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# The Epidemiology of Reversible Cerebral Vasoconstriction Syndrome in Patients at a Colorado Comprehensive Stroke Center

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## Abstract

**Objective—**Vasoactive substances, including marijuana, are known precipitating factors of reversible cerebral vasoconstriction syndrome (RCVS). Our objective was to describe the demographics, suspected etiology, and outcomes of RCVS patients, with specific interest in examining the subset of patients who used marijuana prior to the onset of RCVS.

**Methods—**We identified and described consecutive RCVS cases treated at a regional, high-volume Comprehensive Stroke Center in Colorado (2012–2015). Univariate analyses were performed to examine the associations between the characteristics and outcomes (stroke and discharge disposition) of the RCVS patients by precipitating factors. We compared patients who used marijuana to those who did not and patients who used marijuana to patients who used vasoactive substances aside from marijuana.

**Results—**Forty patients had RCVS. Sixteen (40%) cases were deemed idiopathic and 24 (60%) were secondary to a suspected trigger. Vasoactive substances were the most common suspected trigger ($n$ = 18/24, 75%), 6 (33%) of which were marijuana. Approximately 80% of patients experienced an intracranial hemorrhage, 20% had an ischemic stroke, and yet 78% were discharged home. Patients with RCVS secondary to marijuana were more often male ($p$ = 0.05) and younger ($p$ = 0.02) compared to those who did not use marijuana; no differences were observed in the outcomes. These findings were consistent when examining marijuana versus other vasoactive substances.

**Conclusion—**This study suggests there are demographic differences between patients with RCVS triggered by marijuana compared to the typical RCVS patient. As more states legalize marijuana, medical conditions such as RCVS and their association with marijuana warrants further study and awareness.

### Keywords

cannabis; vasoconstriction; stroke; epidemiology

## INTRODUCTION

Reversible cerebral vasoconstriction syndrome (RCVS) is a neurological syndrome that affects a young population of adults, predominantly occurs in females, and is characterized by both clinical and radiographic features [1–5]. Patients with RCVS often experience acute and severe headaches, which tend to qualify as thunderclap headaches; they may or may not present with neurological symptoms. Segmental cerebral artery vasoconstriction appears as "beading" on imaging and is expected to resolve within 12 weeks from the initial syndrome onset [6–8]. The prognosis for most patients with RCVS is benign, but some patients experience permanent neuro-

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logical deficits or death from intracranial hemorrhages and ischemic strokes [2,5,6,9].

The onset of RCVS is hypothesized to occur spontaneously or due to secondary factors that trigger a disturbance in vascular tone [6]. Approximately 60% of reported RCVS cases have been associated with a likely cause [10] including: vasoactive substances, pregnancy and the postpartum period, receipt of blood products, uncontrolled hypertension, and miscellaneous events such as head trauma, cervical or spinal lesions, and neurosurgical procedures [6,7,11]. Vasoactive substances were the most frequently documented cause in three of the larger RCVS studies that examined 162 [5], 139 [2], and 67 [3] patients over an 18, 17, and three-year period, respectively. Marijuana was the vasoactive substance reported most often as triggering RCVS in a large prospective series by Ducros *et al*. [3], documented in 30% (20/67) of patients. Marijuana was also identified as the triggering factor in several case reports and series[12–15].

Our objective was to systematically describe the demographics, suspected etiology, and outcomes among a cohort of patients with RCVS who were treated at a Comprehensive Stroke Center (CSC) in Colorado. We had a specific interest in examining RCVS triggered by vasoactive substances and marijuana in particular, because Colorado was the first State to pass and implement a law legalizing recreational marijuana.

## METHODS

This retrospective cohort study was conducted at a high-volume CSC in the Denver, CO metropolitan area that serves as a primary referral center across the Rocky Mountain Region. All consecutively admitted patients (≥18 years) diagnosed with RCVS between January 1, 2012 and December 31, 2015 were identified from Neurobase™ (CDM, Evergreen, CO), the Neurology department's prospectively collected database of all patients with a known or suspected diagnosis of stroke. This study was approved by the HealthOne Institutional Review Board; informed consent was waived.

