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The cerebral hemodynamics of repetitive transcranial magnetic stimulation

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Abstract Repetitive transcranial magnetic stimulation (rTMS) has been shown to be effective in the treatment of affective disorders. However, only little is known about hemodynamic physiological and safety aspects of this method. We studied the cerebral hemodynamics as measured by transcranial Doppler sonography in 20 healthy subjects during different rTMS procedures. Mean cerebral blood flow velocity (CBFV), pulsatility index (PI), and oxygen consumption were recorded continuously and averaged directly after the rTMS procedure. RTMS did not influence blood pressure, pulse rate, or blood oxygenation. There was a maximal increase of CBFV in the middle cererbal artery (MCA) of 3.6 % and 5.6 % during 10 Hz and 20 Hz stimulation, respectively. This increase was only seen on the stimulated left hemisphere. The PI remained unchanged during the whole procedure. It is likely that the increase of CBFV is due to dilatation of the small resistance vessels rather than due to vasoconstriction of the MCA. In terms of cerebral hemodynamics, rTMS is a safe and well-tolerated technique with a lower increase of CBFV than that seen in electroconvulsive therapy.

Key words Transcranial magnetic stimulation · Cerebral blood flow velocity · Pulsatility index · Electroconvulsive therapy

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Introduction

In the last years, repetitive transcranial magnetic stimulation (rTMS) has become of increasing interest in the treatment of patients with psychiatric, in particular affective, disorders (Grisaru et al. 1994; Kolbinger et al. 1995; Conca et al. 1996; George et al. 1999). There is evidence that the left frontal lobe is the place of stimulation showing the best therapeutic results in depressive patients (George et al. 1995; Pascual-Leone et al. 1996). However, other parameters of stimulation such as stimulus frequency, stimulus intensity, number of trains, and interstimulus interval are still debated and no common recommendations exist for the optimal way of stimulation. Safety guidelines have been published (Wassermann 1998) and rTMS has been suggested to be a very safe apparative procedure without any severe side effects except mild cognitive impairment shortly after the procedure in very few patients (Amassian et al. 1993; Grafman et al. 1994), but only few studies considered the safety aspects of rTMS under controlled conditions.

To date, one of the most effective apparative procedures at all to influence affective symptoms in psychiatric patients is electroconvulsive therapy (ECT) which is usually performed in narcosis and on the non-dominant hemisphere according to the practice guidelines for major depressive disorder in adults of the American Psychiatric Association (1990). However, ECT may have several side effects, besides the side effects of narcosis, such as transient cognitive impairment (Sackeim et al. 1986; Calev et al. 1991) and massive increase in cerebral blood flow velocity (CBFV) during the seizures (Saito et al. 1995, Vollmer-Haase et al. 1998). The amount of this increase in CBFV is about 100 % with a significantly higher increase in the left middle cerebral artery (MCA) as compared to the right MCA (Saito et al. 1995; Vollmer-Haase et al. 1998). In one study, the pulsatility index (PI) of the MCA decreased by about 50 % on either side (Vollmer-Haase et al. 1998) suggesting a vasodilatation of the small resistance vessels during ECT seizures. Thus, ECT may be contraindicated in patients with impairment of cerebral hemodynamics (e. g., stenosis of the MCA or the internal carotid artery) or a history of cerebral insults.

There are no studies available on the cerebral hemodynamics of rTMS in the treatment of depressive disorders which is normally applied to the left frontal lobe with infrathreshold to suprathreshold stimulus intensity. One study examined the hemodynamic response to repetitive magnetic stimulation in healthy subjects showing a mild increase of CBFV (Niehaus et al. 1999b). In diagnostic rTMS with only one or very few repetitive stimuli and suprathreshold stimulus intensity, an increase of CBFV by about 5 % for single stimuli and by about 8 % for triple stimuli in the ipsilateral MCA was observed (Sander et al. 1995). A recent study did not find any relevant changes of pulse rate or arterial blood pressure before or after rTMS (Niehaus et al. 1999a). During rTMS, an increase of pulse rate and decrease of blood pressure could be observed (Foerster et al. 1997). Therefore, diagnostic rTMS is assumed to be a very safe procedure in terms of cerebral hemodynamics but no experimental evidence exists.

