HIGH LIGHT

Cerebrovascular perfusion in marijuana users during a month of monitored abstinence

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Abstract—*Objective:* To determine possible effects of prolonged marijuana use on the cerebrovascular system during a month of monitored abstinence and to assess how the intensity of current use might have influenced cerebrovascular perfusion in these marijuana users. *Method:* The authors recorded blood flow velocity in the anterior and middle cerebral arteries using transcranial Doppler sonography in three groups of marijuana users who differed in the intensity of recent use (light: n = 11; moderate: n = 23; and heavy: n = 20) and in control subjects (n = 18) to assess the nature and duration of any potential abnormalities. Blood flow velocity was recorded within 3 days of admission and 28 to 30 days of monitored abstinence on an inpatient research unit in order to evaluate subacute effects of the drug and any abstinence-generated changes. *Results:* Pulsatility index, a measure of cerebrovascular resistance, and systolic velocity were significantly increased in the marijuana users vs control subjects. These increases persisted in the heavy marijuana users after a month of monitored abstinence. *Conclusions:* Chronic marijuana use is associated with increased cerebrovascular resistance through changes mediated, in part, in blood vessels or in the brain parenchyma. These findings might provide a partial explanation for the cognitive deficits observed in a similar group of marijuana users.

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Marijuana is the most commonly used drug among young persons.[1] Prolonged effects of marijuana on the neurovasculature might be responsible, in part, for the reports of cognitive deficits observed in some of these users[2] because the acute administration of marijuana or delta-9-tetrahydrocannbinal (THC) causes increases in cerebral blood flow in marijuana users[3] and because reduced cerebral blood flow is observed in recently abstinent chronic marijuana users.[4] It remains to be determined whether the reported changes in cerebral blood flow might persist over an extended period of monitored abstinence, and whether the intensity of current marijuana use might influence the severity or duration of the perfusion deficits associated with use of the drug.

In order to address these issues further, three groups of marijuana users differing in the current intensity of use were tested with transcranial Doppler (TCD) sonography early and late during a month of monitored abstinence. Their data were contrasted with those of control subjects. In order to delineate possible effects of marijuana on cerebral vessels, we opted for TCD because TCD assessment is noninvasive, economical, and rapid.[5] Because TCD is a test that is easily available in clinical neurology settings, it allows for easy replication, unlike some of the more expensive imaging techniques.

Methods. *Subjects.* Fifty-four marijuana users (14 women, 40 men) and 18 control subjects (6 women, 12 men) were studied. Before undergoing blood flow velocity assessment by TCD, all volunteers had undergone medical, neurologic, psychological, and laboratory evaluations. Fourteen marijuana users also met criteria for a diagnosis of antisocial personality disorder and four met Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV criteria for nicotine dependence.[6]

Exclusion criteria, which applied to all subjects, included 1) major medical and psychiatric illnesses including history of hypertension, 2) head injuries with loss of consciousness for greater than 5 minutes, 3) evidence of any neurologic abnormalities by history or examination, 4) HIV seropositivity, and 5) drug (e.g., cocaine, heroin) or excessive alcohol use by DSM-IV criteria for alcohol abuse or dependence. The research protocol was approved by the National Institute on Drug Abuse and Johns Hopkins Bayview Medical Center Institutional Review Boards for Human Research and was carried out in accordance the with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Demographic information and drug use history information were obtained from the Addiction Severity Index (ASI).[7] The metric, joints per week, was determined from the subjects' self-reported drug history. Since the number of marijuana joints per week ranged from 2 to 350, the 54 marijuana users were divided into three groups using the procedure described by Bolla et al.[3] Fifteen marijuana users in the present study were also in the Bolla study. In that procedure, a blunt (cigar-size marijuana smoking material) was equal to four joints (small diameter cigarette-size smoking material). The light group smoked 11.0 ± 3.5 joints per week (n = 11; range 2.2 to 15.0). The moderate group smoked the equivalent of 43.7 ± 16.4 joints per week (n = 23; range 17 to 70). The heavy group smoked the equivalent of 130.8 ± 73.0 joints per week (n = 20; range 78 to 350). Table 1 lists these measures for the control subjects and the three groups of marijuana users. The three groups of marijuana users did not differ in years of use. Other than alcohol, tobacco, and marijuana use reported in table 1, illicit drug use was not self-reported or observed in urine toxicologies obtained during the screening process. Subjects with drug use other than marijuana use were screened out of the present study. Subjects with a lifetime diagno-

