

Methadone Treatment Induces Attenuation of Cerebrovascular Deficits Associated with the Prolonged Abuse of Cocaine and Heroin

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Opiate replacement therapy has been useful in reducing heroin use and in keeping patients in treatment programs. However, neuropsychological and neurophysiological effects of this treatment regimen have not been evaluated systematically. To determine whether methadone treatment reduces the magnitude of cerebral blood flow alternations in polysubstance (heroin and cocaine) abusers, we compared blood flow parameters in control subjects ($n=26$), polysubstance abusers ($n=28$) maintained on methadone for 24 weeks, and polysubstance abusers ($n=22$) who were not seeking treatment. Blood flow velocity was recorded from the anterior and middle cerebral arteries using transcranial Doppler sonography on an outpatient visit. The pulsatility index, a measure of cerebrovascular resistance, was significantly ($p<0.05$) increased in both groups of polysubstance abusers compared to control subjects. Increased pulsatility in the two groups of substance abusers suggests constriction of the small cortical arteries. Nevertheless, the methadone-maintained polysubstance abusers had significantly lower pulsatility values than the nontreatment substance-abusing group. These findings suggest that maintenance on methadone might have significant beneficial neurovascular effects on this population of patients.

Neuropsychopharmacology (2003) **28**, 562–568. doi:10.1038/sj.npp.1300073

Keywords: heroin; cocaine; methadone; cerebral perfusion; cerebrovascular resistance; polysubstance abuse

INTRODUCTION

Nearly a million people in the United States regularly abuse heroin (Community Epidemiology Work Group, 2001). The use of heroin among high school seniors in the United States has also increased (Monitoring the Future Study, 2000). Many heroin-dependent individuals also abuse cocaine, marijuana, and alcohol (Hser *et al*, 2001). These substance abusers are at risk for many medical problems, including collapsed veins, endocarditis, abscesses, cellulitis, hepatitis, pneumonia, lymphadenopathy, spongiform leukoencephalopathy, and HIV/AIDS (Ben Diane *et al*, 2000; Hser *et al*, 2001). Treatment approaches such as methadone, l- α acetomethadol, and buprenorphine, which are useful in reducing heroin use and in keeping patients in treatment

programs (O'Connor and Fiellin, 2000; Johnson *et al*, 2000), might reduce health risks in these patients.

In addition to the acute medical problems listed above, areas of reduced cortical perfusion have been reported in heroin-dependent individuals during early abstinence (Levin *et al*, 1995; Rose *et al*, 1996; Danos *et al*, 1998). Specifically, SPECT scans performed after a clonidine-supported 5-day detoxification schedule revealed reduced perfusion in the frontal, temporal, parietal cortices (Rose *et al*, 1996). The perfusion deficits in these areas were reported to improve after 2 weeks of abstinence (Rose *et al*, 1996). Levin *et al* (1995) also reported that areas of reduced cortical perfusion observed in SPECT scans of polysubstance (heroin and cocaine) abusers improved after several weeks of treatment with buprenorphine. Interestingly, Danos *et al* (1998) found that blood flow, measured by SPECT, in the parietal cortex was correlated with the dose of methadone that heroin-dependent patients were receiving, with methadone causing a substantive increase in perfusion. Further support for the notion that reduced perfusion in heroin-dependent individuals is related to opiate withdrawal comes from a SPECT study of regional cerebral blood flow in humans during naltrexone-precipitated withdrawal from buprenorphine (van Dyck *et al*,

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Received 24 February 2002; revised 11 September 2002; accepted 16 September 2002

Online publication: 25 September 2002 at <http://www.acnp.org/citations/Npp0925002392>

1994). In this study, the severity of the precipitated withdrawal was correlated with a reduction of blood flow in the anterior cingulate cortex. Individuals who abuse both heroin and cocaine might also show reductions in cerebral perfusion secondary to their prolonged use of cocaine. For example, several investigators using position emission tomography (PET) and SPECT (Tumeh *et al*, 1990; Weber *et al*, 1990; Volkow *et al*, 1991; Holman *et al*, 1991; Levin *et al*, 1994, 1995) as well as transcranial Doppler sonography (TCD) (Herning *et al*, 1999) have reported reduced perfusion in cocaine abusers. Thus, cocaine and heroin may potentiate each other's influence on cerebral blood flow.

