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13. ABSTRACT (Maximum 200 words)

The pathophysiology of migraine headache (HA) remains poorly understood as do the mechanisms of action of most anti-migraine drugs. The following is the annual report of a study of cerebral blood flow (CBF) in migraine headache compared to values following treatment with the $5HT_{1d}$ agonist sumatriptan and a headache free state.

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

A total of 5 patients (of 12 to be completed by 9/97) have been studied. CBF in clinical responders (to date, n=4) increased (p=0.04) from a mean (SD) flow of 43.4 (2.9) ml/min/100g prior to treatment, to 51.7 (12.4), 55.1 (11.1), and 52.0 (6.4), at 0.25, 0.5 and 1 hour post sumatriptan respectively. CBF was 56.8 (10.8) in the HA free state. Among non-responders (n=1), CBF decreased from 51.8 to 46.5 ml/min/100g.

CBF is reduced in the HA vs the HA free state. Preliminary evidence suggests that in responders, sumatriptan increases CBF to near HA free levels.

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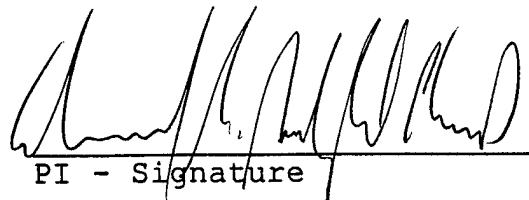
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Introduction

Migraine headaches are severe, often debilitating headaches that have been estimated to effect approximately 10% of the population of the United States[1]. Overwhelmingly, this is a disease of women, with only 25% of the cases occurring in men. Frequency of attack will vary from individual to individual; among female migraineurs, 60% report having at least one severe attack per month[2]. No racial bias has been observed, however an inverse relationship between income and incidence has been reported[1, 2].

Although this disorder has been known since antiquity, the underlying pathophysiology of migraine headache (HA) remains poorly understood. The vascular model, first proposed by Wolff, has been widely accepted[3] and is, to some extent, the model on which interventional therapies are based. In this model, cerebral ischemia precedes the 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, producing acute changes in the diameter of the large, stretch receptor containing arteries of the brain, resulting in a painful stimulus.

It has been presumed that drugs such as ergotamine and sumatriptan alleviate HA pain by reversing cranial vasodilation, while drugs such as the calcium channel blockers prophylax against migraine by preventing the initial vasoconstrictive episode[4].

Unfortunately, attempts to verify this model by measuring cerebral blood flow (CBF) have been disappointing. Table 1 lists studies which have measured CBF in various subtypes and phases of migraine HA. Studies reporting increases, decreases, or a combination of effects on CBF have all appeared in the medical literature. While this list is by no means exhaustive, clearly no consistent pattern of alteration in CBF has emerged to definitively confirm or refute the vascular model. These findings can be

explained in several ways, the first being methodologic limitations. The predominant techniques used in these reports are ^{133}Xe administered by inhalation or carotid injection, and doppler studies of large vessel flow. While ^{133}Xe washout techniques have been widely used, findings with this isotope can be influenced by the properties of its physical decay. ^{133}Xe undergoes gamma decay, emitting photons of two energies (80 KeV and 30-35 KeV). Low energy photons originating from deep within a structure may lack sufficient energy to be imaged, and conversely, superficial structures may disproportionately contribute to the image obtained[5]. Furthermore, in the case of carotid injection of ^{133}Xe, these studies have often followed cerebral angiography, which itself can alter cerebral flow [5]. In the case of doppler ultrasound, flow velocity and vessel diameter can only be measured in large vessels, and then only in discrete segments. Finally, regional analyses or absolute quantitation of flow have not been possible, or readily available at the time many of the studies were conducted.

Because the observed CBF is inconsistent with the Wolff model, attempts have been made to modify the theory. It has been proposed that the vasoconstrictive vasodilatory episode is not a global or hemispheric phenomenon, but rather occurs in isolated large conductance vessels, or segments of these vessels. Since conductance vessels are not the primary determinants of blood flow, vasodilation in these vessels would not be expected to alter blood flow. While an attractive explanation, this model does not adequately explain the mechanism by which aural symptoms are mediated: if aural symptoms are produced by cerebral vasoconstriction, this is either occurring by a differing mechanism, or must be great enough to produce, at least regionally, a significant effect on CBF.

