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Award Number DAMD17-95-2-5025

TITLE: A Comparison of Cerebral Blood Flow in Migraineurs During Headache, Headache-Free and Treatment Periods

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REPORT DATE: January 1999

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	January 1999	Final (15 Sep 95 - 31 Dec 98)

4. TITLE AND SUBTITLE
A Comparison of Cerebral Blood Flow in Migraineurs During Headache, Headache-Free and Treatment Periods

5. FUNDING NUMBERS
DAMD17-95-2-5025

6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Buffalo Institute for Medical Research
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research for Materiel Command
Fort Detrick, MD 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

14. SUBJECT TERMS
Defense Women's Health Research Program

15. NUMBER OF PAGES
21

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Summary

The pathophysiology of migraine remains poorly understood. Sumatriptan has been reported to increase flow velocities in large cerebral arteries, consistent with a vasoconstrictive effect. We report data from a study of tissue cerebral blood flow (CBF) in migraine following treatment with sumatriptan.

Methods:
Otherwise healthy patients with a minimum of one migraine headache per month (IHS criteria) were scanned using $H_2{}^{15}O$, and positron emission tomography, within 24 hours of the onset of migraine headache. Patients were re-imaged 0.25, 0.5 and 1 hours following 6 mg SQ sumatriptan, and after a headache free interval of at least 48 hours.

Results:
Global CBF mean (SD) in migraineurs was of 46.4 (8.3) ml/min/100g prior to treatment, and 46.2 (10.8), 48.1 (10.3), and 46.9 (7.0) ml/min/100g, at 0.25, 0.5 and 1 hour post sumatriptan respectively. Mean CBF was 49.8 (8.4) in the migraine free state. When compared to the headache free state, global CBF was not significantly changed during migraine. Sumatriptan did not have an effect on global CBF.

Regional analysis showed a significant reduction in flow in the occipital region during migraine. This reduction was not substantially reduced by treatment with sumatriptan.

Transcranial Doppler measured blood flow velocity was not changed in any measured vessel except the vertebral artery, where an increase in blow velocity was observed.

Conclusions:
No measurement in CBF is observed during migraine headache compared to the migraine free state. Regional effects, primarily in the occipital region of the brain, are present and sustained through a mini

Introduction

Migraine headaches have been estimated to effect approximately 10% of the population of the United States(1). Although this disorder has been known since antiquity, the pathophysiology of migraine headache remains poorly understood. The vascular model has been widely accepted and remains, to some extent, the model on which interventional therapies are based(2). In this model, cerebral ischemia precedes the headache (HA), and if severe enough, is thought to be responsible for the aural symptoms of classic migraine (migraine with aura). It is proposed that this vasoconstriction is followed by a period of vasodilation, resulting in acute changes in the diameter of the large, stretch receptor containing arteries of the brain, resulting in the actual headache.

Techniques for measuring cerebral blood flow (CBF) have included ^{133}Xe administered by inhalation or carotid injection, and doppler studies of blood flow velocity in large blood vessel. These methods are each associated with certain limitations, including susceptibility to background radiation and scatter, relatively low resolution, and in the case of transcranial doppler (TCD), an inability to measure small vessel flow. These limitations may explain the contradictory findings in the measurement of CBF during migraine headache reported by different centers using the same techniques (Table 1).

Previous work has shown reduced flow in migraine, relative to a HA free state. This study was intended to meet the following objectives:

- To measure global CBF in migraineurs during headache, and headache-free periods using $H_2{}^{15}O$, and PET technology
- To assess regional CBF in migraineurs during these two phases
- To measure the effect of CBF of sumatriptan, a vasoconstrictive drug used for the treatment of migraine
- To perform transcranial doppler measurements of CBF during the headache, and headache free periods
- To measure rates of brain metabolism using PET

Methods

Patients were recruited from the general population via local advertisements, including handbills and postings in regional newspapers. Prior to inclusion, all patients gave written informed consent and underwent screening. Screening included a medical and headache history, laboratory measurements, and a 12 lead electrocardiogram.

Inclusion criteria

- History of migraine headache (IHS Criteria) for a minimum of 1 year
- Age 18 to 65
- Migraine frequency of at least one HA per month

Exclusion criteria

- History of clinically significant cardiac problems
- Concurrent migraine prophylaxis
- Participation in any drug trial within 4 weeks of enrollment
- A history of ischemic heart disease or Raynaud's disease
- Diastolic BP > 95 mm Hg or systolic BP > 160 mm Hg
- History of complex migraine, migraine variants, or chronic daily headaches in the previous year
- Presence of a clinically significant psychiatric or neurologic disorder

Additionally, patients were instructed that use of a non-steroidal inflammatory drug or acetaminophen within 4 hours of scanning, or vasoactive compounds or opiates within 24 hours of scanning would preclude participation during any one migraine episode.