Medical records of identified subjects were reviewed by one of the two registered nurses (AJ and LF); complicated cases were reviewed by a neurologist (JJ). Demographics (age, sex, and comorbid conditions), discharge disposition, and in-hospital mortality were extracted from Neurobase. The suspected cause of RCVS (spontaneous aka idiopathic, or secondary to an identified precipitating factor), symptoms, and complications (ischemic stroke or intracranial hemorrhage) were abstracted from the chart review.

We reported the demographics, suspected cause of RCVS, and outcomes (complications and discharge disposition) for each patient with RCVS. We examined the associations between the demographics, clinical characteristics, and outcomes of the RCVS patients and compared patients who used marijuana to those who did not. Secondarily, we compared patients who used marijuana to patients who used vasoactive substances aside from marijuana. Patients were considered nonmarijuana vasoactive substance users if they used selective serotonin reuptake inhibitors, exercise stimulants, energy drinks, alcohol, triptans, methamphetamine, or sympathomimetic drugs. Data were univariately analyzed using chi-square tests and Fishers exact tests for categorical variables and Wilcoxon two-sample tests for continuous variables. Statistical analyses were performed with SAS (version 9.3, Cary, NC) and are shown as median (interquartile range) or *n* (%). Statistical significance was set at $p < 0.05$.

## RESULTS

In total, 40 patients with RCVS were identified; there were 10, 8, 7, and 15 cases of RCVS in 2012, 2013, 2014, and 2015, respectively. Overall, the median age was 48.5 years. Approximately 70% of the patients were female. Eight (20%) patients arrived directly to the CSC, while 32 (80%) were transferred to the CSC from a separate hospital. The transferred patients arrived from four states (Iowa, Montana, Nebraska, and Wyoming; $n = 7$) and 10 different counties across the state of Colorado ($n = 25$). Within Colorado, 56% ($n = 14$) of patients were transferred from a hospital in the Denver metro area, whereas 44% ($n = 11$) arrived from a hospital outside of the Denver metro area.

Sixteen patients (40%) were identified as having idiopathic RCVS and 24 patients (60%) had an identified precipitating factor. The most common precipitating factor was a vasoactive substance ($n = 18$, 75%), of which 12 (67%) patients used substances other than marijuana and 6 (33%) patients used marijuana. Other precipitating factors included postpartum ($n = 3$), dissection ($n = 2$) and catecholamine surge ($n = 1$). Case specific information, including detailed suspected trigger information, is presented in Table 1.

Twenty-four patients (60%) were admitted to the Neurocritical Care Unit. Patients were most frequently treated with oral verapamil ($n = 33$, 82.5%) followed by oral nimodipine ($n = 11$, 27.5%) and intra-arterial verapamil ($n = 3$, 7.5%).

Thirty-three patients had a total of 49 intracranial hemorrhages, including: subarachnoid ($n = 31$), intraparen-