It has been postulated that a cortical "spreading depression" occurs, associated with regions of decreased flow, mediated at an arteriolar level. This then produces a

responsive dilation of the large vessels, producing pain[6]. This model offers no mechanism by which this cortical depression is triggered, although parallels to epilepsy have been offered[7].

An additional explanation may be that vascular headaches are actually only "vascular" in as much as they arise from injury to vessels within the trigeminal distribution. The release of various mediating substances produces an increase in neurotransmitting peptides of the trigemia (such as substance P), producing the perception of pain. Any changes in flow in this model are merely a response to the perceived pain, or perhaps vascular injury. Ultimately, the etiology of vascular HA may prove to be mediated by a combination of events.

In the central nervous system, positron emission tomography (PET) has been used to detect changes in global CBF and metabolism in a wide variety of disease states. PET has been shown to be a sensitive technique for the evaluation of CBF and glucose uptake in the brain. The greatest experience in the measurement of CBF has been with $H_2^{15}O$. Quantitative measurements of CBF with this tracer have been validated [8], and found to correlate with results obtained by microsphere techniques. Activation studies applying auditory, visual and tactile stimuli have shown regional changes in blood flow [9]. Global changes in CBF measured by $H_2^{15}O$ have been reported following hyperventilation[10], and in migraine HA[11]. The short (123 second) half life of this radionuclide permits multiple flow studies in a short period of time.

^{18}F-fluorodeoxyglucose (FDG) has been extensively used in the evaluation of CNS function. Patterns of reduced glucose uptake have been observed in numerous conditions, including seizure disorders[12], Huntington's disease[13], schizophrenia[14], and Parkinson's disease[15].

Sumatriptan is a relatively new serotonin agonist[16, 17] with selectivity for the ($5HT_{1d}$) receptor subtype. Since sumatriptan has extremely poor penetration across the blood brain barrier, it is thought to act primarily through selective cerebral vasoconstriction.

Hypothesis

The pain of migraine HA is mediated by changes in cerebral blood flow (CBF). These changes are measurable, and effected by current abortive migraine therapy.

Objectives

The objectives of this study, as detailed in the statement of work are:
- To measure global CBF in migraineurs during HA, and HA-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 HA, and HA free periods
- To measure rates of brain metabolism using PET

Methods

To qualify for participation, patients must meet the following criteria: minimum of 1 year history of migraine HA by International Headache Society criteria, age 18 to 65, migraine frequency of at least one HA per month,

Patients were excluded if they were found to have a history of clinically significant cardiac problems, ischemic heart disease, Raynaud's disease, complex migraine, migraine variants, recent chronic daily headaches, or the presence of a clinically significant psychiatric disorder. Exclusion was likewise extended to patients on current therapy with vasoactive compounds, those receiving concurrent migraine prophylaxis, those who had participated in any drug trial within 4 weeks of enrollment, patients with a diastolic BP > 95 mmHg or systolic BP > 160 mmHg.

Patients that otherwise qualified for participation were not scanned for either their acute HA phase or their HA free phase if they have used a narcotic analgesic or abortive therapy with a ergot containing compound within 24 hours of scanning, or used a non-steroidal inflammatory drug or acetaminophen within 4 hours of scanning.

Patients were recruited for the study from the general population through printed advertisements, word of mouth, and articles in the local press. Screening for inclusion consists of a medical and HA history, laboratory measurements (Chem 23, CBC with differential, and urinalysis), and a 12 lead electrocardiogram. Physical examination is performed by one of the physician investigators. Migraineurs who qualify for inclusion are instructed to discontinue any prophylactic medications they are taking, for the duration of the study.

Patients are instructed to report to the positron facility of the Veterans Administration Medical Center (VAMC) within 24 hours of the onset of the HA. Patients undergo catheterization of the radial artery under local anesthesia, for withdrawal of arterial blood during the scan. This is done to obtain a measure of arterial input activity for quantitation of blood flow. Blood from the radial artery is drawn through 0.5 mm diameter Teflon tubing (Alltech, Deerfield, IL) at a rate of 6 ml/min past a beta detector using an infusion/withdrawal pump.