Patients presented to the PET Center of the Veterans Administration Medical Center (VAMC) within 24 hours of the onset of the headache. Prior to PET scanning, transcranial doppler (TCD) measurements of blood flow velocity were made, followed by catheterization of a radial artery under local anesthesia, for withdrawal of arterial blood during the scan.

Patients were positioned in a CTI/Siemens ECAT 951-31R scanner, using a set of targeting lasers referenced to the orbitomeatal line. A thermoplastic face mask extending approximately from nose-tip to hairline was fitted for each patient, and fixed to the scan table. All studies were performed under conditions of reduced sensory input, consisting of dimmed lights, with no conversation permitted during scanning (3). Patients then received a bolus, intravenous injection of 60-80 mCi of $H_2{}^{15}O$, followed by a 120 second image acquisition time.

Patients returned during a headache free (48 hour) state for a follow-up study. Volunteers underwent a second radial artery catheterization and repeat PET scanning, using the previously prepared face mask as a positioning template.

All radionuclides were prepared using a 30 mEv cyclotron (IBA, Brussels, Belgium) and routine radiochemical techniques employed at our institution. Tomographic reconstruction and quantitative modeling were done on SUN workstations.

Blood flow was modeled according to the method of Kano, et al (4). Statistical analysis was done using Systat®; the paired t-test was used to compare pre and post values. For all quantitated variables, α=0.05 was designated as the level of significance. Regional effects were tested using SPM 96.

Results

A total of 12 patients presented during a migraine headache episode, underwent scanning, and are included in the data analysis. A description of patient demographics are provided in Table 2. One patient dropped out of the study after the headache scan.

PET Measurements

$H_2{}^{15}O$ measurements of cerebral blood flow, representing tissue perfusion, are shown graphically via box plot in Figure 1. Individual patient CBF measurements

are provided in Figure 2. In figure 2, values labeled "120 minutes" correspond to the headache free value. All other values represent actual acquisition time. When compared to migraine values, CBF during the migraine free image was approximately 7% higher. While this reduction is consistent with previous reports, this change was not statistically significant.

CBF was not significantly changed at any time point following administration of the vasoconstrictor sumatriptan. Unless noted otherwise, all values are provided as the mean (SD). CBF values (ml/min/100g (SD)) were as follows:

Pre-treatment	**15 min p SUM**	**30 min p SUM**	**60 min p SUM**	**HAF**
46.4 (8.3)	46.2 (10.8)	48.1 (10.3)	46.9 (7.0)	49.8 (8.4)

Change in flow was not related to age of the patient, duration of headache at the time of scanning or presence or absence of aura prior to the migraine. Ten of the twelve patients reported complete, or near complete resolution of migraine by the 60 minute time point. Two subjects reported no clinical relief of headache.

Regional Effects

Results (mapping) of regional analysis of CBF are provided in Figures 3, 4, and 5. These figures are output pages from SPM96, the statistical parametric mapping program used in this analysis. "Cluster level" p values were used to determine significance, and x,y, and z coordinates correspond to the coordinates of the atlas of Talairach and Ternoux. The image is a representation of the SPM projections into the sagittal, coronal and transverse planes of a wireframe style grid. Coordinates given are those for the highest value pixel for the cluster.

Figure 3 represents regions of decreased perfusion compared to the HA free episode. Significant reductions were observed in the occipital portion of the brain. Figure 4 contrasts flow with values seen 60 minutes following SUM with the headache free episode. Interestingly, the region of decreased flow persisted in spite of successful treatment with SUM. This finding is consistent with the

clinical observation of "rebound" headache, or migraine recurrence following clinical relief by sumatriptan or same class compounds. Presumably, this recurrence requires a continuation of the underlying pathophysiology of the migraine, with sumatriptan providing an interruption of a pain perception or feedback mechanisms.

Figure 5 shows regions of increased flow (activation) when untreated migraine pain is contrasted to a spontaneously HA free interval. While these regions do not satisfy the apriori standards for significance (p=0.08), increases in these regions, which correspond to the gyrus frontalis medius and gyrus frontalis inferior, are not unexpected.