We designed a placebo-controlled, single blind, crossover study according to the guidelines of standardized rTMS (Wassermann 1998) to evaluate the effect of therapeutic rTMS in a typical antidepressive stimulation procedure (i. e., infrathreshold stimulus intensity, left frontal lobe stimulation, high stimulus frequency in several trains) on the cerebral hemodynamics as measured by CBFV and PI in the MCA and by systemic blood pressure, pulse rate, and peripheral oxygenation. The results of the typical infrathreshold stimulation were compared to the results of a placebo and of a suprathreshold stimulation.

Methods and materials

Procedure

We enrolled 20 healthy, right-handed subjects without any history of affective disorders according to the ICD 10 classification and of neurological diseases. No drug intake on the day of examination except hormonal contraception was allowed. After giving informed consent, subjects were asked to lie down and rest during the whole procedure. First, a transcranial Doppler sonography (TCD) was performed for the intracranial arteries via the temporal bone window in order to exclude subjects with any abnormalities. Then, the motor threshold for the magnetic stimulation was determined by visual control of the contralateral M. abductor pollicis brevis during stimulation of the primary motor cortex as recommended in the literature (Pridmore et al. 1998). After calculating the stimulus intensity with 95 % and 110 % of the motor threshold for infrathreshold and suprathreshold stimulation, respectively, the ultrasound probes were placed bilaterally on the temporal bone window. Blood pressure was measured before and after the whole procedure. A pulse oxymeter (Nelcor N-180, Pulse oximeter, Hayward, USA) was placed at the index finger and pulse rate and peripheral oxygenation were recorded continuously during the whole procedure. In order to control for the impact of subjective mood changes, we measured the self-rated mood of the subjects before and after the procedure by the Zerssen 28-item scale (Zerssen 1983) which consists of 28 adjective pairs describing the present mood and emotional state of a subject. The study was approved by the local ethics committee.

Magnetic stimulation

The left frontal lobe was stimulated by a figure-eight magnetic coil (magnetic stimulator MagPro, Dantec, Denmark). A single stimulus duration was 200 µs, the stimulus intensity for the infrathreshold and suprathreshold stimulation was 95 % and 110 % of the motor threshold, respectively. For verum stimulation, the coil was held flat on the scalp with the centre placed over the left dorsolateral prefrontal cortex. Subjects were stimulated in random order by placebo stimulation [according to previous studies (e. g., Pascual-Leone et al. 1996; George et al. 1999) coil held in an angle of 90° to the scalp, same acoustic output as in verum stimulation], infrathreshold verum stimulation and suprathreshold verum stimulation. The subjects did not know the order of stimulation. Each total stimulation period consisted of a baseline recording of 3 min duration without any magnetic stimulus, a recording during three trains of 10 Hz stimuli for 5 s (one train per min), and a recording of three trains of 20 Hz stimuli for 2 s (one train per min). The rTMS was applied in accordance to the risk and safety guidelines published in 1998 (Wassermann 1998).

TCD recording

The CBFV was recorded bilaterally and continuously during the whole procedure by 2 MHz probes fixed on the temporal skull bone window with an elastic band. The TCD was performed with a TC 2-64B device (EME company, Überlingen, Germany). The MCA was insonated in a depth between 45 mm and 50 mm. The technique, and in particular the correct identification of the MCA, was carried out according to the literature (Ringelstein et al. 1990). Mean CBFV and PI (calculated as systolic CBFV minus diastolic CBFV divided by diastolic CBFV) were recorded continuously. For statistical analysis, pulse rate, oxygenation, the CBFV and PI were averaged over a time period of 10 s during baseline and after the third train of every stimulation period. Since rTMS produces artifacts in the recording of the Doppler ultrasound signals, it is not possible to average the signals during rTMS appropriately.