It is thus important to relate this discussion to the possible beneficial effects of opiate replacement therapy, which include reduced craving for heroin, reduced needs for drug-seeking behaviors, as well as reduced relapse rates (O'Connor and Fiehn, 2000; Johnson *et al*, 2000). While these treatment approaches would substantially reduce infection rates in that population, the effects of long-term opiate replacement therapy on cerebral blood flow have not been reported. Yet, it is important to know if opiate replacement therapy has positive, negative, or no effects on cerebral blood flow since heroin addicts are often on replacement therapy for extended periods. These issues are of clinical relevance because, if maintenance treatments were to cause additional damage in the brains of these patients, these patients would be at risk for further neuropsychiatric complications. On the other hand, improvement in flow would help to substantiate the need for enlarging the pool of treated patients.

To quantify cerebral blood flow in polysubstance (heroin and cocaine) abusers and to determine how prolonged methadone treatment might influence these changes, we used TCD to compare various indices of blood flow obtained in control subjects to that of polysubstance abusers maintained on methadone for 24 weeks and of polysubstance abusers not seeking treatment. We were thus able to evaluate the effects of methadone when the polysubstance abusers were no longer experiencing the effects of withdrawal during early abstinence.

TCD has proven to be useful in evaluating abnormal hemodynamics in cerebral arteries (Martin *et al*, 1994; Silvestrini *et al*, 1996; Howard *et al*, 1996). An important difference between TCD and other methodologies such as PET or SPECT is that TCD measures blood flow velocity in large arteries rather than cerebral perfusion in small vessels. Pulsatility, an index of vascular resistance, can be obtained from the velocity measures (Arnolds and von Reutern, 1986; Czosnyka *et al*, 1996; Cho *et al*, 1997). Changes in blood flow velocity in large arteries imply constriction, partial obstruction or dilation of these vessels (Martin *et al*, 1994). In addition, changes in cerebral resistance of small cortical blood vessels or pulsatility can be inferred from blood velocity values recorded on large arteries (Cho *et al*, 1997). Blood pressure must be similar or controlled statistically in the comparison groups for these interpretations of velocity and pulsatility to hold. Since the TCD assessment is noninvasive, economical, and rapid, TCD allows for repeated assessments of large samples of subjects, something that is not usually possible with the PET/SPECT imaging studies.

METHODS

Subjects

A total of 28 polysubstance abusers maintained on methadone (Poly/Meth), 22 nontreatment seeking polysubstance abusers (Poly/NTS), and 26 control (CTL) subjects were studied. The methadone-maintained polysubstance abusers were receiving 60–80 mg of methadone per day for 24.3±3.3 weeks as part of an outpatient treatment study at the Archway Clinic of the NIDA-Intramural Research Program (Preston *et al*, 2000). The nontreatment seeking polysubstance abusers were screened to determine whether they wanted treatment before entering this study. Before undergoing blood flow velocity assessment by TCD, all volunteers had undergone medical, neurological, psychological, and laboratory evaluations. All the polysubstance abusers met the DSM-III-R criteria for both heroin and cocaine dependence/abuse using the Diagnostic Interview Schedule (DIS: Robins *et al*, 1988). Demographic information and drug use history information were obtained from the Addiction Severity Index (ASI: McLellan *et al*, 1986). Demographic information for the three groups is listed in Table 1.

Exclusion criteria that applied to all subjects include: (1) major medical and psychiatric illnesses, (2) head injuries with loss of consciousness for greater than 5 min, (3) evidence of any neurological abnormalities by history or examination, (4) HIV seropositivity. The research protocol was approved by the National Institute on Drug Abuse and Johns Hopkins Bayview Medical Center Institutional Review Boards for Human Research. Written informed consent was obtained from all subjects. In addition, this research was carried out in accordance with the Declaration of Helsinki of 1975.

Procedures

Subjects were tested on an outpatient visit. All subjects were assessed for drug use before TCD recording and were required not to smoke tobacco cigarette for 20 min before TCD recording. Resting heart rate and blood pressure were also measured in all subjects. The methadone-maintained polysubstance abusers were tested before their daily methadone dose. 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 transcranial Doppler sonography (Nicolet, Model TC2000). A hand-held ultrasound transducer was directed at the cerebral artery of interest using the correct placement on the skull, angle, and depth setting. A shift in sound frequency in the reflected sound is used to calculate the blood flow velocity in that artery. Blood flow velocities from the other cerebral arteries can be obtained by changing transducer location, angle, and depth setting. A mean velocity (V_m : cm/s), systolic velocity (V_s : cm/s), diastolic velocity (V_d : cm/s), and pulsatility index ($PI = (V_s - V_d)/V_m$) were determined for each artery.