TCD Measurements

TCD velocities for the right and left MCA, right and left vertebral and basilar arteries during HA and HA free intervals are provided in Figure 6. No change in flow velocity was observed in the middle cerebral or basilar arteries. Significant changes in flow velocity were detected in the vertebral arteries, with a mean increase of 3.5 (4.7) cm/sec seen in the left vertebral artery during the migraine phase. Mean flow velocity in the right vertebral artery increased by 3.3 (5.0) cm/sec during headache, however this change was not statistically significant (p=0.067). Peak flow velocity was increased by 27.6 (25.0) cm/sec in the left vertebral artery. The change in the right vertebral artery was not significant.

A statistically significant change in pulsatility index was detected only in the right vertebral artery with a reduction in PI of 0.11 (0.12) noted during the migraine episode.

Metabolism

A single study of brain metabolism was performed in each individual at the time of the HA free study. This was compared to scans from a control group of healthy volunteers utilizing SPM96. The results of this contrast are provided in Figures 7 and 8. While analysis of these data are still underway, it appears that regions of

increased metabolism are present in migraineurs during a spontaneously migraine free interval.

Discussion

Measurement of CBF using PET is the primary endpoint of the study. With global CBF, two findings are of interest. First, while CBF was not changed significantly during the painful episode, it was reduced, consistent with previous reports of reduced flow in migraine HA. Perhaps more important is the finding that CBF is not increased, as would be anticipated by both the classic vascular model, and the so-called spreading depression of Leao in which a hyperemic phase follows initial reductions in flow(5, 6). Figure 2 shows CBF measurements from individual patients. At a glance, it is apparent that changes in CBF are somewhat variable, with both reductions and increases in flow observed. While neither gender, duration of headache, or presence of aura appear to be related to the change in blood flow, it is possible that an as yet unrecognized factor has influenced the degree of change observed in this or previous work.

This study showed that administration of the $5HT_{1d}$ agonist SUM does not alter global or regional CBF in a significant fashion. The observed trend is that of an insignificant (clinically or statistically) increase in flow, somewhat surprising for a potent vasoconstrictor.

While the global CBF measures are interesting, the findings of regional change are far more intriguing. Our study shows decreased regions of flow in the occipital region of the brain, consistent with the single previously reported regional analysis of CBF(7). The most important aspect of this finding is the presence of the previously reported occipital reduction late in the headache phase. The mean time to imaging from headache onset was 10 hours in this study, with a range of 1 to 25 hours. All of these time points are significantly beyond that reported earlier, and beyond what is predicted by both the vascular and "spreading depression" models. It suggests a sustained neurologic event.

Another striking finding of the regional analysis is the complete absence of change in regional flow following SUM administration. Sixty minutes following SUM, the vast majority of patients reported clinical relief of pain. Their CBF study was unchanged from the untreated headache phase. This is consistent with the recurrence of migraine pain following treatment, particularly with shorter half-lived agents such as SUM. We are interpreting these findings to show a continuation of the migraine episode, with SUM then having a mechanism of action consistent with a lysis of as yet unidentified feedback mechanism for perception of pain in migraine.

The lack of substantive change in TCD measured velocity in the middle cerebral artery is consistent with observations made in other reports. Our observation of increased flow velocity in the vertebral arteries, while consistent with a vasoconstrictive episode, suggests reduced flow long into the painful episode. Since most previous investigations of migraine headache have not insonated the vertebral arteries, it is difficult to know how prevalent our findings are, however the vertebral artery vasoconstriction we observed is consistent with the reduced occipital perfusion observed during migraine. Since TCD measurements were not made throughout the treatment phase, whether this increase in velocity is sustained remains unknown.

Conclusions

The primary objectives of this study have been met; further analysis of the data, particularly metabolic data, is underway to insure accurate interpretation of our findings.

The findings of this study can be summarized as follows:
An increase in CBF during the HA phase of migraine, predicted by the vascular hypothesis is not present. This finding is consistent with previously reported data.

SUM does not appear to have a significant effect on global or regional CBF, in spite of clinical response.

Regional analysis of PET images reveals an expected activation of some pain centers of the brain, but also unanticipated persistence of activation following successful treatment of migraine, consistent with the clinical observation of rebound headache, and suggestive of a mechanism of action for SUM.

TCD does not show a difference in flow velocity in commonly insonated vessels between the HA and HA free state of migraineurs, with the exception of vertebral arteries. Increased flow velocity seen during headache is consistent with the regional changes observed using PET. This increased velocity appears to be sustained far longer that earlier migraine theories have suggested.

Brain metabolism in migraineurs appears to be altered, suggestive of a neurogenic mechanism.

