Decreased vasoreactivity to right cerebral hemisphere pressure in migraine without aura: a near-infrared spectroscopy study

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Abstract

Objective: Several studies have reported changes in cerebrovascular reactivity during the interictal period of migraine. To characterize mechanisms of migraine, we compared changes in total haemoglobin (THbl) and regional oxygen saturation (rSO2) of the right and left frontal lobes in response to intracranial pressure changes during the interictal period of migraine.

Methods: Twelve right-handed migraineurs without aura and twelve age- and sex-matched healthy volunteers were asked to perform a head-down maneuver to increase intracranial venous pressure. Initial THbl was designated as 1.0, and all subsequent THbl measurements, which was proportional to the change in cerebral blood flow, were expressed as a value relative to this baseline.

Results: The head-down maneuver resulted in a significantly smaller increase in right-sided THbl in migraineurs when compared to volunteers (migraineurs, \(0.1 \pm 0.04\); volunteers, \(30 \pm 13\); \(P = 0.027\)), but there was no significant difference in left-sided THbl when comparing migraineurs and volunteers. Further, the head-down maneuver produced a significantly smaller increase in right-sided THbl than in left-sided THbl in migraineurs (right side, \(0.1 \pm 0.04\); left side, \(0.35 \pm 0.08\); \(P < 0.0001\)), but produced a significantly greater increase in right-sided THbl than in left-sided THbl in volunteers (right side, \(30 \pm 13\); left side, \(0.44 \pm 0.13\); \(P = 0.030\)). The head-down maneuver resulted in a smaller decrease in right-sided rSO2 in migraineurs when compared to volunteers (migraineurs, \(-4.1 \pm 2.2\%\); volunteers, \(-16 \pm 9.1\%\)), but produced a significantly greater decrease in left-sided rSO2 in migraineurs when compared to volunteers (migraineurs, \(-1.3 \pm 1.1\%\); volunteers, \(2.8 \pm 0.63\%\); \(P = 0.0037\)).

Conclusions: These data indicate that pressure-related vasoreactivity is suppressed in the right hemisphere of migraineurs during the interictal period.

Significance: The suppression of vasoreactivity in the right hemisphere might be related to the pathogenesis of migraine.

Keywords: Migraine; Nirs; Hemisphere; Head-down; Total haemoglobin; Vasoreactivity

1. Introduction

Migraine is a relatively common condition, affecting approximately 7% of men and 18% of women (Lipton et al., 2001). While the etiology of migraine remains poorly understood, some studies implicate extracranial arterial vasodilation and extracranial neurogenic inflammation as pathogenic mechanisms (Chapman et al., 1960; Graham and Wolff, 1938). Other studies have demonstrated decreases in regional cerebral blood flow (CBF), hypoperfusion during the interictal period, and changes in cerebrovascular reactivity (Backer et al., 2001; Calandre et al., 2002; Dora and Balkan, 2002; Facco et al., 1996; Heckmann et al., 1998; Levine et al., 1987; Podreka et al., 1987). The activated and then suppressed Blood-oxygenation level-dependent effect propagated into the contiguous occipital lobe in patients of migraine with or without aura (Cao et al., 1999). These findings would imply the relationship between migraine pathophysiology and spreading depression (Milner, 1958). In addition, differences between the physiology of cortical neurons in migraineurs and that of nonmigraineurs are suggested by magnetoencephalography (Barkley et al., 1990). Differences in energy metabolism are also suggested by magnetic resonance spectroscopy studies. Anaerobic glycolysis may occur in the brains of patients...
with migraine during the interictal period (Watanabe et al., 1996). This might be consistent with the finding that many patients with long-standing migraine show an abnormally high number of scattered foci of increased T2 signal intensity on MRI studies, suggesting the cumulative effect of repeated ischemia (Fezekas et al., 1992; Robbins and Friedman, 1992; Soges et al., 1988). Thus, the pathophysiology of migraine would be related to the abnormality of vessel autoregulation, which possibly induces repressed blood flow, blood oxygen and metabolism of neurons.