Patients undergo transcranial doppler (TCD) study of blood flow velocity (FV) and vessel diameter. Following TCD, volunteers are positioned in a CTI/Siemens ECAT scanner, using a set of targeting lasers referenced to the orbitomeatal line. A thermoplastic face mask extending approximately from nose-tip to hairline is 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(18). Patients receive a bolus, intravenous injection of 60-80 mCi of $H_2^{15}O$, followed by a 120 second image acquisition time. Following baseline CBF determination, patients receive a subcutaneous dose of 6 mg sumatriptan, measurements of CBF are repeated 15, 30 and 60 minutes following administration of sumatriptan, with the 60 minute interval used as the primary marker of response.

Patients are then asked to return during a HA free state for a follow-up study. All follow-up studies are done 48 hours after the last pain free interval. Volunteers will undergo a second radial artery catheterization and repeat PET scanning, using the previously prepared face mask as a positioning template. During the second session, only a single blood flow determination will be made, but the volunteer will receive an injection of FDG for measurement of cerebral glucose utilization.

All radionuclides are prepared using a 30 mEv cyclotron (IBA, Brussels, Belgium) and routine radiochemical techniques employed at our institution[19]. Tomographic reconstruction and quantitative modeling are done on SUN workstations.

Blood flow is modeled according to the method of Kano, et al(20). Statistical analysis is done using Systat®[21] with the paired t-test used to compare primary parametric endpoints. For all quantitated variables, $\alpha=0.05$ is designated as the level of significance. Assuming a two tailed test, this study is designed to detect a 10% change in blood flow (power = 0.94).

Results

A total of 17 patients have qualified for this study, with 5 patients imaged to date. A total of 12 patients will be imaged by the end of the study

CBF HA Phase
Individual measurements of CBF during the HA phase are illustrated in Figure 1. CBF in clinical responders (to date, n=4) increased (p=0.04) from a mean (SD) flow of 43.4 (2.9) ml/min/100g prior to treatment, to 51.7 (12.4), 55.1 (11.1), and 52.0 (6.4) ml/min/100g, at 0.25, 0.5 and 1 hour post sumatriptan respectively. This is illustrated in Figure 2 Among non-responders (n=1), CBF decreased from 51.8 to 46.5ml/min/100g

HA vs HA Free
CBF was 56.8 (10.8) in the migraine free state. Only one patient, the sumatriptan non-responder had higher blood flow measurements during the headache phase.

Regional analysis
Regional analysis using the statistical parametric mapping (SPM) technique will be undertaken in year two of the study.

TCD
Individual measurements of flow velocities are found in Table 2. No patterns of altered blood flow have emerged to date, consistent with the TCD migraine literature. With the addition of more data points, several approaches will be used to compare values, including comparisons of left/right differences, stratified by pain side.

FDG
A representative metabolic image is shown in Figure 3. No systematic analysis of metabolic images has been undertaken in year one of the study, however from this an other images of metabolism, regions of altered metabolism appear visible.

Discussion

Our findings of reduced CBF, reversed by sumatriptan are contrary to the vascular model of vasoconstriction followed by vasodilation. While the theory of spreading depression would allow for reduced flow, the effect as reported is transient, and inconsistent with an ischemia capable of producing cerebral infarction. Intriguingly, our findings would be consistent with dilation of arterio-venous shunts. These vessels have been shown to be sensitive to the effects of sumatriptan, and closure of shunts would explain increase CBF following sumatriptan treatment. To date, unlike previous animal studies, such shunts have not been demonstrated within the human brain.

Study Difficulties

The primary obstacle encountered in this study been patient participation during an acute episode of migraine headache. From patient follow-up, this has been felt to be due to two major factors:

Patient ability to participate
Some screened patients have had a change in their ability to participate in the study. Reasons have included changed work schedules, move from the region, and a change of heart regarding the risks of participation.
Action: Replacement patients are screened to offset these losses
Ability to contact study group during a HA episode
Some patients have noted problems activating the study pager (primary means of contacting the study center). Numerous tests of the pager system (including tests for pager "dead-zones") have led us to conclude that most problems are due to incompatibility with some phones (non-touch tone) and phone systems (some digital systems) coupled with limited understanding of pager activation by patients.
Action: Increased patient instruction of pager activation, including distribution of instructions in business card format; addition of voice activated options via the phone-mail system.

Conclusions

With data analyzed to date, it appears possible to conclude that, consistent with previous reports using PET, CBF is reduced in the HA vs the HA free state in migraine. CBF is

increased following administration of sumatriptan in patients responsive to this

treatment.