Data analysis

Data were collected in an electronic database and calculated by the statistical software program SPSS version 8.0. Data are presented as arithmetic mean and simple standard deviation or as percentage. Comparison between different stimulation periods and between the two hemispheres were performed by the nonparametric Friedman-test with the Wilcoxon-test as post-hoc test. Differences in sex and in the order of stimulation were tested by the nonparametric Mann-Whitney-U-test and by the Kruskal-Wallis-analysis, respectively. Significance level was set at $p = 0.05$.

Results

The mean age of the 20 subjects was 32.0 ± 6.6 years (range 26 to 50); 11 were female, 9 were male. The mean motor threshold was 58.1 ± 11.5 A/µs, the mean infrathreshold stimulation was 56.4 ± 11.1 A/µs, and the mean suprathreshold stimulation was 62.9 ± 10.3 A/µs. Blood pressure did not change significantly before or after the whole procedure (diastolic mean 78.5 ± 6.5 before and 76.8 ± 7.8 after; systolic mean 125.0 ± 10.6 before and 121.0 ± 10.3 after; all figures in mmHg). All subjects had normal intracranial blood flow profiles and were included in the statistical analysis. The self-rated mood of the subjects as measured by the 28-item Zerssen scale did not change significantly during the procedure either (score 14.6 ± 9.4 before and 14.0 ± 10.7 after). No subject reported any adverse event in 24 h following the procedure.

Table 1 Oxygenation and pulse rate during different types of rTMS in 20 healthy subjects presented as arithmetic mean and simple standard deviation. No significant differences as analyzed by the Friedman test

	Placebo stimulation			infrathreshold stimulation			suprathreshold stimulation		
	baseline	10 Hz	20 Hz	baseline	10 Hz	20 Hz	baseline	10 Hz	20 Hz
Pulse rate (bpm)	67.6 ± 9.6	67.0 ± 9.0	66.5 ± 9.1	67.1 ± 8.3	67.2 ± 8.8	68.2 ± 9.2	67.3 ± 7.9	67.6 ± 8.1	68.0 ± 7.9
Oxygenation (%)	98.3 ± 1.5	98.2 ± 1.3	98.3 ± 1.1	98.3 ± 1.0	98.6 ± 1.2	98.6 ± 1.0	98.4 ± 1.0	98.4 ± 1.3	98.5 ± 1.3

Table 2 CBFV and PI in the right and left MCA during different types of rTMS (placebo, infrathreshold, suprathreshold) in 20 healthy subjects. Data are presented as arithmetic mean and simple standard deviation. * (p < 0001) and † (p < 0007) denote a significant difference between the three periods of measurement (baseline, 10 Hz, and 20 Hz stimulation) within one stimulation type as compared by the Friedman-test. No further significant differences within the different stimulation periods could be detected

	Placebo stimulation			infrathreshold stimulation			suprathreshold stimulation		
	baseline	10 Hz	20 Hz	baseline	10 Hz	20 Hz	baseline	10 Hz	20 Hz
CBFV (cm/s):									
right MCA	62.2 ± 15.4	61.5 ± 14.5	61.5 ± 15.4	60.5 ± 14.9	61.2 ± 15.4	62.7 ± 14.4	61.8 ± 15.4	63.3 ± 15.9	64.5 ± 16.1†
left MCA	61.9 ± 14.1	62.0 ± 13.8	62.5 ± 13.8	60.3 ± 14.6	63.3 ± 15.5	63.6 ± 15.2*	60.6 ± 16.2	62.8 ± 16.0	64.0 ± 16.6*
Pulsatility index:									
right MCA	0.91 ± 0.14	0.94 ± 0.15	0.90 ± 0.14	0.92 ± 0.15	0.95 ± 0.15	0.91 ± 0.13	0.90 ± 0.14	0.90 ± 0.13	0.88 ± 0.15
left MCA	0.86 ± 0.10	0.91 ± 0.14	0.90 ± 0.12	0.90 ± 0.12	0.89 ± 0.10	0.88 ± 0.11	0.92 ± 0.11	0.92 ± 0.13	0.90 ± 0.13

Nonparametric testing did not reveal any impact of the sex or of the order of stimulation on the different parameters. Therefore, the following results are presented for the total subject group.

