Regional Cerebral Hemodynamics During Migraine and Cluster Headaches Measured by the $^{133}$Xe Inhalation Method

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SYNOPSIS

Measurements of noninvasive regional cerebral blood flow (rCBF) were made by the $^{133}$Xe inhalation method in 71 patients with different types of headache and 32 age matched normal controls. Flow gray (Fg) was calculated by two compartmental analysis from the x-ray subtracted gamma curves, and extracerebral flow indices (EFI) were calculated as an estimate of the percentage contribution by extracerebral tissues.

During the headache phase, mean Fg in a group (N = 13) with classic and common migraine was significantly higher compared to a comparable group (N = 12) measured in the headache-free interval. Serial measurement made during progression in the severity of the migraine headaches showed accompanying increases in the mean Fg as the headache worsened. In 24 patients with severe migraine studied 2-48 hours after the headache subsided, the mean Fg values remained significantly increased during this immediate post-headache interval compared with patients who were headache-free for six days or longer. Serial measurements made during and after the headache showed progressive reduction of mean Fg values to normal within six days after the headache subsided. Marked cerebral dysautoregulation was present during the migraine headache and showed progressive recovery as the headache subsided. Reduction of the head pain by administration of codeine decreased hemispheric Fg values but did not change the high flows in the basilar artery territory. Conversely, administration of ergotamine did not change hemispheric Fg values but reduced rCBF in brain stem-cerebellar regions. Significant regional reductions of Fg correlating with the neurological deficit was measured during the prodrome of classic migraine and during the headache and post-headache intervals of complicated migraine.

During cluster headaches, mean Fg values were also significantly increased and the extracerebral flow indices showed marked increases with highest values recorded at the site of the headache.

It was concluded that cerebral hyperperfusion during migraine headaches is mainly due to post-ischemic reactive hyperemia but may be compounded by functional hyperemia due to the head pain itself.

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INTRODUCTION

There are a limited number of reports available concerning measurements of cerebral blood flow (CBF) during attacks of migraine. The majority of these have been made by the intracarotid injection of $^{133}$Xe performed at the time of angiography,1-5 despite the fact that the carotid puncture itself may alter CBF. There are a few reports of CBF measured with $^{133}$Xe inhalation method in patients with migraine but most of them were made during early stages in the development of this method.5,7 In general, but with some notable exceptions, the observations presently available have been cited to support the classical view that the prodromal phase of migraine is associated with cerebral vasoconstriction and the headache phase with cerebral vasodilatation.

Careful perusal of currently available publications indicates that it is not clear whether all migraine headaches are preceded by vasoconstriction and are caused by reactive hyperemia since CBF values have been reported to be normal in some cases during the headache phase.5 It is also unclear whether some headaches begin at the outset with painful cerebral
hyperemia and tend to be self-perpetuating, since they may be compounded by cerebral vasodilatation as a reaction to pain in the head. Nor is it clear whether cerebral vasoconstriction occurring in the prodromal phase of migraine is focal in nature and whether the vertebrobasilar system as well as the carotid system may play a role in the pathogenesis of migraine. Furthermore, we have been unable to find any reports of concurrent measurement of both extracranial and intracranial hemodynamics during attacks of migraine.

Recent improvements in the $^{133}$Xe inhalation method for measuring regional cerebral blood flow (rCBF) now make it possible to estimate the extracranial hemodynamics as well as to measure intracranial blood flow from various regions of both hemispheres as well as the brain stem and cerebellum in the distribution of the vertebrobasilar circulation.10,11

The purpose of the present communication is to report measurements of rCBF in patients with migraine, cluster headache and muscle contraction headache, which were designed to provide information concerning the following points:

1) To provide sequential rCBF measurements during and after headache.

2) To see if there is any discernible pattern of regional vasoconstriction which corresponds to the neurological symptoms or of regional vasodilatation which correlates with the site of the headache.

3) To determine what part of the head pain itself may play in the cerebral hemodynamics of migraine by measuring the regional pattern of blood flow in the headache phase as well as after its relief by administration of codeine.

4) To test cerebral autoregulation by orthostatic reduction of the cerebral perfusion pressure both during attacks of migraine and after the headache has subsided.

5) To estimate concurrently both extra- and intracranial blood flow during the headache interval.

6) To measure any pharmacological effects of the administration of ergotamine on the rCBF during headache.