Statistical Analysis

A group (CTL, Poly/Meth, Poly/NTS) by gender analysis of variance (ANOVA) was used to test for differences in

Table 1 Demographic Measures and Drug History

	CTL		Poly/Meth		Poly/NTS	
	Mean	SD	Mean	SD	Mean	SD
<i>Demographic measures</i>						
African American (%)	80.8		88.2		95.2	
Gender (% male)	58.7		60.7		77.8	
Age (years)	31.1	8.5	38.8*	8.4	34.9	7.1
Education (years)	13.2	1.8	11.6	1.4	11.9	1.4
Weight (pounds)	161.5	29.4	156.9	33.8	168.5	37.1
Monthly income (€)	990	984	1704 ^a	2335	1749 ^a	2714
<i>Type of job</i>						
Laborer: mover, factory worker, construction, housecleaning, etc	Laborer	4	Laborer	8	Laborer	10
Skilled laborer: auto mechanic, meat cutter, etc	Skilled laborer	4	Skilled laborer	6	Cook	2
Driver: truck or taxi	Cook	3	Driver	2	Clerical work	4
	Driver	4	Clerical work	4	Clerk	2
	Clerical work	7	Clerk	4	Unemployed	2
	Clerk	2	Unemployed	3	Laborer	10
	Student	2	Laborer	8	Cook	2
<i>Drug history measures</i>						
Cocaine (days/30)			19.3	10.2	17.7	7.0
Cocaine (years)			12.2	9.0	9.1	6.0
Heroin (days/30)			28.6	5.7	20.2	6.7
Heroin (years)			15.7	8.8	11.9	7.1
Alcohol (days/30)	1.2	2.2	5.4	7.9	8.6	9.2
Alcohol (years)	5.4	7.6	11.5	12.9	15.2	9.7
Marijuana (days/30)			1.6	3.1	4.4	7.7
Marijuana (years)			8.2	10.6	8.5	8.4
Cigarettes/day	4.8	8.8	13.7	8.8	18.8	12.5
Cigarettes (years)	8.3	11.6	18.3	11.1	18.5	8.2

*The mean for the Poly/Meth subjects was significantly ($p < 0.05$) higher than that of the CTL subjects using the Bonferroni *post hoc* procedure. ^aIncome includes illegal income.

Table 2 Cardiovascular and Blood Chemistry Measures

	CTL		Poly/Meth		Poly/NTS	
	Mean	SD	Mean	SD	Mean	SD
<i>Cardiovascular</i>						
Heart rate	73.3	11.1	71.4	12.4	71.6	12.4
Systolic blood pressure	124.6	11.3	136.8*	16.4	129.1	9.8
Diastolic blood pressure	77.9	9.1	82.4	12.8	77.0	8.4
<i>Blood chemistry</i>						
Hematocrit	39.8	2.8	40.0	4.7	41.7	4.5
Hemoglobin	13.6	1.0	13.6	1.4	14.2	1.5
Cholesterol	187.2	45.6	174.4	45.5	173.0	31.5

*The mean for the Poly/Meth subjects was significantly ($p < 0.05$) higher than that of the other groups using the Bonferroni *post hoc* procedure.

cardiovascular and blood chemistry measures. A group (CTL, Poly/Meth, Poly/NTS) by gender by side (right vs left) analysis of covariance (ANCOVA) was used to test for differences in flow velocity parameters. Age, systolic, and diastolic blood pressures were covariates in the ANCOVA to control for differences among the groups on these measures (see Tables 1 and 2). Bonferroni multiple comparison *post*

hoc procedure was used to test for differences among means.

RESULTS

Cardiovascular and blood chemistry values (cholesterol, hematocrit, and hemoglobin) are displayed in Table 2.

Group differences were only found for systolic blood pressure. No interactions involving gender were significant for any blood flow velocity measures.