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Table 1

Reference	HA type	How measured	CBF	Comments
Increased				
(8)	Common	TCD of middle, anterior and posterior cerebral arteries, internal carotid	↓ relative FV in all arteries unchanged PI	
(9)	Classic	^{133}Xe, inhalation - spontaneous or arteriography, induced	decreased during aura, increasing to hyperemia during HA	Report hyperemia outlasting HA
(10)	common	^{133}Xe, inhalation	hyperemia compared to normals and HA free	
(11)	Classic & common	^{133}Xe, inhalation	108.5ml/min/100 g HA vs 80.5ml/min/100g in matched, HA free migraineurs and 83.5 in age matched healthy volunteers	
(12)	Classic & common spontaneous + induced	^{133}Xe, carotid injection	56.8ml/min/100g/min HA vs 47.9 HA free	
Mixed				
(10)	Classic	^{133}Xe inhalation	2 groups of patients reported, a hyperemic and an oligemic subtype	compared to normal controls
(13)	Classic	^{133}Xe inhalation, SPECT	hypoperfusion early in headache hyperperfusion late in headache	CBF measured at presentation, 2-6 hours, and 1 week
(14)	Classic, common, cluster	TCD of the supratrochlear, vertebral, and carotid (internal, external, & common) arteries	↑ relative FV in internal carotid ↓ relative FV in the vertebral and external and common carotid; ↓ flow in supratrochlear	
Decreased				
(15)	Common	$H_2{}^{15}O$ PET	52.7 ml/min/100g during HA, 59.7 ml/min/100g while HA free	No regional quantitation
(8)	Classic	TCD of middle, anterior and posterior cerebral arteries, internal carotid	↑ relative FV unchanged PI	
(16)	Classic , migraine acompangée	^{123}I-IMP SPECT	decreased regional changes in migraine acompangée	studied in HA free period only
(17)	Classic	^{133}Xe, carotid injection	Hyperemia during prodrome, followed by oligemia during HA	See Olesen 1990

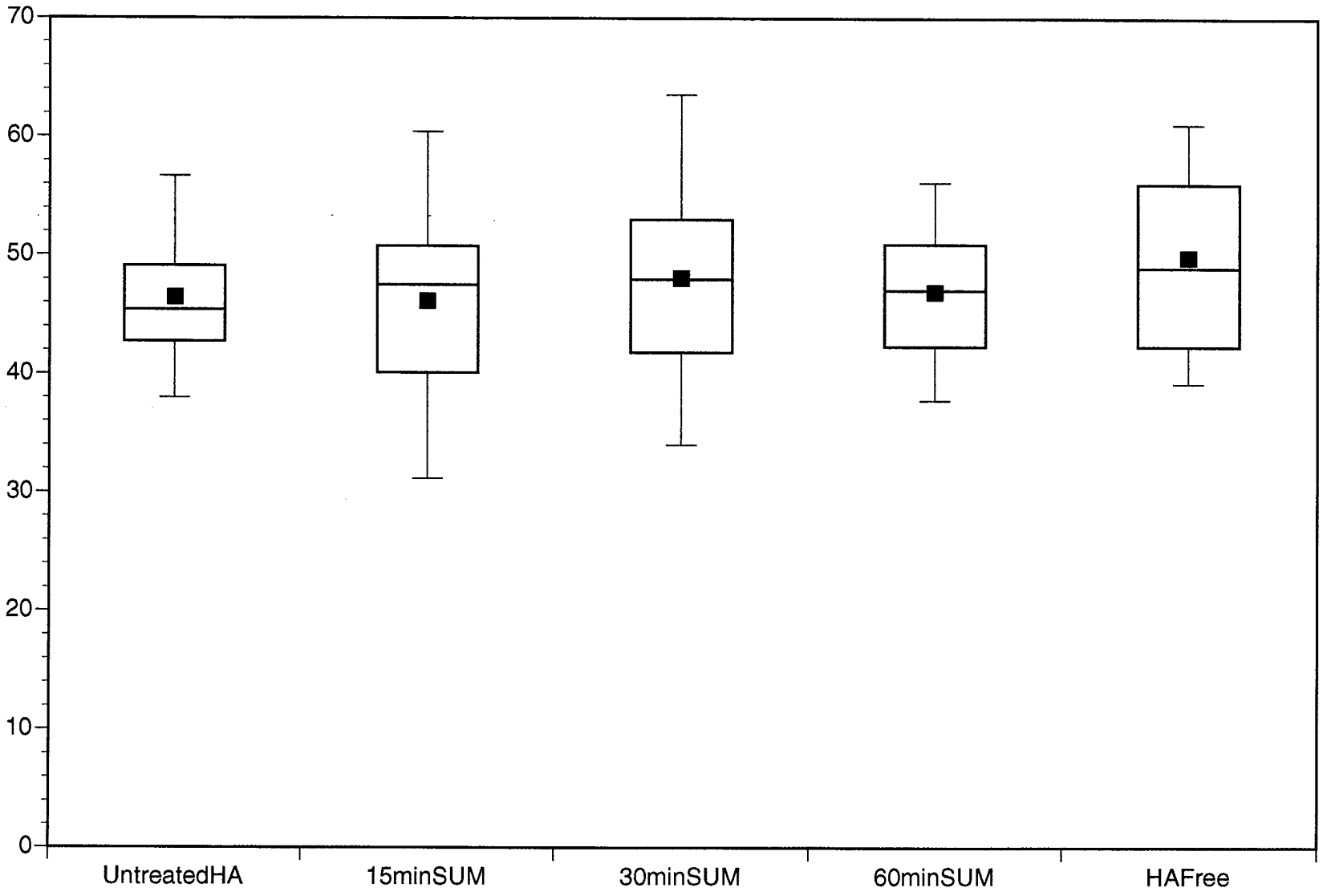
TCD transcranial doppler, HA headache, FV flow velocity, PI pulse intensity, CBF cerebral blood flow