7) To evaluate the potential usefulness of rCBF measurements in the clinical investigation and differential diagnosis of migraine and related headaches.

Case Material

Measurement of rCBF were made in 71 patients with various types of headache, including 15 males and 56 females, ranging in age from 15 to 75 years (mean ± SD = 35 ± 13 years). The 75-year-old suffered from chronic muscle contraction headache. Thirty-two age-matched normal volunteers were similarly investigated for purposes of comparison. As shown in Table 1, patients were subdivided according to the recommendations of the Ad Hoc Committee on the Classification of Headache12 into Classic Migraine (N = 14), Complicated (Hemiplegic) Migraine (N = 5), Common Migraine (N = 24), Cluster Headache (N = 9) and Muscle Contraction Headache (N = 19). All the patients were carefully interviewed and examined by two neurologists separately to assure the clinical diagnosis of migraine. Patients with classic migraine had distinct prodromal periods, followed by unilateral headache, nausea and vomiting. Two patients with a history of typical basilar artery migraine of the Bickerstaff type13 were also included in the classic migraine group. In cases with complicated migraine all had residual unilateral hemiparesis or hemisensory loss during and after the prodrome and headache. Patients with common migraine had frequent unilateral headaches but sometimes the headaches were bilateral; they were also associated with nausea and vomiting and there was a family history of migraine. Patients with cluster headaches were older, usually male, who complained of unilateral retro-orbital headaches occurring in clusters with unilateral laceration and redness of the eye and nasal congestion on the side of the headache. None of the patients had any evidence of other neurological disease. All vasoactive medications were stopped at least two days prior to the initial rCBF measurement. Attempts were made to obtain rCBF measurements during the prodromal phase, the headache phase and after the headache had subsided.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Cases</th>
<th>Age in Years (M ± SD)</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic Migraine</td>
<td>14</td>
<td>31 ± 11</td>
<td>2 males 12 females</td>
</tr>
<tr>
<td>Complicated Migraine</td>
<td>5</td>
<td>32 ± 14</td>
<td>1 male 4 females</td>
</tr>
<tr>
<td>Common Migraine</td>
<td>24</td>
<td>33 ± 13</td>
<td>2 males 22 females</td>
</tr>
<tr>
<td>Cluster Headache</td>
<td>9</td>
<td>43 ± 9</td>
<td>7 males 2 females</td>
</tr>
<tr>
<td>Muscle Contraction Headache</td>
<td>19</td>
<td>37 ± 15</td>
<td>3 males 16 females</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>35 ± 13</td>
<td>16 males 56 females</td>
</tr>
<tr>
<td>Normal Volunteers</td>
<td>32</td>
<td>35 ± 12</td>
<td>17 males 15 females</td>
</tr>
</tbody>
</table>
Methods

Regional cerebral blood flow was measured by a modification of the $^{133}$Xe inhalation method described by Obst et al. In brief, $^{133}$Xe gas is mixed with room air (5-6 mCi/L) and is inhaled by means of a close-fitting transparent plastic face mask. After inhalation of $^{133}$Xe for one minute, the desaturation curves from the head probes and entidial $^{133}$Xe activity are recorded throughout the ensuing ten minutes by means of a PDP 11-5 computer. Sixteen collimated NaI crystal scintillation detectors are mounted perpendicular to the skull, by means of a modified plastic motorcycle helmet, over both cerebral hemispheres as well as over the brain stem and cerebellar regions. The symmetry of the probe placement and the relationship of the individual probes to the bony landmarks of the skull were checked for accuracy by taking x-rays of a subject's head with the helmet and probes in place.

The output from each detector was fed in parallel to two separate discriminators adjusted to accept pulses between 67.5 and 94.5 KEV for gamma activity and between 23.5 and 38.5 for x activity. The arterial concentration of $^{133}$Xe was estimated from the entidial $^{133}$Xe activity of expired air. The estimate of the arterial concentration was used to correct for recirculation of $^{133}$Xe to the head. Each head curve was deconvoluted by the computer, using a two compartmental model in which the faster clearing compartment is considered to represent primarily gray matter flow (Fg) and the second compartment to represent the flow of white matter plus some contamination from the extracerebral tissue.