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Table 1 *Demographic measures and drug history*

Demographic measures	Control, n = 18, mean (SD)	Marijuana users		
		Light, n = 11, mean (SD)	Moderate, n = 23, mean (SD)	Heavy, n = 20, mean (SD)
Age, y	24.2 (3.2)	25.5 (6.3)	22.6 (4.9)	21.6 (2.8)
Education, y	13.0 (1.7)	12.2 (1.6)	11.7 (1.8)	11.2 (1.5*)
Shipley, IQ	102.5 (13.8)	98.8 (11.8)	95.7 (11.8)	97.0 (10.7)
Women, %	33.3	27.3	26.1	25.0
African Americans, %	88.9	81.8	78.3	100.0
Drug history measures				
Alcohol, d/30 d,† CV‡	0.6 (1.1)	3.4 (4.7)	3.7 (4.8)	6.2 (6.3*)
Alcohol, y§	1.2 (2.4)	1.4 (3.3)	3.4 (5.8)	2.5 (3.3)
Marijuana, d/30 d		15.9 (3.7)	24.5 (7.1)	29.2 (3.4)
Marijuana, y‖		5.6 (3.8)	7.2 (5.8)	6.1 (3.1)
Last use to early test, d		4.0 (1.5)	2.6 (1.9)	2.2 (0.9)
Median (range)		4 (2 to 7)	2 (1 to 10)	2 (1 to 4)
Cigarettes/day, CV	0.6 (1.5)	4.7 (5.3)	5.9 (5.8)	8.9 (9.2*)
Cigarettes, y	4.8 (11.0)	4.5 (4.9)	3.7 (4.2)	4.1 (2.6)

* $p < 0.05$ Alcohol days and cigarettes/day: heavy > control.
† The number of days of substance use in the last 30 days from the ASI.[7]
‡ Variable was used as a covariate in the analysis of blood flow velocity measures.
§ Years of substance use calculated from ASI.[7]
‖ The three groups of marijuana users did not differ on this measure [$F(2,50) = 0.40$, $p > 0.5$].

CV = covariate; ASI = Addiction Severity Index.

sis of alcohol abuse or dependence by DSM-IV criteria were also screened out of the study.

Procedures. TCD measurements were made within 72 hours of admission to our closed clinical research ward. A second measurement was made after 28 to 30 days of monitored abstinence on the research ward. Our closed research ward was assessable only to authorized staff and no visitors were permitted. Random urine samples were collected for urine toxicologies. The control subjects were tested once during an outpatient visit since it is difficult to recruit control subjects who would be willing to spend a month on a closed research ward and none of the measures were expected to change over this period.

Resting heart rate and blood pressure (BP) were measured in all subjects. Measurements were made within 72 hours of admission and at 28 to 30 days after admission to the clinical unit for the marijuana users. These cardiovascular measures were recorded on an outpatient visit for the control subjects as a comparison.

Blood flow velocity was determined using a temporal window (zygomatic arch) for four arteries: right and left middle (MCA) and right and left anterior (ACA) cerebral arteries using pulsed TCD sonography (Nicolet, Model TC2000). The evaluation of all four arteries took from 15 to 20 minutes. Mean velocity (Vm: cm/second), systolic velocity (Vs: cm/second), diastolic velocity (Vd: cm/second), and pulsatility index (PI = [Vs-Vd]/Vm) were determined for each artery. Any possible acute effects of nicotine on TCD measures were eliminated by testing subjects 20 minutes or longer after cigarette smoking. Caffeinated beverages were not allowed for 2 hours or more before the recording session. In one marijuana user, the 28-day TCD recording from the anterior cerebral arteries was not obtained due to recording difficulties. Thus, the evaluation of the effects of a month of monitored abstinence is based on 54 subjects for the MCA and 53 subjects for the ACA.