**Table 1. Characteristics and outcomes of 40 RCVS patients**

| Case-year | Age | Sex | Idiopathic or secondary RCVS | If secondary RCVS, suspected cause | Treatment | Complications | Discharge disposition |
|---|---|---|---|---|---|---|---|
| 1-2012 | 56 | F | Secondary | Vertebral dissection | Oral nimodipine | SAH | Home |
| 2-2012 | 46 | F | Idiopathic | NA | Oral and IA verapamil | SAH; IS | Home |
| 3-2012 | 32 | F | Secondary | Postpartum | Oral nimodipine; Oral and IA verapamil | SAH; IPH | Home |
| 4-2012 | 25 | F | Idiopathic | NA | Oral verapamil | SAH; IPH | Home |
| 5-2012 | 27 | F | Idiopathic | NA | Oral nimodipine; oral verapamil | SAH | Home |
| 6-2012 | 27 | F | Secondary | Supplements for body building, including stimulants | Oral verapamil | None | Home |
| 7-2012 | 26 | F | Secondary | Postpartum | Oral verapamil | None | Home |
| 8-2012 | 53 | F | Idiopathic | NA | Oral verapamil | SAH | Home |
| 9-2012 | 38 | F | Secondary | Marijuana; methamphetamine | None | SAH | Inter-hospital Transfer |
| 10-2012 | 63 | F | Idiopathic | NA | Oral nimodipine | SAH; IPH | Home |
| 11-2013 | 56 | M | Idiopathic | NA | Oral verapamil | SAH | Home |
| 12-2013 | 49 | F | Idiopathic | NA | Oral verapamil | SAH; IPH | Home |
| 13-2013 | 48 | M | Idiopathic | NA | Oral verapamil | None | Home |
| 14-2013 | 41 | F | Secondary | SSRI (sertraline); triptan (sumatriptan); Sensa | Oral verapamil | SAH; IPH | Home |
| 15-2013 | 53 | F | Secondary | SSRI (cytolopram); hydroxyzine | Oral verapamil | SAH | SNF |
| 16-2013 | 29 | M | Secondary | Energy drink | Oral verapamil | SAH; SDH | Home |
| 17-2013 | 50 | F | Secondary | Methamphetamine; SSRI (cytolopram) | Oral verapamil | SAH; IPH; IS | Rehabilitation Facility |
| 18-2013 | 67 | M | Idiopathic | NA | None | IS | Home |
| 19-2014 | 52 | F | Secondary | SSRI (citalopram); trazodone | Oral verapamil | SAH | Home |
| 20-2014 | 51 | F | Idiopathic | NA | Oral verapamil | IPH; IS | Home |
| 21-2014 | 63 | F | Idiopathic | NA | Oral verapamil | SAH | Home Health |
| 22-2014 | 61 | F | Secondary | Sympathomimetic (guaifenesin and dextromethorphan liquid); aspirin/paracetamol/caffeine; albuterol and ipratropium | Oral verapamil | SAH | Home |
| 23-2014 | 38 | F | Secondary | Postpartum | Oral verapamil | SAH | Home |
| 24-2014 | 66 | M | Secondary | Triptan (sumatriptan) | Oral verapamil | SAH; IVH | Home |
| 25-2014 | 56 | F | Idiopathic | NA | Oral verapamil | SAH | Home |
| 26-2015 | 40 | F | Secondary | SSRI (escitalopram); acetaminophen, butalbital, and caffeine | Oral nimodipine; Oral verapamil | SAH | Home |
| 27-2015 | 30 | M | Secondary | Marijuana; cocaine; ecstasy; SSRI (fluoxetine); lorazepam | Oral nimodipine; Oral verapamil | SAH | Home |
| 28-2015 | 38 | M | Secondary | Alcohol | Oral nimodipine; Oral verapamil | None | Home Health |
| 29-2015 | 20 | M | Secondary | Marijuana | Oral verapamil | SAH | Home |
| 30-2015 | 20 | M | Secondary | Marijuana | Oral nimodipine | SAH | Home |
| 31-2015 | 57 | F | Idiopathic | NA | Oral nimodipine | SAH | Rehabilitation Facility |
| 32-2015 | 58 | F | Secondary | Triptan (sumatriptan) | Oral verapamil | SAH; IPH | Home |
| 33-2015 | 46 | F | Idiopathic | NA | Oral nimodipine; oral and IA verapamil | SAH; IVH; IS | Rehabilitation Facility |
| 34-2015 | 59 | F | Secondary | Marijuana (inhaled and consumed "edible") | Oral verapamil | SAH; IS | Died |
| 35-2015 | 23 | M | Secondary | Hash (marijuana) | Oral verapamil | None | Home |
| 36-2015 | 42 | M | Idiopathic | NA | Oral verapamil | SAH; IPH; IVH; IS | Home |
| 37-2015 | 54 | M | Secondary | Catecholamine surge | Oral verapamil | SAH; IPH; IVH; IS | Skilled Nursing Facility |
| 38-2015 | 32 | F | Secondary | Methamphetamine; SSRI (fluoxetine) | Oral verapamil | SAH; IPH | Rehabilitation Facility |
| 39-2015 | 60 | F | Idiopathic | NA | Oral verapamil | SDH; IPH | Home |
| 40-2015 | 51 | F | Secondary | Cervical dissection | Oral nimodipine; oral verapamil | IS | Skilled Nursing Facility |