The spectrum subtraction technique was used to minimize extracerebral contamination. As x-rays have shorter tissue penetration they are derived mainly from extracerebral tissues and may be subtracted from the gamma curves. A normalizing factor was used to equalize the counting efficiency for x-rays and gamma rays. Fg values computed from the x-ray subtracted gamma curves were used for analysis in the present study. The extracerebral flow index (EFI) was calculated as an estimate of percentage contribution by extracerebral tissue by the following formula:

$$EFI = F(g-c) - F(g)/F(g)100$$

where F (g-c) is the value obtained from x-ray subtracted gamma curves and F (g) is the value obtained by pure gamma curves. Erectal partial pressures for carbon dioxide (PACO$_2$), oxygen (PO$_2$) and $^{133}$Xe were recorded from the face mask during the rCBF measurements along with the sleep pressure, pulse and skin temperature. The reproducibility of the present method determined by two consecutive measurements in twenty-four normal volunteers showed that the correlation coefficient was $r = 0.89$ (p < 0.001) for the mean hemispheric Fg and $r = 0.76$ (p < 0.001) for the brain stem-cerebellar Fg. The measurement error expressed as the coefficient of variation of the difference between two consecutive measurements was 5.6% for the left hemisphere, 4.3% for the right hemisphere and 10.3% for the brain stem-cerebellar flow values.

The protocol used for all rCBF measurements and the form describing the procedure were approved by the Bio-Safety Committee and Institutional Review Boards for Human Investigation of Baylor College of Medicine and the Methodist Hospital.

All the results were analyzed either by Student's t-test or the paired t-test and were not considered significant unless they achieved a level of confidence above 95%.

Results

Regional Cerebral Blood Flow During and After Migraine Attacks

Figure 1 displays the mean Fg values recorded for all probes in patients with classic and common migraine.

Fig 1—The mean Fg values in patients with classic common migraine are significantly increased during headache period and also during the period of 2-48 hours after subsidence of headache compared with intervals during headache-free interval or age-matched normal volunteers.
compared with age-matched normal volunteers. During the headache phase, the mean Fg values in a group of 13 patients with migraine (5 classic and 8 common) was \(108.5 \pm 10\) ml/100g brain/min (mean ± SD). This was significantly higher than during the headache-free interval (headache absent for five days or longer) in a group of 12 migraineurs (\(80.5 \pm 9.0\) ml/100g brain/min) and 32 age-matched normal volunteers (\(83.5 \pm 8.9\) ml/100g brain/min): \(p < 0.001\). In 24 patients with migraine (10 classic, 14 common) studied during the period of 2 to 48 hours after subsidence of headache, mean Fg remained significantly increased (\(97.4 \pm 8.6\) ml/100g brain/min) compared with migraineurs during the headache-free interval and, when compared with normal volunteers, although significant reduction was observed when compared with values of patients during the headache interval. There was no significant difference in Fg values between groups of classic and common migraine, either the headache or during the post-headache intervals. There was no significant difference in PECO\(_2\) or mean arterial blood pressure (MABP) among the different groups.

Five patients with migraine (2 classic and 3 common) were studied during both the headache and headache-free intervals 5 to 14 days later. All 5 migraineurs showed an increase in mean Fg during the headache interval by 31.4 ± 16% compared with the headache-free interval (Fig. 2). Figure 3 displays serial measurements of regional Fg values during progressive worsening of the migraine headache compared to the headache-free values two weeks later in a 46-year-old female with classic migraine who presented with photopsia followed by left fronto-temporal headache. During the early phase of the headache, as shown by the cross-hatched bars to the left of the regional flow measurements indicated by the circle, there was a mean increase of 57% above the headache-free value in the regional Fg with the highest values in the left occipital (174 ml/100g brain/min), right sylvian-opercular (158 ml/100g brain/min) and brain stem-cerebellar (186 ml/100g brain/min) regions. Subsequent measurements were made as the headache progressed in seventy 45 minutes later, as shown by the solid bars to the right of the regional flow measurements indicated by the circle. As the headache progressed, there were further increases in mean Fg with maximum percentage increases in the left frontal, right parietal and bilateral inferior temporal regions. There was some correlation in increased Fg values with the site of the headache. Considering that PECO\(_2\) was lower during the second study (32.8 mmHg) compared to the first study (35.0 mmHg) and to the study made in the headache-free interval (38.0 mmHg), the hyperperfusion was actually underestimated during the serial measurements.