Statistical analysis. A group (three groups of marijuana users and control subjects) by sex analysis of variance (ANOVA) was used to test for differences in cardiovascular measures. An ANOVA with time (less than 72 hours vs 28 days) as well as dose groups (light, moderate, and heavy) between subject factor was used to determine if any of the cardiovascular measures were affected by the month of abstinence for the marijuana users.

An analysis of covariance (ANCOVA) was used on the blood flow velocity measures. A group (three groups of marijuana users and control subjects) by sex by side (right vs left) were the factors in each ANCOVA. The analysis compared the blood flow velocity data of the control subjects with that of the marijuana users collected early in abstinence. The covariates in ANCOVA were days of alcohol use in the last month and the cigarettes smoked per day since these variables differed across groups (see table 1). An ANCOVA with time (less than 72 hours vs 28 days) and side as well as the between-subject factor, dose group (light, moderate, and heavy), was used to determine if any of the blood flow velocity measures changed during the month of abstinence for the marijuana users. After each ANCOVA, post hoc tests were made using the Bonferroni procedure on the appropriate means. Statistical testing was performed with SPSS, version 11 (Chicago, IL).

Results. *Drug history and cardiovascular measures.* The drug history measures are reported in table 1. While the subject groups differed significantly by years of education [$F(3,64) = 3.67$, $p < 0.05$], there were no significant differences in Shipley estimates of IQ across groups. Cardiovascular measures are shown in table 2. Heart rate and systolic BP were similar for control and marijuana groups. Heart rate for the marijuana subjects tested at 28 to 30 days after admission was significantly greater than the values obtained within 72 hours of admission. No differences in systolic BP between the control and marijuana groups were observed. There were also no differences in systolic BP between the two test times for the marijuana groups. Diastolic BP for the marijuana users was significantly lower than that of the control subjects at the beginning of their inpatient stay. Diastolic BP did not differ

Table 2 *Cardiovascular measures*

Measure/time	Control	Marijuana users		
		Light	Moderate	Heavy
Heart rate, BPM				
<72 h	71.8 (8.9)	72.4 (10.0)	69.9 (10.7)	68.8 (12.5)
28–30 d		80.4* (9.6)	81.8* (9.4)	80.9* (10.6)
Systolic blood pressure, mm Hg				
<72 h	124.8 (11.5)	121.5 (14.4)	127.7 (15.0)	128.5 (15.0)
28–30 d		124.6 (8.2)	128.8 (15.6)	126.6 (12.0)
Diastolic blood pressure, mm Hg				
<72 h	78.8 (9.0)	68.3† (9.3)	69.3† (10.7)	70.0† (10.2)
28–30 d		69.1 (9.8)	71.8 (10.4)	68.6 (10.4)

Values are mean (SD).

* The means for the marijuana subjects tested at 28–30 days after admission is greater than the values obtained within 72 hours of admission [test time effect for marijuana groups: $F(1, 50) = 53.5$, $p < 0.001$]. Each early–late Bonferroni post hoc comparison was also significant at $p < 0.05$.

† The means of the diastolic blood pressure for the marijuana subjects tested within 72 hours after admission are lower than those of the control subjects [group effect for all groups: $F(3, 64) = 3.42$, $p < 0.05$] followed by post hoc comparisons ($p < 0.05$).

BPM = beats per minute.

among the three marijuana groups. There were no significant differences in diastolic BP throughout the stay of the marijuana users on the closed research unit.

TCD measures. No sex-related differences were observed in any of the TCD measures. There were no significant sex main effects or group by sex interactions in any of the MCA measures. There were no significant sex main effects or group by sex interactions in any of the ACA measures. In view of the lack of significant group by sex interactions in the analyses between the control subjects and marijuana users, sex was not considered in the analyses of the blood velocity values over time.

Vs and Vm for the MCA were higher for marijuana users in comparison to those for control subjects [Vs: $F(3,62) = 4.59$, $p < 0.002$; Vm: $F(3,62) = 3.14$, $p < 0.05$]. Vs and Vm did not differ among the marijuana groups (light, moderate, heavy). Figure 1A shows the means for the Vs measures for the control subjects and three marijuana groups. The results for Vm (not shown) were similar to Vs and Vd measures and were not significantly different in any of the groups. Figure 1B shows the means for the Vd measures for the control and three marijuana groups. The marijuana users also had higher PI values than the control subjects [$F(3,62) = 3.72$, $p < 0.02$]. PI did not differ among the marijuana groups (light, moderate, heavy). Figure 1C shows the means for PI for the control and marijuana groups.