The goal of the present study was to characterize changes in cerebral vessel autoregulation during the interictal period of migraine. A head-down maneuver and near-infrared spectroscopy (NIRS) were employed to measure changes in cerebral blood flow and oxygen saturation in the right and left frontal lobes as indicators of cerebrovascular reactivity to pressure.

2. Patients and methods

Twelve right-handed patients with migraine without aura and twelve right-handed healthy age- and sex-matched volunteers (3 men, 9 women in each group; age, 41 ± 4.3 years in migraineurs, 40 ± 4.5 years in volunteers) participated in this study. Migraine was diagnosed according to the criteria of the International Headache Society (Headache Classification Committee of the International Headache Society, 1988). None of the subjects exhibited permanent neurological deficits, such as paresis. All migraineurs underwent magnetic resonance imaging (MRI) or computerized tomography (CT), which demonstrated no lesions in the frontal lobes. Informed consent was obtained from all subjects.

All subjects were asked to perform head-down maneuvers. The head-down maneuver consisted of the patient sitting down, followed by three episodes of dropping their head to their knees for 15 s each time. The head-down maneuver results in elevated venous pressure and an increase in frontal lobe pressure, which usually leads to pressure.

Over the course of these maneuvers, total haemoglobin concentration (THbl) and cerebral oxygen levels (rSO2) were measured using NIRS (TOS-96 monitor, Tostec Inc., Japan), with the TOS-96 detector placed on both sides of forehead (Litscher et al., 1998). Each light emitter and light detector of two channels were placed with a distance of 4 cm between them using a double-faced adhesive tape. The light emitter emitted infrared light of 760, 800, and 860 nm wavelength, with an impulse duration of 0.2 ms and a impulse frequency of 50 Hz. Data were measured with a sample rate of 0.2 Hz. Since emitters and detectors were strongly adhered to forehead, movement artifacts were not observed in all cases of this study. THbl was calculated as the sum of oxygenated and deoxygenated haemoglobin, and rSO2 was determined as the percentage of oxygenated haemoglobin in relation to THbl. Initial THbl was designated as 1.0, and all subsequent THbl measurements (every 5 s) were expressed as a value relative to this baseline. The change in THbl is proportional to the change in CBF (Holzschuh et al., 1997; Villringer et al., 1997). rSO2 was also measured every 5 s. THbl and rSO2 are represented as mean ± SEM. ANOVA was used for comparison of THbl and rSO2 in migraineurs and volunteers. A statistically significant difference was defined as P < 0.05.

3. Results

Table 1 summarizes the changes in right- and left-sided THbl and rSO2 in migraineurs and volunteers at baseline and during the head-down maneuver. The head-down maneuver resulted in a significantly smaller increase in right-sided THbl in migraineurs when compared to volunteers (migraineurs, -0.1 ± 0.04; volunteers, 0.30 ± 0.13; corresponding F-value = 5.579, degree of freedoms = 1, P = 0.0274), but there was no difference in left-sided THbl when comparing migraineurs and volunteers (migraineurs, 0.35 ± 0.08; volunteers, 0.44 ± 0.13, corresponding F-value = 0.353, degree of freedoms = 1, P = 0.5583). It is to be noted that right-sided THbl in volunteers showed a huge range of values. Further, the head-down maneuver produced a significantly smaller increase in right-sided THbl when compared to left-sided THbl in migraineurs (right side, -0.1 ± 0.04; left side, 0.35 ± 0.08; corresponding F-value = 25.07, degree of freedoms = 1, P < 0.0001), but produced a significantly greater increase in right-sided THbl than in left-sided THbl in volunteers (right side, 30 ± 13; left side, 0.44 ± 0.13; corresponding F-value = 5.352, degree of freedoms = 1, P = 0.0304). The head-down maneuver also resulted in a relatively smaller decrease in right-sided rSO2.