Table 2

Patient Demographics

Characteristic	Value
Age (mean (SD))	40.25 (10.8)
Gender, Male/Female	4/8
With/Without Aura	5/7
Smokers/Non-Smokers	2/10
Headache duration (hrs)	10.0 (6.8)

Figure 1 - Migraineur CBF, ml/min/100g



p NS, comparison to baseline values

Figure 2
Individial patient CBF measurements

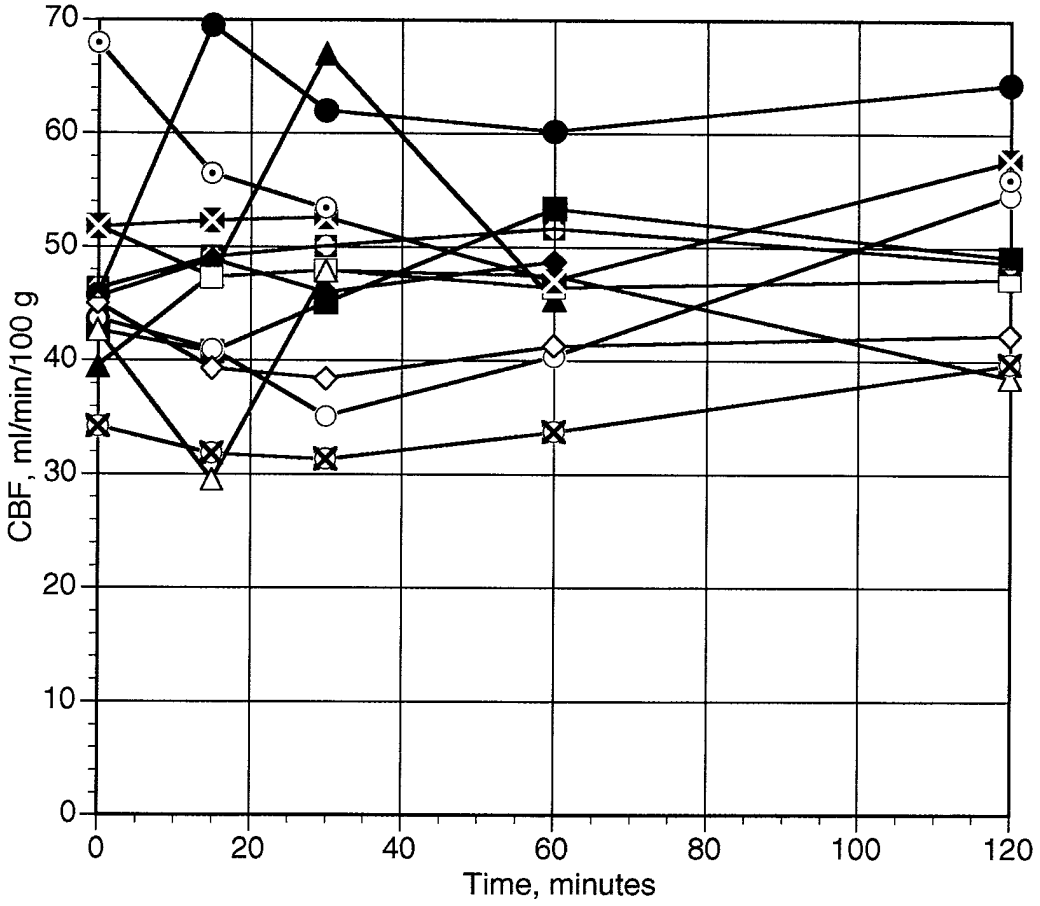
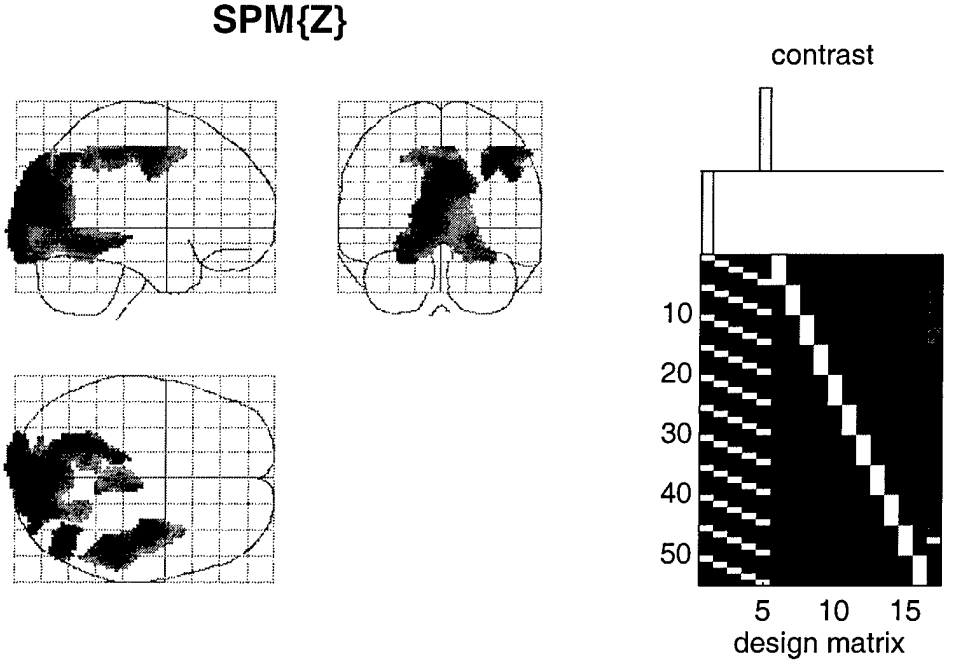


