Cerebral blood flow changes in the different phases of migraine

Marco Bartolini
Roberto Baruffaldi
Isabella Paolino
Mauro Silvestrini
Department of Neuroscience, Polytechnic University of Marche, Ancona, Italy
Reprint requests to: Prof. Mauro Silvestrini
Clinica Neurologica, Università Politecnica delle Marche
Azienda Ospedaliera Ospedali Riuniti
Via Conca, 71 - 60020 Torrette di Ancona (AN) - Italy
E.mail: masilvestrini@libero.it

Summary
The haemodynamic changes that take place in migraine are reviewed focusing on cerebral blood flow (CBF) data measured with different techniques in patients suffering from migraine with and without aura during the different phases of attacks and in interictal periods. Special attention is paid to the factors underpinning the conflicting cerebral blood flow data and to pathophysiological implications of the CBF changes detected in migraineurs.

KEY WORDS: CBF changes, migraine, pathophysiology.

Introduction
The changes in cerebral blood flow (CBF) that take place in the various phases of migraine attacks and in interictal periods have been extensively evaluated using different experimental approaches (1,2). These investigations have raised a number of interpretive problems, the most prominent of which is an inconsistency of CBF data across studies. One explanation for these discrepancies probably relates to the inherent nature of migraine attacks themselves, which are paroxysmal and usually long-lasting, thus preventing the execution of complete studies from symptom onset to remission. Moreover, as attacks vary in severity, duration and associated phenomena (including presence of symptoms of aura), it is difficult to compare CBF data obtained in different patients and even in the same patients assessed during different attacks. Another possible explanation probably relates to the study methods adopted, which range from simple, non-invasive techniques like transcranial Doppler ultrasonography to very sophisticated approaches like functional magnetic resonance imaging (fMRI), and provide different and often inhomogeneous information. The data reviewed in this paper have been obtained with techniques that are capable of detecting regional changes in CBF with good spatial resolution.

Xenon blood flow studies
The first investigations of the haemodynamic changes taking place during migraine attacks, particularly migraine with aura, used the Xenon blood flow technique. The earliest study dates back to 1969 (3); since then, more than 30 studies of patients with and without aura, investigated at different times from symptom onset, have been performed using intra-arterial Xenon injection or inhalation during spontaneous or induced attacks (1). During the aura phase, most investigations described reductions in CBF in posterior brain regions lasting from 30 to 60 minutes (4,5). After this time, CBF returned to normal or remained slightly decreased (6,7). The extent of CBF, ranging from 17 to 35%, never reached the ischaemic threshold (6,8). An anterior spread of oligemia across neurovascular boundaries, at a rate of 2-3 mm/min, was also reported (8). In the headache phase, CBF has been reported to be increased (9,10), reduced (11), and unchanged (6,12) in different studies performed in patients suffering from migraine with or without aura.

Single photon emission computerized tomography (SPECT) studies
Single photon emission tomography studies with different tracers, allowing semi-quantitative assessments of regional CBF (rCBF), have generally detected reduced perfusion, usually corresponding to the topography of the aura symptoms reported during attacks of migraine with aura (13,14), and normal and symmetrical CBF during migraine without aura (14). Most investigations found no haemodynamic changes between attacks (15). Patchy CBF changes were observed in migraine patients with and without aura in a single study (16).

Positron emission tomography (PET) studies
Positron emission tomography furnishes quantitative measurements of CBF. The poor time resolution of this technique, despite its good spatial resolution, makes it unsuitable for widespread application to migraine investigations, given that rapid changes in pathophysiological phenomena take place during attacks. A very interesting, fortuitous finding, reported by Woods and co-workers, was a migraine attack that began during scanning in a 21-year-old woman suffering from migraine without aura during a...
PET study of CBF in which she was participating as a normal volunteer (17). The researchers noted hypoperfusion spreading bilaterally starting from the visual association cortex within a few minutes of the start of a bilateral occipital throbbing headache and progressing anteriorly across vascular and anatomical boundaries. During the attack the patient had transient difficulties in focusing, which some interpreted as an atypical aura (1).