Table 1. The ΔTHbl and ΔrSO2 at head down

<table>
<thead>
<tr>
<th></th>
<th>Migraineurs</th>
<th>Volunteers</th>
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</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>3/9</td>
<td>3/9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41 ± 4.3</td>
<td>40 ± 4.5</td>
</tr>
<tr>
<td>ΔTHbl(R)</td>
<td>-0.1 ± 0.04</td>
<td>30 ± 13</td>
</tr>
<tr>
<td>ΔTHbl(L)</td>
<td>0.35 ± 0.08</td>
<td>0.44 ± 0.13</td>
</tr>
<tr>
<td>ΔrSO2(R)</td>
<td>-4.1 ± 2.2</td>
<td>*-16 ± 9.1</td>
</tr>
<tr>
<td>ΔrSO2(L)</td>
<td>1.3 ± 1.1</td>
<td>2.8 ± 0.63</td>
</tr>
</tbody>
</table>

THbl, total haemoglobin, Initial THbl is designated as 1.0; rSO2, regional oxygen saturation (%); R, right; L, left; mean ± SEM is indicated; *, P < 0.05.
in migraineurs than in volunteers (migraineurs, –4.1 ± 2.2%; volunteers, –16 ± 9.1%, corresponding $F$-value = 1.675, degree of freedom = 1, $P$ = 0.209), but resulted in a significantly greater decrease in left-sided rSO$_2$ in migraineurs than in volunteers (migraineurs, –1.3 ± 1.1%; volunteers, 2.8 ± 0.63%; corresponding $F$-value = 10.534, degree of freedom = 1, $P$ = 0.0037).

Fig. 1 shows two representative cases in healthy volunteers. The head-down maneuver resulted in a generally equivalent increase in right- and left-sided THbl (Fig. 1A). Further, it produced a decrease in right-sided rSO$_2$ and an increase in left-sided rSO$_2$ (Fig. 1A). Another representative case is shown in Fig. 1B. The head-down maneuver resulted in a greater increase in right-sided THbl than in left-sided THbl (Fig. 1B). It also produced a marked decrease in right-sided rSO$_2$ and a small increase in left-sided rSO$_2$ (Fig. 1B). In both of these cases, the head-down maneuver resulted in an increase in right-sided THbl and a decrease in right-sided rSO$_2$.

Fig. 2 shows two representative cases in migraineurs. The head-down maneuver produced no change in right- or left-sided THbl and resulted in a small increase in right- and left-sided rSO$_2$ (Fig. 2A). Another representative case is shown in Fig. 2B. The head-down maneuver resulted in a decrease in right-sided THbl and an increase in left-sided THbl (Fig. 2B). Further, it produced a decrease in left-sided rSO$_2$, but had no appreciable effect on right-sided rSO$_2$ (Fig. 2B).

4. Discussion

The present study demonstrated that a head-down maneuver produced a significantly smaller increase in right-sided THbl in migraineurs when compared to volunteers. In migraineurs, the maneuver produced a significantly smaller increase in right-sided THbl than in left-sided THbl, but also produced a significantly greater increase in right-sided THbl than in left-sided THbl in healthy volunteers. The head-down maneuver also produced a decrease in right-sided rSO$_2$ in volunteers, but had no appreciable effect on right-sided rSO$_2$ in migraineurs. These data indicate that vasoreactivity to pressure was suppressed in the right hemisphere in migraineurs. It is to be noted that the migraine attacks of some patients were mainly unilateral confined to the right or left, but the frequent side of the migraine attacks did not have any effect on the change in THbl and rSO$_2$.