FIGURE 3



P values & statistics: /home/david/spm5

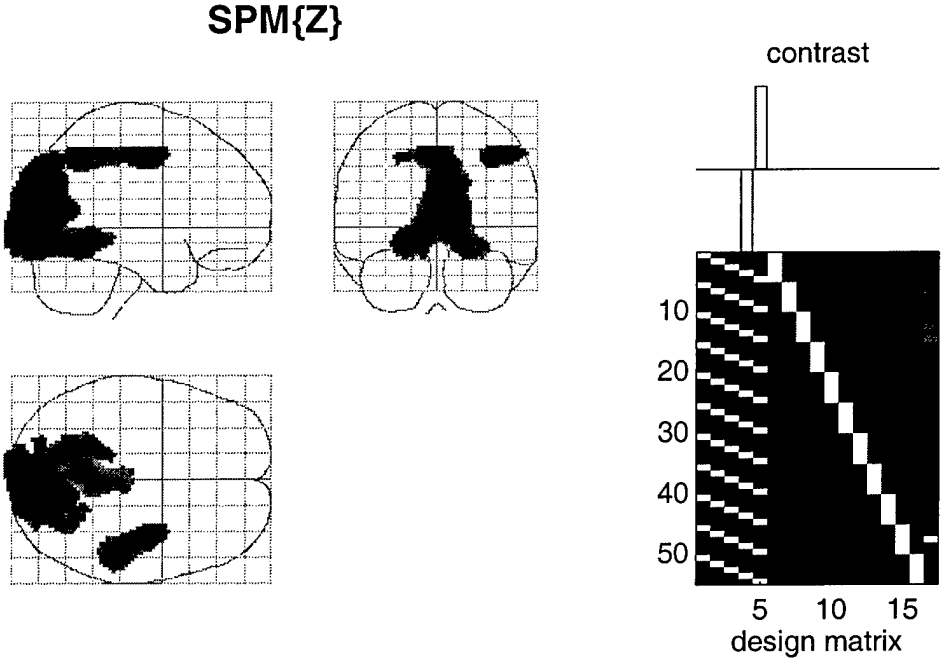
set-level {c}	cluster-level {k,Z}	voxel-level {Z}	uncorrected k & Z	x,y,z {mm}
0.422 (4)	**0.001 (7947, 4.71)**	**0.010 (4.71)**	**0.000** **0.000**	**6 -92 32**
		0.097 (4.13)	0.000	-2 -94 32
		0.337 (3.73)	0.000	-10 -94 12
	0.215 (1048, 3.68)	**0.379 (3.68)**	**0.016** **0.000**	**48 -38 50**
		0.417 (3.64)	0.000	44 -24 52
		0.467 (3.59)	0.000	32 -12 40
	0.542 (312, 3.57)	**0.491 (3.57)**	**0.157** **0.000**	**36 -66 48**
		0.557 (3.50)	0.000	44 -70 44
		0.888 (3.14)	0.001	34 -58 48
	0.513 (607, 3.16)	**0.877 (3.16)**	**0.056** **0.001**	**-12 -54 44**
		0.942 (3.03)	0.001	4 -26 50
		0.981 (2.89)	0.002	2 -34 44