Vs for the ACA was higher for marijuana users as compared to the control subjects [Vs: $F(3,62) = 5.68$, $p < 0.002$]. Vs values did not differ among the marijuana groups (light, moderate, heavy). Figure 2A shows the means for the Vs measures for the control subjects and three marijuana groups. Vd and Vm values were not significantly different among the groups. Figure 2B shows the means for the Vd measures for the control and three marijuana groups. The marijuana users also had higher PI values than the control subjects [$F(3,62) = 4.02$, $p < 0.01$], but PI did not differ among the marijuana groups (light, moderate, heavy). Figure 2C shows the plot of mean PI for the control and marijuana groups.

An ANCOVA with time and side and dose group (light, moderate, and heavy) was used to determine if any of the blood flow velocity measures changed during the month of abstinence for the marijuana users. For the MCA, the time by group interaction for Vs and PI was significant [Vs: $F(2,49) = 3.80$, $p < 0.05$; PI: $F(2,49) = 3.43$, $p < 0.05$]. This interaction indicated that there was a significant change over time for some of the marijuana groups. There was a significant decrease late in abstinence in Vs values for the light marijuana users compared to early abstinence (see figure 1A). A significant increase was observed for the heavy users late during the course of abstinence in comparison to the earlier time of testing (see figure 1A). PI for the light and moderate marijuana users decreased significantly from early to late abstinence (see figure 1C).

For the ACA, the time by marijuana group interaction was significant for Vs [$F(2,48) = 5.31$, $p < 0.01$], Vm [$F(2,48) = 3.35$, $p < 0.05$], and PI [$F(2,48) = 3.14$, $p < 0.05$]. Vs for the heavy marijuana users increased during the month of monitored abstinence (see figure 2B). PI values were reduced late in abstinence for the light marijuana users (see figure 2C).

Discussion. The main findings of the study are that, in comparison to control subjects, marijuana users show 1) elevated systolic and mean blood flow velocity in the MCA and ACA; 2) higher PI values in both the MCA and ACA; 3) no significant improvements in systolic velocity during a month of monitored abstinence; and 4) improvement in PI values only for the light and moderate marijuana users during the month of monitored abstinence. The present measurements, obtained during a month of observed abstinence from marijuana users, document poten-