Middle Cerebral Artery

The group main effect for mean velocity for the middle cerebral artery was significant (V_m : $F(2,67) = 3.28$, $p < 0.05$) after controlling for age ($F(1,67) = 8.97$, $p < 0.005$). The other covariates were not significant (systolic blood pressure: $F(1,67) = 3.06$, $p > 0.05$; diastolic blood pressure: $F(1,67) = 0.18$, $p > 0.05$). The group main effect for V_s for the MCA was significant (V_s : $F(2,67) = 4.93$, $p < 0.01$) after controlling for age ($F(1,67) = 11.11$, $p < 0.001$). The other covariates were not significant (systolic blood pressure: $F(1,67) = 2.01$, $p > 0.05$; diastolic blood pressure: $F(1,67) = 0.80$, $p > 0.05$). Figure 1 shows the means for systolic velocity averaged over both right and left middle cerebral artery. Mean systolic velocity for the Poly/Meth group is significantly ($p < 0.01$) faster than that of the CTL group using the Bonferroni multiple comparison *post hoc* procedure. The group main effect for diastolic velocity for the middle cerebral artery was not significant (V_d : $F(2,67) = 2.70$, $p > 0.05$) after controlling for age ($F(1,67) = 5.34$, $p < 0.03$) and systolic blood pressure ($F(1,67) = 4.08$, $p < 0.05$). Figure 2 shows the means for diastolic velocity averaged over both right and left MCA. The group main effect was significant for PI ($F(2,69) = 9.70$, $p < 0.002$) after controlling for diastolic blood pressure ($F(1,67) = 4.34$, $p < 0.05$). Age ($F(1,67) = 3.13$, $p < 0.05$) and systolic blood pressure ($F(1,67) = 1.72$, $p < 0.05$) were not significant covariates. Figure 3 shows the means PI averaged over both right and left middle cerebral artery. The mean for the Poly/Meth group was significantly ($p < 0.02$) larger than the CTL group and significantly ($p < 0.05$) smaller than the Poly/NTS group (the Bonferroni multiple comparison *post hoc* procedure). There was no significant group by side interaction for any of the middle cerebral artery measures.

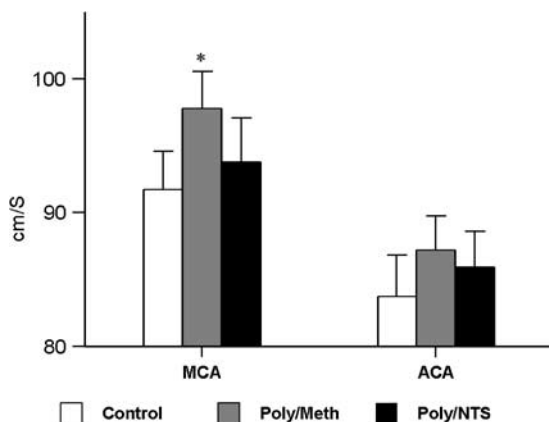


Figure 1 Group means and standard errors for systolic velocity are plotted for both arteries. The asterisk indicates that the mean for the MCA of the Poly/Meth group is significantly greater than that of the control group ($p < 0.01$) using the Bonferroni *post hoc* procedure.

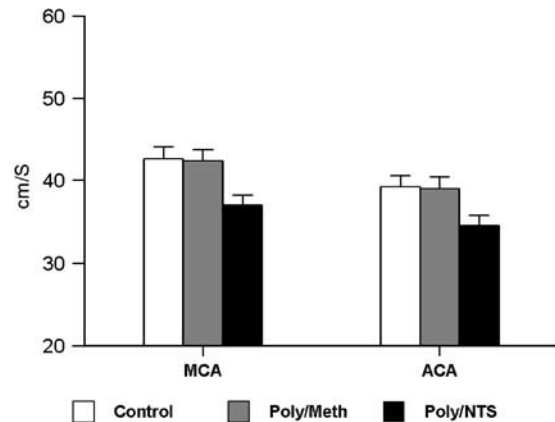


Figure 2 Group means and standard for diastolic velocity are plotted for both arteries. No significant differences were observed among the group for either artery.