Height threshold {u} = 2.33, p = 0.010
Extent threshold {k} = 164 voxels, p = 0.299
Expected voxels per cluster, E{n} = 164.3
Expected number of clusters, E{m} = 3.3

Volume {S} = 181845 voxels or 261.8 Resels
Degrees of freedom due to error = 39.0
Smoothness FWHM {mm} = 17.0 19.2 17.0
{voxels} = 8.5 9.6 8.5

SPM96 (david) - 28/04/1999 (14:16)

FIGURE 4



P values & statistics: /home/david/spm5

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		0.235 (3.86)		0.000	4 -94 26
		0.250 (3.84)		0.000	16 -74 14
	0.328 (801, 3.81)	**0.268 (3.81)**	**0.031**	**0.000**	**44 -24 52**
		0.768 (3.29)		0.000	38 -8 48

Height threshold {u} = 2.33, p = 0.010
Extent threshold {k} = 164 voxels, p = 0.299
Expected voxels per cluster, E{n} = 164.3
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Volume {S} = 181845 voxels or 261.8 Resels
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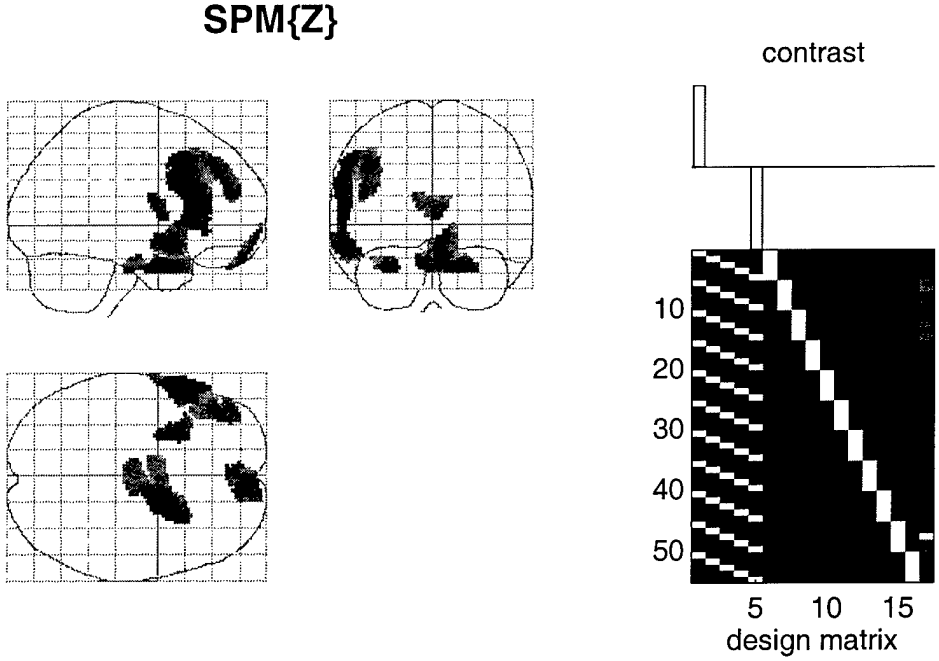
Smoothness FWHM {mm} = 17.0 19.2 17.0
{voxels} = 8.5 9.6 8.5

SPM96 (david) – 28/04/1999 (14:16)

FIGURE 5



P values & statistics: /home/david/spm5

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		0.147 (4.01)		0.000	-60 24 26
		0.262 (3.82)		0.000	-60 26 6
	0.323 (219, 3.82)	**0.264 (3.82)**	**0.231**	**0.000**	**-28 10 -26**
		1.000 (2.38)		0.009	-40 18 -22
	0.504 (614, 3.61)	**0.450 (3.61)**	**0.054**	**0.000**	**24 12 -28**
		0.497 (3.56)		0.000	22 4 -28
		0.685 (3.38)		0.000	12 0 -30
	0.832 (242, 3.24)	**0.812 (3.24)**	**0.209**	**0.001**	**10 68 -4**
		0.882 (3.15)		0.001	6 62 -16
		0.907 (3.10)		0.001	10 56 -22
	0.940 (206, 2.88)	**0.983 (2.88)**	**0.245**	**0.002**	**6 0 8**
		0.996 (2.74)		0.003	-6 -2 14