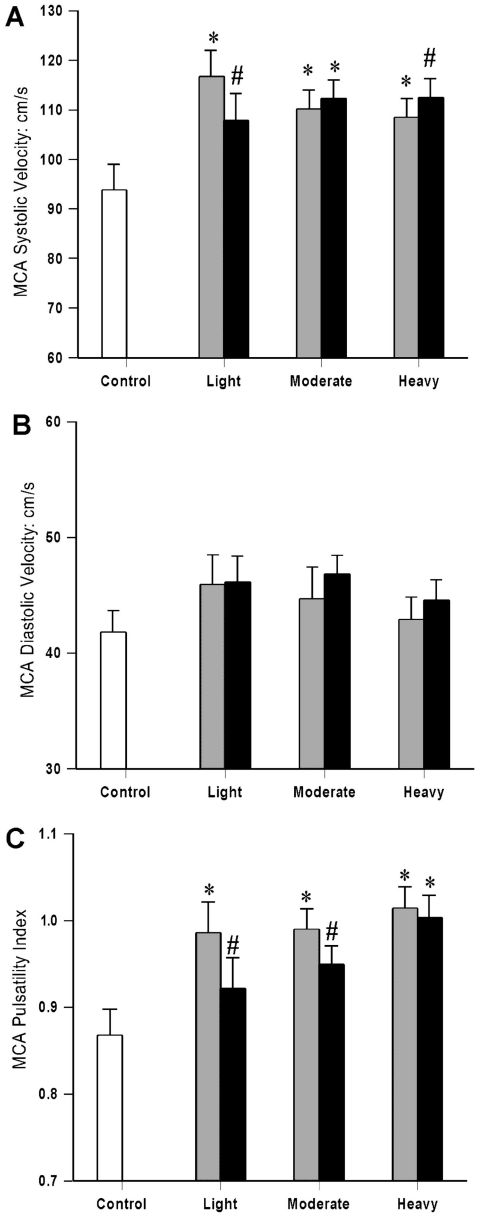

Figure 1. Mean systolic velocity is plotted for middle cerebral artery (A). Measurements were made within 72 hours of admission (gray bars) and after 28 days of monitored abstinence (black bars) for the marijuana users and at an outpatient test day for the control subjects (white bars). The error bar indicates the standard error. The asterisks indicate differences ($p < 0.05$) between the control and the marijuana groups at each test time using the Bonferroni procedure. The pound signs indicate significant decreases from early to late testing for the light group and increases from early to late testing for the heavy group. Mean diastolic velocity is plotted for the control subjects and the three marijuana groups for middle cerebral artery (B). No significant differences among the experimental groups were observed for diastolic velocity. Mean PI values are plotted for middle cerebral artery (C). The asterisks indicate differences ($p < 0.05$) between the control and the marijuana groups at each test time using the Bonferroni procedure. The pound signs indicate a significant reduction in PI from early to late abstinence for the light and moderate groups.

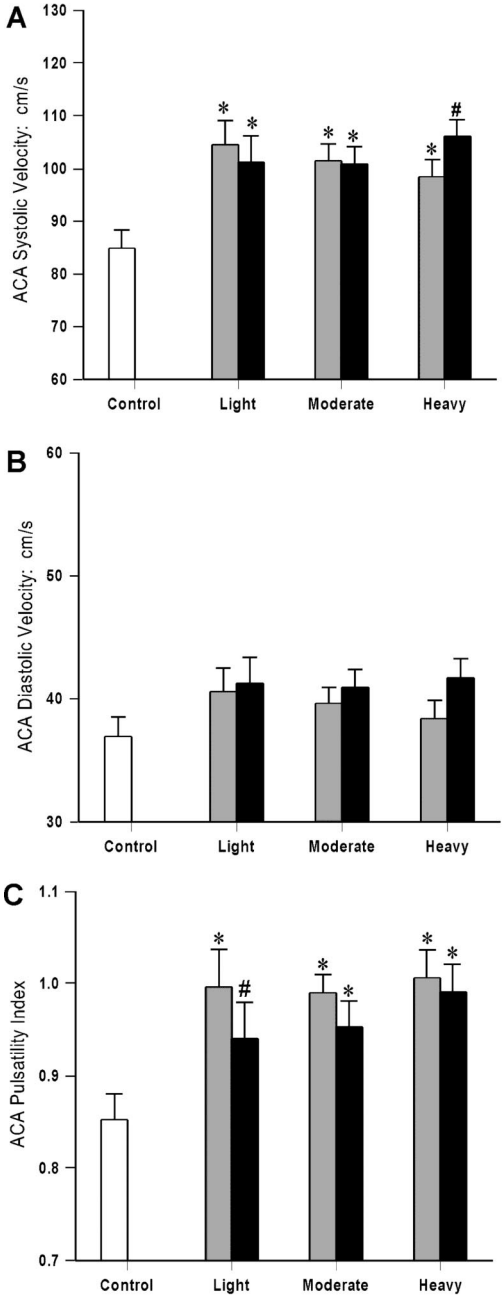

Figure 2. Mean systolic velocity is plotted for anterior cerebral artery (A). Recordings were made within 72 hours of admission (gray bars) and after 28 days of monitored abstinence (black bars) for the marijuana users and at an outpatient test day for the control subjects (white bars). The asterisks indicate differences ($p < 0.05$) between the control and the marijuana groups at each test time using the Bonferroni procedure. The pound signs indicate significant increases from early to late testing for the heavy group. Mean diastolic velocity is plotted for the control subjects and the three marijuana groups for the anterior cerebral artery (B). No significant differences were observed among the experimental groups. Mean PI values are plotted for anterior cerebral artery (C). The asterisks indicate differences ($p < 0.05$) between the control and the marijuana groups at each test time using the Bonferroni procedure. The pound signs indicate a significant reduction in PI from early to late abstinence for the light group.

tially prolonged marijuana-mediated changes in vascular hemodynamics.