Edible, marijuana infused food; F, female; IA, Intra-arterial; IPH, intraparenchymal hemorrhage; IS, ischemic stroke; IVH, intraventricular hemorrhage; M, male; NA, not applicable; RCVS, reversible cerebral vasoconstriction syndrome; SAH, subarachnoid hemorrhage; SDH, subdural hematoma; SNF, skilled nursing facility; SSRI, selective serotonin reuptake inhibitors.

chymal ($n$ = 12) and intraventricular ($n$ = 4) hemorrhages, and subdural hematomas ($n$ = 2). Nine (22.5%) patients had an ischemic stroke. There was one (2.5%) in-hospital death. Despite 82% of patients experiencing an intracranial hemorrhage, over three-quarters of the patients were discharged home.

## Marijuana versus nonmarijuana use

Marijuana was the sole identifiable trigger in four of the six cases; two patients smoked daily, one used concentrated hash, and one inhaled marijuana and consumed a marijuana-infused food ("edible"). The two remaining patients used marijuana in combination with other drugs.

**Table 2. Characteristics and outcomes of patients with RCVS at a Colorado Comprehensive Stroke Center by marijuana use, 2012–2015**

| | Marijuana use($n$ = 6) | Non-marijuana use($n$ = 34) | $P$-value |
|---|---|---|---|
| Age, years | 26.5 (20–38) | 50.5 (38–56) | **0.02** |
| Female | 2 (33.3%) | 26 (76.5%) | **0.05** |
| No comorbidities | 0 (0%) | 9 (29.0%) | 0.30 |
| History of | | | |
| Smoking | 2 (33.3%) | 6 (19.4%) | 0.59 |
| Recreational drug use[a] | 6 (100%) | 4 (12.9%) | n/a |
| Migraines | 2 (33.3%) | 9 (29.0%) | >0.99 |
| Symptoms of RCVS | | | |
| Thunderclap headache | 2 (33.3%) | 24 (70.6%) | 0.16 |
| Seizure | 1 (16.7%) | 3 (8.8%) | 0.49 |
| Focal deficits | 3 (50.0%) | 21 (61.8%) | 0.67 |
| Nausea/vomiting | 3 (50.0%) | 21 (61.8%) | 0.67 |
| Other[b] | 3 (50.0%) | 16 (47.1%) | >0.99 |
| NCCU admission | 3 (50.0%) | 21 (61.8%) | 0.67 |
| Treatment: oral verapamil | 4 (66.7%) | 29 (85.3%) | 0.28 |
| Outcomes | | | |
| Ischemic stroke | 1 (16.7%) | 8 (23.5%) | >0.99 |
| Intracranial hemorrhage | 5 (83.3%) | 28 (82.4%) | >0.99 |
| Discharge disposition | | | 0.06 |
| Home/home health | 4 (66.7%) | 27 (79.4%) | |
| Rehabilitation facility | 0 (0%) | 4 (11.8%) | |
| Skilled nursing facility | 0 (0%) | 3 (8.8%) | |
| Interhospital transfer | 1 (16.7%) | 0 (0%) | |
| Died | 1 (16.7%) | 0 (0%) | |

RCVS, reversible cerebral vasoconstriction syndrome.

[a]Did not present $p$-values for history of recreational drug use since the tested characteristic overlaps with the group definition.

[b]Other symptoms included: dizziness, fatigue, abdominal/neck/back pain, and photophobia.

Data are presented as $n$ (%) or median (interquartile range).