Height threshold {u} = 2.33, p = 0.010
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{voxels} = 8.5 9.6 8.5

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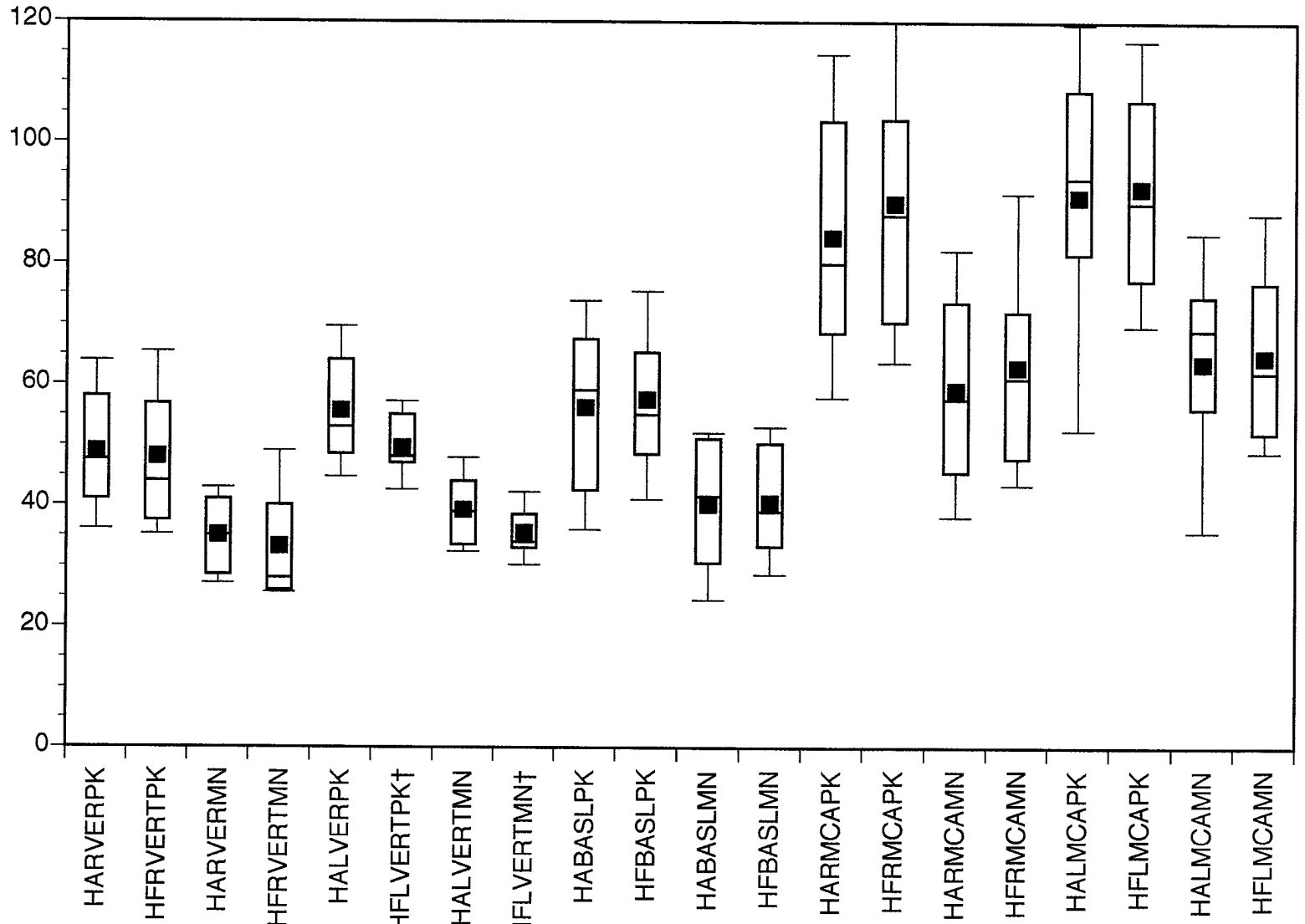
Figure 6
Blood Flow Velocity (cm/sec)
Spontaneous Migraine vs Migraine Free Intervals



†, p<0.05