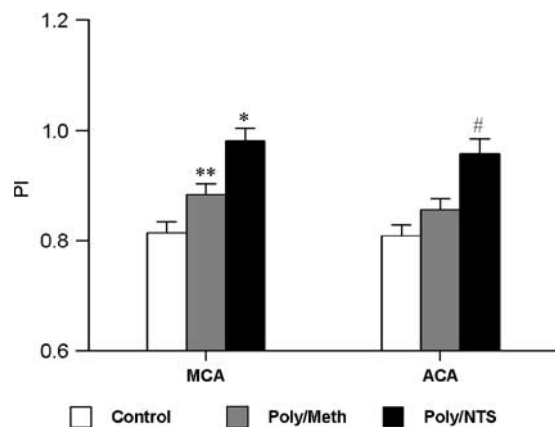


Figure 3 Group means and standard errors for the pulsatility index are plotted for both arteries. The double asterisk indicates that the mean for the MCA of the Poly/Meth group is significantly greater than that of the control group ($p < 0.02$) using the Bonferroni *post hoc* procedure. The single asterisk indicates that the mean for the MCA of the Poly/NTS group is significantly greater than that of the Poly/Meth group ($p < 0.05$) using the Bonferroni *post hoc* procedure. The pound sign indicates that the mean for ACA of the Poly/NTS group is significantly greater than the other groups ($p < 0.05$ or greater).

Anterior Cerebral Artery

The group main effect for mean velocity for the anterior cerebral was not significant (V_m : $F(2,67) = 2.08$, $p > 0.05$) with no significant covariate in the analysis (age: $F(1,67) = 2.42$, $p > 0.05$; systolic blood pressure: $F(1,67) = 0.38$, $p > 0.05$; diastolic blood pressure: $F(1,67) = 0.01$, $p > 0.05$). The group main effect for systolic velocity for the anterior cerebral artery was not significant (V_s : $F(2,67) = 1.45$, $p > 0.05$) with no significant covariate in the analysis (age: $F(1,67) = 3.49$, $p > 0.05$; systolic blood pressure: $F(1,67) = 0.20$, $p > 0.05$; diastolic blood pressure: $F(1,67) = 0.34$, $p > 0.05$). Figure 1 shows the means for systolic velocity averaged over both right and left anterior cerebral artery. The group main effect for diastolic velocity for the anterior cerebral artery was not significant (V_d : $F(2,67) = 1.55$, $p > 0.05$) with no significant covariates in the analysis (age: $F(1,67) = 2.66$, $p > 0.05$; systolic blood pressure: $F(1,67) = 1.16$, $p > 0.05$; diastolic blood pressure: $F(1,67) = 1.16$, $p > 0.05$).

$F(1,67) = 0.39$, $p > 0.05$). Figure 2 shows the means for diastolic velocity averaged over both right and left anterior cerebral artery. The group main effect was significant for PI ($F(2,69) = 8.63$, $p < 0.001$) after controlling for diastolic blood pressure ($F(1,67) = 6.02$, $p < 0.02$). Age ($F(1,67) = 0.01$, $p > 0.05$) and systolic blood pressure ($F(1,67) = 2.60$, $p > 0.05$) were not significant covariates in the latter analysis. Figure 3 shows means PI averaged over both right and left anterior cerebral artery. The mean PI for the Poly/NTS group was significantly larger than the CTL group ($p < 0.04$) and the Poly/Meth group ($p < 0.01$) using the Bonferroni multiple comparison *post hoc* procedure. There was no significant group by side interaction for any of the anterior cerebral artery measures.

Effects of Current Drug Use in the Poly/Meth Group

A total of 17 methadone-maintained subjects had a urine toxicology positive for heroin and/or cocaine at the time of the TCD testing and 11 subjects did not. To test whether the current drug use in the methadone-maintained subjects might have produced differences in the TCD measures, drug status (current use vs no current use) by side ANOVA was performed for all of the TCD measures. The means and results of these analyses are presented in Table 3. There were no differences between the methadone-maintained subjects who currently used drugs and those who did not on any of the blood flow velocity measures or PI.

Controlling for Effects of Tobacco Smoking

We attempted to eliminate the acute effects of nicotine on TCD measures by testing subjects 20 min or longer after cigarette smoking. Nevertheless, it was still possible that the effects of prolonged smoking might have confounded our pulsatility results. Thus, an analysis of covariance (group and side as factors) was performed on the PI values, with number of years of cigarette smoking used as the covariate to control for the prolonged effects of smoking. In the analysis for the PI from the MCA, the group main effect was significant for PI ($F(2,71) = 19.21$, $p < 0.0001$) whereas years of smoking ($F(1,71) = 0.014$, $p < 0.50$) was not a significant covariate. In the analysis for the PI from the ACA, the group main effect was significant for PI ($F(2,71) = 13.50$,

$p < 0.0001$) whereas years of smoking ($F(1,71) = 0.467$, $p < 0.50$) was not a significant covariate.