![Graph showing mean cerebral Fg values in migraineurs comparing headache-free interval with headache phase.](image)

To further observe the time course of rCBF change, serial measurements during headache and at intervals up to 5-6 days after the headache had subsided were performed in two patients with migraine (Fig. 4). In both cases, there were high mean Fg values during the headache phase which showed gradual and progressive reduction as the headache subsided.

In contrast to the significant increase in rCBF during the headache and immediate post-headache intervals, reduction in rCBF was demonstrated in one patient with classic migraine during the prodromal interval and in two patients with complicated migraine, one during the headache phase and the other during the post-headache interval. These three cases of migraine will be briefly described. Case No. 1 was a 28 year old woman with classic migraine studied during her late prodromal phase when she complained of loss of sensation in her left arm. There were reduced mean Fg values in both hemispheres (68 ml/100 g brain/min) and the lowest Fg
values (52 ml/100g brain/min) were noted in the post-central gyrus correlating with the neurological deficit. Case No. 2 was a 32 year old woman with complicated migraine who presented with sensory loss and weakness in her left arm associated with right-sided, throbbing headache at the time of the rCBF measurement. There was a zone of reduced flow with surrounding hyperemia observed in the right parietal region. Fg values in the right parietal region were significantly reduced (77.3 ml/100g brain/min) compared to all the other regions which showed marked hyperemia (126.1 ± 24.1 ml/100g brain/min). A similar pattern of rCBF was also observed even after the headache had subsided in a third patient with complicated migraine who also complained of sensory loss in her left arm. In this patient, Fg values measured 18 hours after headache had subsided showed significant focal reduction in the right parietal region correlating with the neurological deficit while all other regions showed marked hyperemia (Fig. 5).

Effect of Analgesics and Ergotamine on rCBF During Migraine Headaches

In order to evaluate the possible contribution of head pain itself as a cause of the increased CBF during the migraine attack, changes in CBF were examined during the interval of severe headache and subsequently after the pain was partially relieved by oral administration of 90 mg of codeine in a patient with classic migraine (Fig. 6). Forty-five minutes after the codeine administration the patient reported improvement of his headache and the rCBF measurement was repeated. Flow values of both hemispheres were reduced but brain stem-cerebellar values were unchanged. The mean Fg value in the left hemisphere was still increased compared to the mean hemispheric Fg value during the headache-free period.

The effect of sublingual ergotamine (2 mg) on regional Fg values during headache was also investigated in three patients (Fig. 7). Thirty minutes after ergotamine administration, there was no significant change in mean hemispheric Fg values but Fg values in the brain stem-cerebellar regions were reduced in all three patients. One case reported relief of headache after ergotamine.
Testing Cerebral Autoregulation in Patients with Migraine

Cerebral autoregulation was tested by decreasing cerebral perfusion pressure during orthostatic hypotension induced by tilting the patient 30 degrees head-up by the use of a tilt table in 12 patients with migraine during either the headache, post-headache or headache-free intervals. Effective MABP was reduced by 9.4 ± 2.8 mm Hg in these patients by postural tilting. Quantitative analysis of impairment of cerebral autoregulation was made by means of the following formula which provides an autoregulation index:

$$\text{Autoregulation Index} = \frac{\text{DCBF}}{\text{Mean Fg}} \times \frac{\text{MABP}}{\text{DABP}}$$

where DCBF equals the change in the mean cerebral Fg values when the MABP was changed from the steady state level during head-up tilt (DABP). In normal volunteers, where autoregulation is intact, the autoregulation index should be zero or close to zero and any deviation from zero will be in direct proportion to the degree of dysautoregulation. Dysautoregulation was found to be present in four cases during either the headache phase or the period up to 36 hours following the subsidence of headache, but was no longer present after the second day in eight cases (Fig. 8). A typical example of a case showing cerebral dysautoregulation during the headache phase was a 29-year-old woman with complicated migraine who showed diffuse reduction in Fg value by 26% (from 128.0 to 95.4 ml/100g brain/min) during orthostatic tilting compared to the steady state Fg values while supine.
Regional Cerebral Blood Flow Measurements During Cluster Headaches

The mean Fg value measured in a group of seven patients during typical cluster headaches (94.8 ± 12.4 ml/100g brain/min) was significantly higher than during the headache-free period measured in five patients (73.1 ± 5.2 ml/100g brain/min). In three patients with cluster headaches rCBF measurements were repeated during both the headache and the headache-free interval (one to 36 hours later). In these three patients there was an average mean Fg increase by 44.5% during the headache phase compared to the headache-free interval (Fig. 9). It was noted that unlike the natural history of classic and common migraine, the return of rCBF values to normal occurred more rapidly as the headache subsided in cluster headaches. For example, the mean Fg values one hour after the subsidence of a typical cluster headache in one patient showed no difference from the mean Fg value measured three weeks later. Another typical case of serial rCBF measurements before and during a cluster headache is illustrated with regional pattern of EFI values during headache in Figure 10.