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Appendices

Table 1

Reference	HA type	How measured	CBF	Comments
Increased				
(22)	Common	TCD of middle, anterior and posterior cerebral arteries, internal carotid	↓ relative FV in all arteries unchanged PI	
(23)	Classic	^{133}Xe, inhalation - spontaneous or arteriography, induced	decreased during aura, increasing to hyperemia during HA	Report hyperemia outlasting HA
(24)	common	^{133}Xe, inhalation	hyperemia compared to normals and HA free	
(25)	Classic & common	^{133}Xe, inhalation	108.5ml/min/100 g HA vs 80.5ml/min/100g in matched, HA free migraneurs and 83.5 in age matched healthy volunteers	
(26)	Classic & common spontaneous + induced	^{133}Xe, carotid injection	56.8ml/min/100g/min HA vs 47.9 HA free	
Mixed				
(24)	Classic	^{133}Xe inhalation	2 groups of patients reported, a hyperemic and an oligemic subtype	compared to normal controls
(27)	Classic	^{133}Xe inhalation, SPECT	hypoperfusion early in HA hyperperfusion late in HA	CBF measured at presentation, 2-6 hours, and 1 week
(28)	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				
(11)	Common	H$_2$^{15}O PET	52.7 ml/min/100g during HA, 59.7 ml/min/100g while HA free	No regional quantitation
(22)	Classic	TCD of middle, anterior and posterior cerebral arteries, internal carotid	↑ relative FV unchangedPI	
(29)	Classic , migraine acompangée	^{123}I-IMP SPECT	decreased regional changes in migraine acompangée	studied in HA free period only
(30)	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

Migraine
TCD
Peak Flow Velocity

Patient	RVertHA	RVert	LVertHA	LVert	RMCAHA	RMCA	LMCAHA	LMCA	BAHA	BA
FP	34	52	45	48	59	64	59	72	36	48
VM	50	53	53	47	83	85	107	83		83
BM	66	44	58	48	71	63	100	90	48	
KJ	41		47		90		105		69	
CC	55	61	56	47	100	105	93	112	62	63
Mean	49.20	52.50	51.80	47.50	80.60	79.25	92.80	89.25	53.75	64.67