Reported increased cerebral blood flow velocities with increased PI observed in other patient populations are thought to be due to increased cerebrovascular resistance secondary to vasoconstriction of both small and large cortical vessels.[8] These changes might be secondary to increased cerebral perfusion pressure when vascular autoregulation is impaired.[9] Although caution must be taken when comparing different methods of assessing cerebral perfusion, the present study extends previous reports of marijuana-associated alterations in blood flow measured by SPECT,[10] PET,[4] or MRI.[11] For example, a study, using dynamic susceptibility contrast MRI, revealed significant increases in cerebral blood volume in marijuana users as compared to control subjects over a month of monitored abstinence.[11] Because increased blood volume has been reported to occur in areas of reduced perfusion,[12] it is possible that our present observations and those of others[11] might reflect similar distal perfusion deficits in marijuana patients. In contrast to the decreases observed during abstinence, acute administration of marijuana increases cerebral blood flow.[3] Taken together, those observations and ours are consistent with reports indicating that the acute effects of marijuana are opposite to those observed during withdrawal.[13]

The PI values of the marijuana users in the present study are higher than those of control subjects in this and other studies.[14] The marijuana users showed elevated PI values that are somewhat higher than those of patients with chronic hypertension[15] and diabetic patients[16] who show mean PI values ranging from 0.87 to 0.89. However, their PI values are lower than those reported for patients with multi-infarct dementia who have mean values of 1.20 to 1.27.[17] Given that the PI values from the present marijuana users fall between the ranges of less affected patients[15,16] and those patients with neurologic impairment,[17] we suggest that our findings might be secondary to abnormalities in small vessels because similar MCA PI values have been reported to reflect small-vessel diseases.[18]

Although we are suggesting that our observations are associated with marijuana use, it is also possible to suggest that they might be consequent to the concurrent use of other substances since cocaine users also show abnormalities in TCD indices.[19] This is probably not the case because the marijuana users in our study reported the use of no other substances except for alcohol and tobacco (see table 1). In fact, prospective subjects who reported other abuse of other substances or had urine tests positive for other substances were excluded from the study. Subjects with excessive use of alcohol were also screened out of this study. An analysis of covariance was also used in order to control for subjects with even modest use of these substances. These analyses revealed that neither alcohol nor tobacco use contributed to any of the differences in blood flow velocity observed between the control subjects and marijuana users. Furthermore, preliminary data from this laboratory have documented that chronic cigarette smoking does not alter PI.[20]

The changes in cerebrovascular flow observed in the present study might be related to the blood pressure differences between the control and marijuana groups. In the present study, systolic blood flow velocity was increased in marijuana users compared to control individuals. However, diastolic blood pressure was lower in the marijuana users, findings that are opposite of what might be expected if pressure and velocity were directly related. Furthermore, changes in cerebrovascular blood flow velocity appear to be related to blood pressure changes only when there is a loss of cerebral autoregulation.[9] It is more likely that the changes in blood pressure and blood flow velocity in the anterior and middle arteries might both be associated with withdrawal from the prolonged use of marijuana. In any case, the present observations suggest that more research is needed to study the effects of chronic marijuana use on cerebral and peripheral vascular systems.

A number of possible scenarios might be responsible for our present observations because of reported effects of the marijuana on the sympathetic and parasympathetic nervous systems. Specifically, marijuana administration is known to cause postural hypotension with dizziness as a result of drug-induced decreases in peripheral resistance.[21] These effects are thought to be mediated by CB1 receptors located on neurons and smooth muscle[22] and via stimulation of non-CB1 or non-CB2 receptors located on endothelial cells[23] which can also cause vasodilation.[24] This suggestion is consistent with our finding that the marijuana users in the present study had low resting diastolic blood pressure throughout the month of abstinence. The marijuana-associated cerebrovascular changes might be due to changes in the density of CB1 receptors in the brain and blood vessels as a result of the use of high doses of the drug. Chronic injections of THC have been shown to increase in the number of these receptors in the brain.[24] Therefore, it is possible that chronic intake of marijuana by drug users might affect cerebrovascular resistance through changes mediated in blood vessels or in the brain parenchyma.

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