Regional Cerebral Blood Flow Measurements During Muscle Contraction Headaches

The mean Fg value in patients with muscle contraction headache was 81.7 ± 9 ml/100g brain/min during the headache interval (N = 7) and 79.5 ± 9.5 ml/100g brain/min during the headache-free interval (N = 12), neither of these values were significantly different from values obtained in age-matched normal volunteers. Among the patients with evident anxiety and tension however, the regional distribution of flow showed relative increases in the frontal and brain stem-cerebellar regions during headache.

Extracerebral Flow Index (EFI)

Table 2 summarizes the EFI values compared between normal volunteers and during and after the various types of headache. EFI was significantly increased during cluster headaches (15.4 ± 8.7) and migraine headaches (8.8 ± 3.9), compared with normal volunteers (5.8 ± 4.5) indicating an increase in extracerebral blood volume and/or flow. The elevation of the EFI values ceased promptly as the headache subsided both in cluster headache and classic or common migraine. Patients with muscle contraction headache did not show any significant difference of EFI values compared with those of normal volunteers.
Table 2
Extracerebral Flow Index (EFI)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>EFI (g/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Volunteers</td>
<td>5.8 ± 4.6 (N = 32)</td>
</tr>
<tr>
<td>Cluster Headache</td>
<td>15.4 ± 5.7 (N = 7)*</td>
</tr>
<tr>
<td>Headache-free</td>
<td>6.4 ± 2.4 (N = 5)</td>
</tr>
<tr>
<td>Migraine (Classic and Common)</td>
<td>8.8 ± 3.9 (N = 13)*</td>
</tr>
<tr>
<td>Post Headache</td>
<td>5.3 ± 3.7 (N = 24)</td>
</tr>
<tr>
<td>Headache-free</td>
<td>4.9 ± 3.5 (N = 12)</td>
</tr>
<tr>
<td>Muscle-Contraction Headache</td>
<td>5.8 ± 4.0 (N = 7)</td>
</tr>
<tr>
<td>Headache-free</td>
<td>5.4 ± 3.2 (N = 12)</td>
</tr>
</tbody>
</table>

\[ EFI = \frac{F_{g} - F_{g'}}{F_{g} \times 100} \quad *p < 0.05\]

DISCUSSION

Methodological Considerations

Since the \(^{133}\text{Xe}\) inhalation method for the measurement of regional cerebral blood flow was first introduced by Mallett and Veall,\(^{16,19}\) a number of modifications have been made to minimize contamination of the cerebral \(^{133}\text{Xe}\) clearance curves by the radioactivity derived from extracranial sources such as the scalp, air passages and sinuses.\(^{10,20}\)

In the application of the technique to the study of migraine, in which changes of extracranial blood flow as well as the cerebral circulation seem to play an important role in the pathophysiological mechanisms, it is important to obtain accurate estimates of cerebral blood flow. In the present study every effort possible was made to minimize extracerebral contamination. The spectrum subtraction technique was used to correct for extracerebral flow contamination as originally proposed by Oldendorf,\(^{14}\) by Crawley et al.\(^{15}\) recently by Risberg et al.\(^{16}\) and Meyer et al.\(^{11}\) This method is based on the fact that \(^{133}\text{Xe}\) generates radioactivity at two energy levels: x-ray activity at 31 KEV and gamma activity at 81 KEV. Since gamma activity has considerably greater tissue penetration than x-ray activity, then the majority of x-ray activity is derived from extracranial sources. Calculation of the percentage correction for extracerebral contamination derived from subtraction of x-ray activity from gamma activity provides an estimate of extracerebral circulation as EFI. For normal volunteers EFI is low and constant, being in the order of 6%. When extracerebral blood flow is increased, as occurs due to a collateral circulation in patients with bilateral internal carotid occlusion, EFI is greatly increased to the order of 20-30%.\(^{11}\)