The head-down maneuver induces an increase in intracranial venous pressure (Kotani et al., 1993; Mavrocordatos et al., 2000; Terada and Takeuchi, 1993). As shown in volunteers, increased venous pressure in the frontal lobe with the head-down maneuver usually resulted in elevated THbl, which was proportional to the change in CBF (Table 1, Fig. 1) (Holzschuh et al., 1997; Villringer et al., 1997). However, in migraineurs, the head-down maneuver resulted in decreased right-sided THbl, despite an elevation in venous pressure. This indicates an abnormality of the cerebrovascular response to pressure (Table 1, Fig. 2).
Dilatation and constriction of cerebral vessels are regulated by the autonomic nervous system, and their dysregulation is closely related to the pathogenesis of migraine (Thomsen and Olesen, 1995). During the interictal period, cerebrovascular response to various tasks, such as ergometer stress, breath holding or visual stimulation, is altered in migraineurs when compared to that in healthy volunteers (Backer et al., 2001; Dora et al., 2002; Heckmann et al., 1998). In this study, the cerebrovascular reactivity to pressure was suppressed in the right hemisphere. This alteration in cerebrovascular response in migraineurs may contribute to a metabolic strain on the central nervous system. Such a disturbance in metabolic homeostasis can induce onset of migraine via activation of the trigeminovascular system (May and Goadsby, 1999; Schoenen, 1998). Further, the progressive decrease in CBF observed during migraine may act to restore central nervous system homeostasis (Bolay et al., 2002; Leao, 1944).

The right hemisphere shows greater age-related declines in cortical activity than the left hemisphere (Cabeza, 2002; Goldstein and Shelly, 1981). Since the processing of spatial information is preferentially handled by the right hemisphere, any decline in right-sided activity in older people, who do not need spatial information so frequently as younger people, may result in depression of cortical activity, and thereby contribute to suppression of cerebrovascular reactivity to right hemispheric pressure (Anderson et al., 1991; Nebes, 1974; Sergent et al., 1992; Stephan et al., 2003).

Indeed, we have reported that head-down maneuver produced a greater increase in right side THbl in subjects under 70 years of age when compared to subjects older than 70 years. In contrast, the head-down maneuver had no effects on left side THbl, irrespective of subjects’ age (Shinoura and Yamada, 2005). The volunteers in the present study were relatively young, which accounts for the greater increase in right-sided THbl than in left-sided THbl with the head-down maneuver. Thus, significantly smaller increase in right-sided THbl in migraineurs of young age seems abnormal. Interestingly, right-sided THbl in volunteers showed a huge range of values. It seems that the subjects with enormously higher right-sided THbl values had several common characters such as high tension or high activity. Further investigations are needed to evaluate the cause of enormously high values in right-sided THbl.

Which mechanisms are responsible for decreases in right-sided vasoreactivity in migraineurs? Migraine can be triggered by emotional stress, and the right hemisphere plays a role in mediation of distress, empathy and unpleasant feelings (Bensafi et al., 2002; Eisenberger et al., 2003; Fanciullacci et al., 1998; Stronks et al., 1999; Shamay-Tsoory et al., 2003; Waldie, 2001; Wacogne et al., 2003). The right medial prefrontal cortex is highly activated by stress and modulates autonomic function in rats (Sullivan and Gratton, 1999). Stress-regulating coping strategies are mediated preferentially by the right hemisphere (Henry, 1997; Schore, 1997, 2002; Spivak et al., 1998; Wittling,
Thus, stress may affect right hemispheric function, leading to cerebrovascular dysregulation.

The head-down maneuver produced a greater decrease in left-sided rSO\textsubscript{2} in migraineurs when compared with volunteers, and produced a smaller decrease in right-sided rSO\textsubscript{2} in migraineurs when compared with volunteers (Table 1, Figs. 1 and 2). This may result from stronger sympathetic vasoconstriction during the postural change, thereby producing reflexive decreases in rSO\textsubscript{2} in left hemisphere of migraineurs (Anderson et al., 1991). In this study, we measured vasomotor reactivity in frontal lobes, but if we obtain the data about vasomotor reactivity in other lobes such as occipital, the pathophysiology of migraine might be more clear.

In summary, vasoreactivity to pressure during the interictal period is decreased in the right hemisphere of subjects with migraine without aura.

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References