Rvert: Right vertebral artery
Lvert: Left vertebral artery
RMCA: Right middle cerebral artery
LMCA: Left middle cerebral artery
BA: Basilar artery
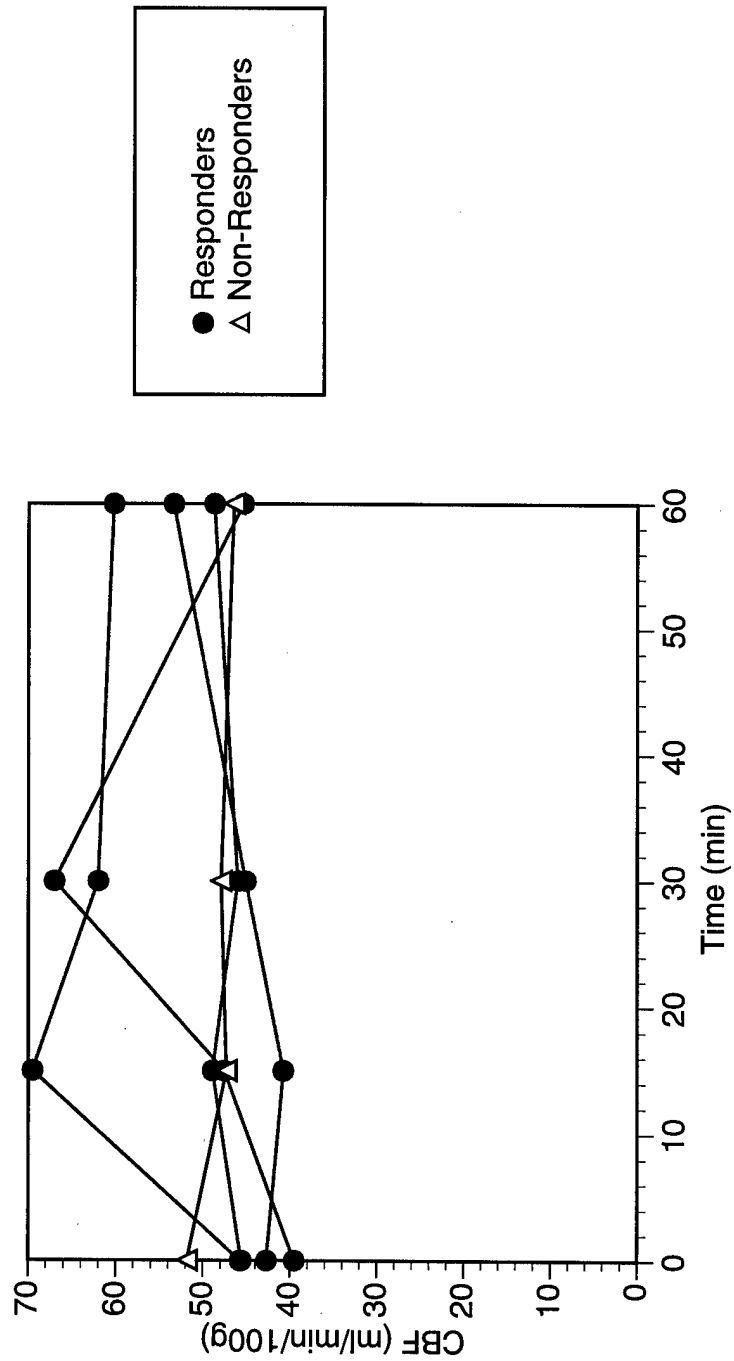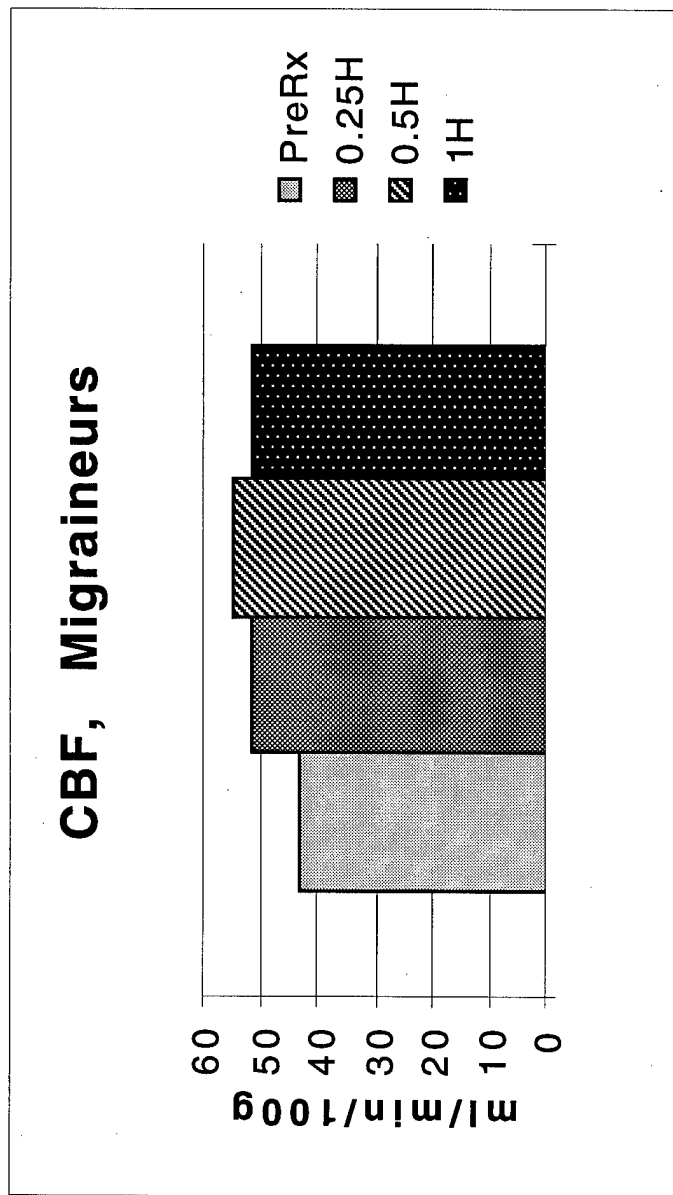HA suffix designates Headache Phase

Figure 1

Figure 2

CBF, Migraineurs

ml/min/100g

Legend: PreRx, 0.25H, 0.5H, 1H

Figure 3

FDG uptake, migraine free interval