The use of a modified motorcycle helmet permits application of the probes to the scalp so that moderate pressure is sustained without discomfort which also reduced extracerebral contamination.\(^{11,21}\) The validity for flow values obtained from probes placed over the brain stem and cerebellar regions has been discussed in detail elsewhere.\(^{11,21}\)

Changes in Cerebral Hemodynamics During Attacks of Migraine

Since O'Brien\(^{5}\) originally reported a reduction of CBF during early stages of migraine attacks, a number of reports have confirmed the pattern of cerebral hemodynamic changes during migraine attacks.\(^{14-5,7}\) Skinho\(^{2}\) offered the hypothesis that the cerebral vasodilation occurring during the headache phase may be attributed to post-ischemic reactive hyperemia following the cerebral vasoconstriction occurring during the prodromal stage. He found increased lactate and decreased bicarbonate in the cerebrospinal fluid in patients following migraine attacks, which he attributed to enhanced anaerobic metabolism resulting from cerebral ischemia during the prodromal phase similar to the lactic acidosis and reactive hyperemia known to occur following cerebrovascular occlusion.\(^{22-24}\) Post-ischemic reactive hyperemia, as an explanation for the headache phase of migraine has been widely accepted by clinicians for the following reasons:

1) Neurological deficits associated with the prodromal interval of migraine may persist for several hours. The average duration of a scintillation scotoma, for example, has been calculated to last for 20 minutes\(^{25}\) which if due to ischemia might be expected to result in reactive hyperemia.

2) It is apparent from clinical observations that the neurological deficits due to cerebral vasoconstriction in the prodromal phase may continue into the headache interval and in some cases persist as complicated migraine.\(^{25}\)

3) Frequent and severe attacks of migraine are known to result in persistent neurological deficits due to cerebral infarction.\(^{27}\)

4) Biochemical studies of the cerebrospinal fluid during severe migraine attacks show similar changes to those occurring in cerebral infarction in patients with unquestionable stroke.\(^{28}\)

5) Computer assisted tomography in patients with complicated migraine have shown evidence of cerebral infarction in some cases.\(^{29,30}\)

Nevertheless, regional cerebral blood flow measurements should provide objective and quantitative information relevant to the following questions concern-
ing the cerebral hemodynamic changes during attacks of migraine and related vascular headaches: 1) Is the cerebral vasoconstriction during the early stages of migraine regional or generalized and if regional does it correlate with the neurological deficit? 2) Is the cerebral vasodilatation during the headache interval regional or generalized and if regional does it correspond to the zone of maximal head pain? 3) What is the time course of the reactive hyperemia in migraine? 4) Is cerebral autoregulation impaired during the migraine attack?

The present study provided answers to some of these questions. Regional cerebral blood flow was diffusely reduced during the prodrome of one case with classic migraine but the maximal regional reduction was the sylvian-opercular area contralateral to the hand that was numb. Focal reductions of gray matter flow corresponded consistently with the neurological deficit in patients with complicated migraine even during the headache interval as well as during the interval after the headache subsided. In cases of complicated migraine the zone of ischemia was always surrounded by hyperemia of other brain regions. These data indicate that cerebral vasosconstriction does indeed occur during the prodromal phase of classic and complicated migraine and is maximal in those brain regions responsible for the neurological deficits whether transient or persistent. These measurements would also lend some support to the view that while regional vasosconstriction does occur during the prodromes of migraine, there is also rapid spread over one or both hemispheres as has been suspected previously.¹

Reactive hyperemia has been reported to last for 6.6 days on the average.³¹ Judging from the present series of patients with migraine increased cerebral blood flow persists at least two days after the headache has subsided, although the increased extracranial blood flow subsides rapidly just as the headache subsides. Since it is well known that cerebral ischemia produces much greater lactacidosis and reactive hyperemia than scalp and muscle tissue, this is taken as some confirmative evidence that the headache phase of migraine is due to reactive hyperemia.

The present measurements failed to reveal any significant differences in the pattern and time course of cerebral hyperperfusion between classic migraine and common migraine in both the headache and the post-headache interval. This supports the view that common migraine may also be preceded by a cerebral vasosconstrictive phase even though this is not recognizable clinically as a clear-cut prodrome.