Among the six marijuana users, there were five with SAHs, one with ischemic stroke, and one death.

Patients with RCVS triggered by marijuana were younger and less often female than the overall RCVS population at our institution who did not use marijuana (Table 2). The presenting symptoms, treatment, and outcomes were similar in marijuana users versus nonmarijuana users (Table 2).

### Marijuana versus other vasoactive substances

Among vasoactive substances ($n$ = 18), 12 (67%) patients used substances other than marijuana and 6 (33%) patients used marijuana. We compared secondary RCVS attributable to marijuana ($n$ = 6) to other vasoactive substances ($n$ = 12) to elucidate any differences between these two precipitating factors, which are commonly grouped together (Table 3). The patients with RCVS secondary to marijuana were younger and less often female than the patients who used other types of vasoactive substances, though these associations were not statistically significant. The clinical characteristics and outcomes did not differ between the marijuana users and vasoactive substance users who developed RCVS.

## DISCUSSION

We examined the epidemiology and prognosis of RCVS cases treated at our regional, high-volume CSC. Overall, vasoactive substances were the most common precipitating factor; marijuana was used prior to the diagnosis of RCVS in 15% of the cases. This study highlights interesting differences in the demographics of patients with RCVS associated with marijuana compared to RCVS overall. The typical nonmarijuana RCVS patient was female and middle aged (77% female, 51 years), and the vasoactive substance users were similar demographically (75% female, 41 years). In contrast, the marijuana users were 33% female and 26.5 years old.

The overall population of RCVS patients at our institution aligns with RCVS patients described in the literature; the patients are predominantly female with a mean age in the forties [1–4,9,16]. However, there were demographic differences between patients with RCVS triggered by marijuana and our broader RCVS population, specifically that they were mostly male (67%) and half as old. This finding makes sense given that a 2014 report from the Colorado state health department identified that males report marijuana use more than females [17]. Ducros *et al*. [3] also noted a higher percentage of males with RCVS triggered by marijuana (71%) compared to their overall RCVS population (36%) and Wolff

**Table 3. Characteristics and outcomes of patients with RCVS at a Colorado Comprehensive Stroke Center by marijuana use, 2012–2015**

| | Marijuana use (*n* = 6) | Non-marijuana vasoactive substances (*n* = 12) | *P*-value |
|---|---|---|---|
| Age, years | 26.5 (20–38) | 41 (32–53) | 0.09 |
| Female | 2 (33.3%) | 9 (75.0%) | 0.14 |
| No comorbidities | 0 (0%) | 1 (10.0%) | >0.99 |
| History of | | | |
| Smoking | 2 (33.3%) | 4 (40.0%) | >0.99 |
| Recreational drug use[a] | 6 (100%) | 3 (30.0%) | n/a |
| Migraines | 2 (33.3%) | 4 (40.0%) | >0.99 |
| Symptoms of RCVS | | | |
| Thunderclap headache | 2 (33.3%) | 9 (75.0%) | 0.14 |
| Seizure | 1 (16.7%) | 1 (8.3%) | >0.99 |
| Focal deficits | 3 (50.0%) | 8 (66.7%) | 0.63 |
| Nausea/vomiting | 3 (50.0%) | 6 (50.0%) | >0.99 |
| Other[b] | 3 (50.0%) | 5 (41.7%) | >0.99 |
| NCCU admission | 3 (50.0%) | 2 (16.7%) | 0.27 |
| Treatment: oral verapamil | 4 (66.7%) | 12 (100%) | 0.10 |
| Outcomes | | | |
| Ischemic stroke | 1 (16.7%) | 1 (8.3%) | >0.99 |
| Intracranial hemorrhage | 5 (83.3%) | 10 (83.3%) | >0.99 |
| Discharge disposition | | | 0.33 |
| Home/home health | 4 (66.7%) | 9 (75.0%) | |
| Rehabilitation facility | 0 (0%) | 2 (16.7%) | |
| Skilled nursing facility | 0 (0%) | 1 (8.3%) | |
| Interhospital transfer | 1 (16.7%) | 0 (0%) | |
| Died | 1 (16.7%) | 0 (0%) | |

RCVS, reversible cerebral vasoconstriction syndrome.