Another important finding was reported by Weiller and coworkers in 1995 (18). In this study, nine spontaneous right-sided headache attacks were investigated within six hours of migraine onset. The effect on CBF of symptomatic treatment with sumatriptan was also considered. During attacks, a significant increase in rCBF was observed in the anterocaudal cingulate cortex and in the visual and auditory association cortices. An 11% increase in rCBF was also observed in medial brainstem structures. Activation of the latter areas persisted after attack abortion induced by subcutaneous administration of sumatriptan. These findings were among the first to suggest the involvement of an imbalance in activity between brainstem nuclei regulating antinociception and vascular control in migraine.

Functional magnetic resonance imaging (fMRI) studies

Functional magnetic resonance imaging, with the three techniques of diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), and blood oxygenation level-dependent (BOLD) imaging, is increasingly being used in migraine investigations. The two features of fMRI that make it particularly useful for studying a transient phenomenon such as a migraine attack are its fast time of acquisition and the possibility it offers to assess both haemodynamic and metabolic parameters. In addition, data can be obtained without using isotopes. The most widely applied approach is probably PWI. This technique allows three parameters to be measured: relative CBF, relative cerebral blood volume (CBV), and mean transit time (MTT). In a study of 28 spontaneous episodes of migraine, Sanchez del Rio and co-workers (19) assessed seven cases during the visual aura phase, seven during the headache following the aura, and 14 during an attack of migraine without aura. The main findings were a reduction in relative CBF and CBV during the aura phase with an increase in MTT in the occipital cortex contralateral to the affected hemifield. These changes persisted in the headache phase and remained well above the threshold associated with ischaemic injury (maximum reduction: 37%). By contrast, there were no significant haemodynamic changes during the attacks of migraine without aura.

Concluding remarks

To conclude this brief review, it is important to note that in spite of the apparently incompatible data reported by the various studies, certain features of CBF appear to be consistent across techniques:

1. During visual aura, there is a reduction in CBF that is most often posterior in origin and appears to migrate anteriorly over time. The extent of this reduction is smaller than that associated with ischaemic injury.

2. Attacks of migraine without aura do not appear to be associated with significant haemodynamic changes; the most important exception concerns PET data from a single case (17) who also presented transient difficulties in focusing, which were interpreted as an atypical visual aura.

3. During interictal periods, CBF appears to be similar to that of healthy subjects in both migraine with and without aura.

Cerebral blood flow studies have helped to clarify some important issues in the pathophysiology of migraine. Functional and anatomical changes in the brain structures of migraineurs detected using MRI have been documented for several years (20). The selective and progressive alteration in iron homeostasis in the periaqueductal grey matter identified in migraine and in chronic daily headache suggested a specific, localized dysfunction in the control of the trigeminovascular nociceptive system. The growing use of sophisticated techniques capable of recording haemodynamic and metabolic data simultaneously with good temporal and spatial resolution is expected to allow further insight into several aspects of the pathophysiology of migraine. A recent fMRI study performed with the BOLD imaging technique is a case in point (21). The authors investigated the changes in blood oxygenation and CBV during attacks of migraine with and without aura induced by visual stimulation, and observed hyperoxia and increased CBV in the red nucleus and substantia nigra. These data suggest a role for brainstem structures in the generation of migraine attacks and are expected to contribute to early recognition of focal and persistent brain dysfunction in paroxysmal diseases, like the different types of migraine, and to help in the monitoring of their spontaneous and pharmacologically-mediated evolution.

References

5. Skyhoj Olsen T, Friberg L, Lassen NA. Ischemia may be the primary cause of neurologic deficits in classic migraine. Arch Neurol 1987;44:156-161

M. Bartolini et al.
CBF in migraine