Tests of cerebral autoregulation in the present series of patients with migraine also supported the view that the cerebral hyperemia was secondary to previous ischemia¹⁷,²³,³²-³⁴ and these patients with migraine showed cerebral dysautoregulation during the headache phase and for an interval of 1-2 days thereafter.

Since there was no significant difference in MABP between the headache and headache-free intervals, the possibility that the increased CBF during migraine attacks is due to increased blood pressure in the presence of dysautoregulation may be excluded. However, frequently associated symptoms during the migraine attack such as dizziness and vertigo on arising and increase of severity of the headache when the head is lowered or during exercise and excitement, are explained by impaired autoregulation.

Pharmacological Action of Analgesics and Ergotamine on Cerebral Blood Flow During Migraine Attacks

It has been postulated that the head pain itself during a migraine attack might augment the measured cerebral blood flow due to an overall increase in cerebral metabolism as a result of this pain.³ For example, pain induced cerebral vasodilatation might account for the flow increases in the cerebral hemisphere opposite to the side of the hemicephalalgia (Fig. 6). It was found that the reduction of the severity of the head pain by codeine reduced the hemispheric blood flow bilaterally but to the greatest extent in the hemisphere contralateral to the head pain, but not in the brain stem-cerebellar regions. It was therefore concluded that during migraine headache the cerebral reactive hyperemia may become compounded by increases in cerebral blood flow secondary to the head pain itself.

On the other hand, sublingual administration of ergotamine did not decrease cerebral hemispheric flow but markedly decreased the hyperperfusion in the brain stem-cerebellar regions, confirming that cerebral hyperemia in the basilar artery territory plays an important role during migraine headaches. The exact pharmacological effect of ergotamine during migraine is still disputed. The present observations suggest that it has a selective vasoconstrictive effect on the dilated cerebral vessels during the migraine process. Animal experiments should determine whether ergotamine shows specific pharmacological effects on certain vascular systems.

Cluster Headache

Despite currently accepted views that cluster headaches are vascular in origin, the pathophysiological similarities and/or differences between migraine and cluster headache remain disputed.³⁵⁻³⁷ To date, there has been only a single report on rCBF measurements made during a cluster headache.³⁸

In the present series, the following statements summarize comparative observations of the cerebral hemodynamic changes during cluster headache and migraine:
1) During cluster headaches the mean hemispheric Fg values were increased in both hemispheres as much as or more than those seen in migraine headache when compared with the headache-free interval.

2) Higher mean Fg values observed in the contralateral hemisphere to the headache were far more frequent in cluster headaches than were seen in migraine headache. In cluster headaches the highest values were often seen in precentral, parietal and sylvian-opercular regions in the contralateral hemisphere to the head pain, and possibly were secondary to the head pain itself.

3) The increased rCBF measured during cluster headaches ceased promptly as the headache subsided while cerebral hyperperfusion in migraine headaches persisted for as long as two days.

4) The increase in extracerebral circulation was much greater in cluster headaches than in migraine headaches and was higher on the same side as the headache. (Fig. 10).

It is concluded that the cerebral hyperperfusion during cluster headaches is limited to the period of headache and is more related to head pain than to post-schematic hyperemia. The primary cause of cluster headache appears to be a profound hyperemia of the extracerebral vessels.

The Potential Usefulness of Regional Cerebral Blood Flow Measurements in Migraine and Related Vascular Headaches

To date, diagnosis and clinical classification of the various types of headache such as migraine, cluster headache and muscle contraction headache have been primarily based on the clinical history, physical examination and non-quantitative tests such as the CT scan and the EEG. Although the potential usefulness of rCBF measurements to clinical investigations by confirming the nature of vascular headaches was shown by Mathew et al by utilizing the carotid injection method, the 133Xe inhalation method is non-invasive and may be used on an out-patient basis for the diagnosis and pharmacological investigation of the treatment of vascular headaches. The highly consistent findings of cerebral hyperperfusion during and for some days after a migraine headache make the measurements a reliable way of separating this condition from patients with muscle contraction headache who show normal rCBF values. The differentiation from cerebral arteriovenous malformation and brain tumor is also aided by serial measurements which show normal values in the headache-free interval in migraine and cluster headaches but persistent elevation in arteriovenous malformation and persistent abnormality in brain tumor. Serial tests of cerebral autoregulation and extracerebral flow indices likewise should assist in the non-invasive differentiation of these common clinical problems.

REFERENCES