[a]Did not present *p*-values for history of recreational drug use since the tested characteristic overlaps with the group definition.

[b]Other symptoms included: dizziness, fatigue, abdominal/neck/back pain, and photophobia.

Data are presented as n (%) or median (interquartile range).

and Jouanjus [18] described a young, predominantly male group of patients with strokes after marijuana use.

Although marijuana is a known cause of RCVS, studies specifically examining the subset of marijuana users with RCVS are lacking. Singhal *et al*. [2] compared characteristics of RCVS patients based on triggers, but the triggers were grouped as vasoactive drugs, postpartum, and other triggers. In their study, the patients who used vasoactive drugs were 74% female and an average of 40 years; these findings more closely resemble the vasoactive substance users in our study rather than specifically the marijuana users.

Recreational marijuana has been legalized in Colorado, Washington, Oregon, Alaska, Washington DC, and more recently in California, Nevada, Maine, and Massachusetts. The legalization of marijuana has been associated with the rise in use among adults and a decreased perception of harm [19,20]. The expansive adoption of laws legalizing marijuana for recreational use may give the impression that marijuana is safe. Data from the Colorado Department of Public Health and Environment demonstrates an increase in the number of marijuana-related emergency department visits and calls to the Rocky Mountain Poison and Drug Center after the opening of recreational marijuana stores compared to the preceding years [21].

The public should be made aware of the association between marijuana use and RCVS. Although most patients recover from RCVS, some experience permanent deficits or even death [2,5,6,9]. In our study, one of the six patients (17%) who used marijuana and then developed RCVS died. This is a high mortality for an otherwise generally healthy, young population. The demographics of the patients with RCVS who used marijuana mimic a study in France that found increased cardiovascular complications following marijuana use, specifically in young males [22] and a review of the literature described a temporal relationship between cannabinoid use and stroke, suggesting that for cannabinoid users, RCVS may be a mechanism of stroke [18].

Our study has several limitations. First, the diagnosis of RCVS is confirmed when a patient has repeat imaging at approximately three months or earlier to confirm the reversibility of the disease [6–8]. We did not have access to postdischarge imaging scans at our institution, and the retrospective study design did not allow us to request these data ahead of time. Nonetheless, the characteristics of our population, symptoms at onset, and outcomes follow the same patterns as previously published literature, supporting the suspected diagnosis of RCVS. Second, patients did not routinely have toxicology screens performed; the documentation of drug use in our series is

primarily based upon patient report. These data were obtained retrospectively and are limited to what was documented in the patient's chart. We could be underreporting the patients who were exposed to marijuana. However, using patient report of drug use is not an uncommon practice [22,23]. Third, identifying the exact trigger of RCVS is complex. Two of the patients who used marijuana also used other vasoactive drugs causing an uncertainty as to whether it was specifically the marijuana or the additional substances that triggered RCVS. Cervical artery dissection is a condition known to be associated with RCVS. In our study, we listed dissection as a trigger of RCVS, but the timing of which condition comes first is still unknown [3,7,24,25].

Despite the limitations, we believe our study is unique in that it presents the patient characteristics and outcomes for not only all RCVS patients at our institution, but specifically focuses on RCVS secondary to marijuana. Medical conditions, such as RCVS, and their association with marijuana are important areas of study as more states legalize recreational marijuana.

## CONCLUSIONS

Our study suggests there are demographic differences between patients with RCVS triggered by marijuana compared to the typical RCVS patient. Patients who used marijuana prior to the onset of RCVS were more often male and in their 20's, whereas most RCVS patients are female and in their 40's; these demographic differences are important for clinicians to consider when determining a patient's diagnosis. The relationship between RCVS and marijuana warrants further study because this disease, which could have serious health consequences, is potentially preventable in some patients.

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