviation, n (%), or median (interquartile range).

ICU indicates intensive care unit.

would be expected for the general population [SAMHSA 2019]. To the best of our knowledge, the potential association between marijuana use and aortic dissection has been examined by only 1 other group, who described a type A dissection in a 56-year-old man who smoked marijuana and had a family history of both aortic aneurysm and dissection [Mason 2019].

Our study has a number of limitations that need to be acknowledged. Our analysis is retrospective and largely observational in nature. Not all dissection patients underwent toxicology screening at presentation, such that an element of selection bias cannot be eliminated. Our study population is small, and consequently, it is difficult to draw broad-ranging conclusions from such an underpowered analysis.

The legalization of marijuana for both medical and recreational use has paved the way for greater adverse cardiovascular events related to its increased use. Although marijuana has already been associated with ischemic heart disease, we suggest that all of the elements are in place for it to potentially increase the risk for aortic dissection as well, particularly if the patient has a preexisting aortic aneurysm or uses other illicit sympathomimetic agents, such as cocaine or amphetamines. We suggest that clinicians should have a lower threshold for considering the diagnosis of acute aortic dissection in any younger patient presenting with chest pain or associated symptoms who has a history of recent marijuana consumption.

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