DISCUSSION

Pulsatility index was increased in polysubstance abusers not seeking treatment compared to controls and methadone-maintained subjects. The mean PI values (0.81 ± 0.10) observed in 30 to 40-year-old control subjects in the present study are comparable to those observed by other researchers (Martin *et al*, 1994; Steinmeier *et al*, 1993; Arjona and Prula, 2002). Specifically, mean normative or control values for PI values in the middle cerebral artery for persons under 40 years of age were reported to be 0.82 with 95% confidence interval from 0.78 to 0.87 (Martin *et al*, 1994), 0.84 with a standard deviation of 0.16 (Steinmeier *et al*, 1993), and 0.76 with a standard deviation of 0.08 (Arjona and Prula, 2002). The methadone-maintained polysubstance abusers had elevated PI values, but these were lower than the nontreatment seeking polysubstance abusers (see Figure 3). Methadone treatment for 24 weeks, however, did not completely reverse these PI increases caused by abuse of multiple drugs.

The present observations using TCD sonography in this sample of polysubstance abusers are consistent with our previous reports (Herning *et al*, 1999, 2001, 2002; Jones *et al*, 2000) and support the suggestion that drug abuse is associated with abnormal cerebral hemodynamics. Studies of pulsatility indices in other patient populations suggest that increased cerebrovascular resistance is because of vasoconstriction of small cortical vessels (Martin *et al*, 1994; Biedert *et al*, 1995; Cho *et al*, 1997; Grubb *et al*, 1998). Patients with multi-infarct dementia have reported mean MCA PI values of 1.27 ± 0.15 (Biedert *et al*, 1995) and of 1.20 (standard deviation not given) (Sattel *et al*, 1996). Chronic hypertensives (Cho *et al*, 1997) and diabetic patients (Lee *et al*, 2000) have been reported to have PI increases, which correspond to means of 0.89 (standard deviation not given) and 0.87 ± 0.22 , respectively. Middle cerebral artery PI values were found to be correlated with MRI measures of small vessel diseases characterized by periventricular hyperintensity (PI cutoff point for detection: 1.17), deep white matter hyperintensity (PI cutoff point for detection: 0.96), and lacunar disease (PI cutoff point for detection: 0.96) (Kidwell *et al*, 2001). When considered with these observations, our findings suggest that the repeated use of heroin and cocaine may contribute to a state of vascular insufficiency with a mean PI value of 0.98 that cannot be completely reversed by methadone. These observations also suggest that chronic abuse of these drugs might be associated with damage in the brain parenchyma.

This study also found that mean and systolic blood flow velocity in the middle cerebral artery was increased in methadone-maintained polysubstance abusers as compared with the control subjects after statistically correcting for a difference in age. While systolic blood pressure was also higher for the methadone-maintained subjects, systolic blood pressure was not related to the group differences as revealed by the analysis of covariance. This increase in blood flow velocity in the methadone-maintained polysubstance abusers relative to control subjects suggests a

Table 3 Effects of Current Drug Use on Cerebral Blood Flow Velocity Measures in Poly/Meth Group

TCD measure	Nonusers (N = 11)		Current users (N = 17)		F ^b	Probability
	Mean ^a	SD	Mean	SD		
MCA V _m (cm/s)	62.421	14.549	62.914	13.033	0.009	0.924
MCA V _s (cm/s)	97.378	22.411	97.995	20.411	0.006	0.940
MCA V _d (cm/s)	42.201	10.134	42.510	9.291	0.007	0.932
MCA PI	0.883	0.101	0.882	0.123	0.001	0.986
ACA V _m (cm/s)	60.351	14.508	57.036	12.270	0.483	0.493
ACA V _s (cm/s)	90.136	17.391	85.282	20.371	0.517	0.479
ACA V _d (cm/s)	40.977	8.969	37.693	11.083	0.797	0.380
ACA PI	0.838	0.103	0.866	0.122	0.476	0.496

^aMean of the right and left artery over all subjects in this group. ^bdf = 1,26.

constriction in the middle cerebral artery as reported in other studies that have used patients with vascular disorders (Silvestrini *et al*, 1996; Howard *et al*, 1996). Since our observations of increased systolic velocity in the methadone patients are in contrast to those found in cocaine abusers (Herning *et al*, 1999), these changes might be secondary to the specific effects of methadone on the neural controls of the cerebral vasculature.

Since these polysubstance abusers used both cocaine and heroin, an important question that remains unanswered is whether the perfusion changes observed in the nontreatment seeking polysubstance abusers were due to the prolonged use of both substances or only to the prolonged use of cocaine. Previous studies found reduced perfusion in recently abstinent heroin abusers, findings possibly attributable to opiate withdrawal (Rose *et al*, 1996). The present study reported increased cerebral resistance in methadone-maintained polysubstance abusers and nontreatment seeking polysubstance abusers who recently used both cocaine and heroin. Several groups of investigators have reported reduced flow or metabolism in cocaine abusers (Tumeh *et al*, 1990; Weber *et al*, 1990; Volkow *et al*, 1991; Holman *et al*, 1991; Levin *et al*, 1994, 1995; Herning *et al*, 1999). Moreover, increased flow resistance, using TCD, has been found to persist even after a month of monitored abstinence (Herning *et al*, 1999). Thus, it is possible that the increased flow resistance observed in the polysubstance abusers in the present study might be due solely to the prolonged use of cocaine. This question could be resolved by evaluating cerebral perfusion in a sample of individuals who have a history of abusing only heroin and are currently abstinent from all opiates. Such patients are difficult to find, however.

It is important to note that methadone-maintained polysubstance abusers who were currently using cocaine and heroin had similar blood flow velocity values as those methadone-maintained polysubstance abusers who were not currently using these drugs. Thus, recent use of other drugs appears not to directly affect blood flow velocity measures in the methadone-maintained subjects since both groups of methadone-maintained subjects have blood flow velocity values with similar means and standard deviations. Thus, the improved measures in the methadone-maintained subjects might possibly be because of the prolonged effects of methadone.

It is also possible to suggest that these difference in flow resistance are attributable to cigarette smoking because smoking has been reported to cause acute changes in vascular flow (Cruickshank *et al*, 1989; Kodaira *et al*, 1993; Morioka *et al*, 1997). However, observations on the effects of cigarette smoking on the cerebral vasculature conflict with each other, with some investigators reporting increases (Kodaira *et al*, 1993) and others reporting decreases in cerebral blood flow lasting during smoking and 5 min after smoking (Cruickshank *et al*, 1989; Morioka *et al*, 1997). More importantly, however, our analysis of covariance revealed that the number of years that the subjects smoked did not influence the PI results. Furthermore, preliminary data from this laboratory have also documented that chronic cigarette smoking does not alter the pulsatility index (Herning *et al*, unpublished).

Since this was a cross-sectional study, our results might be secondary to other uncontrolled factors. In an attempt to

rule out other possible confounds, all the volunteers underwent extensive medical, neurological, psychological, and laboratory evaluations. In addition, the methadone-maintained polysubstance abusers were tested after a uniform period of treatment (24.3±3.3 weeks). Other factors related to social economic status could have also contributed to these abnormalities. However, all of the subjects came from similar income groups, with some control subjects actually making less money than the substance abusers. Nevertheless, it is still necessary to consider the possibility that these blood flow differences might be because of undetermined differences between drug abusers who seek and those who do not seek treatment.

In conclusion, this is, to our knowledge, the first study to evaluate cerebral blood flow by TCD in polysubstance abusers maintained on methadone for an extended period. Our findings suggest that the vasculature of 30 to 40-year-old polysubstance abusers might be compromised, thus putting them at risk for cerebrovascular accidents (Strandgaard, 1993; Jamrozik *et al*, 2000), small vessel diseases (Lee *et al*, 2000; Kidwell *et al*, 2001), and/or cognitive impairments (Anstey and Smith, 1999; Rabbitt and Lowe, 2000). Our study reveals that treatment with methadone can reduce these abnormalities, although this therapeutic approach did not normalize these measures. Finally, our present observations further strengthen the view that heroin and cocaine abuse might result in parenchymal damage secondary in flow deficits to various brain regions of drug abusing subjects. Such damage might then be accompanied by various degrees of clinically significant neurobehavioral syndromes, the treatment of which will necessitate a more thorough neuropsychiatric approach that takes into account possible changes in cerebrovascular hemodynamics.

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