In Table 1, the oxygenation and the pulse rate are presented separately for the different stimulation periods. There were no significant changes in these two parameters during the whole examination procedure. In Table 2, the CBFV and the PI are presented separately for the right and left MCA and for the different stimulation periods. There were no significant changes between baseline and placebo stimulation neither in the right nor in the left MCA. As compared to baseline, infrathreshold stimulation produced a significant increase of CBFV in the left but not in the right MCA during 10 Hz stimulation ($p < 0.001$) and during 20 Hz stimulation ($p < 0.001$). During suprathreshold stimulation, a significant increase of CBFV both during 10 Hz stimulation ($p < 0.005$) and during 20 Hz stimulation ($p < 0.001$) was produced. CBFV also increased in the right MCA but only during 20 Hz stimulation significantly as compared to baseline ($p < 0.005$). The total increase of CBFV was 5 % during 10 Hz stimulation and 5.5 % during 20 Hz stimulation for infrathreshold intensity and 3.6 % during 10 Hz stimulation and 5.6 % during 20 Hz stimulation for suprathreshold intensity (all values on the left hemisphere).

Figure 1 shows the interhemispheric shift of CBFV as presented by the differences between the left and the right MCA separately for the different stimulation periods. During placebo stimulation a significant shift in favour of the left hemisphere was observed during 10 Hz ($p < 0.05$) and during 20 Hz ($p < 0.003$) stimulation. A significant shift to the left MCA was also observed during infrathreshold and during suprathreshold stimulation both during 10 Hz and

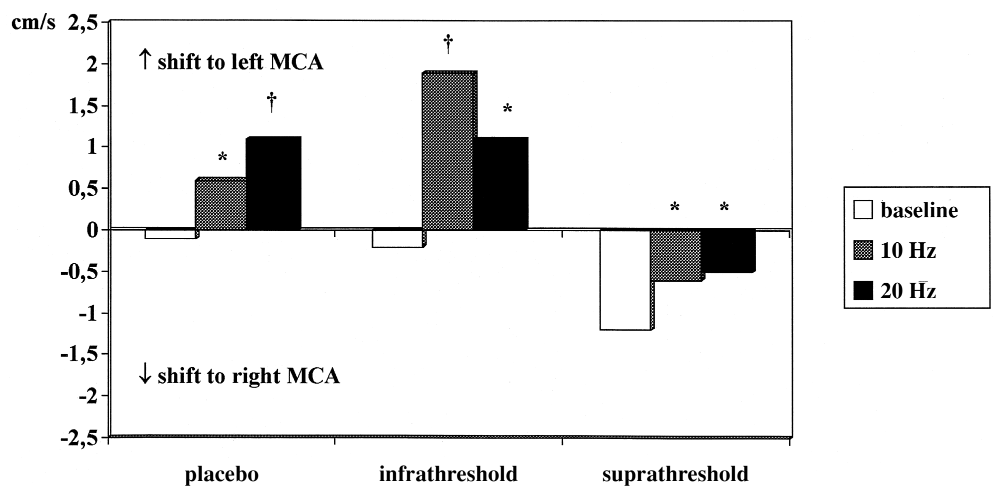

Fig. 1 Difference of CBFV between the left and the right hemisphere during different types of rTMS in 20 healthy subjects. *($p < 0.05$) and †($p < 0.01$) denote a statistically significant difference as compared to baseline (Friedman test with post-hoc Wilcoxon test)

during 20 Hz stimulation ($p < 0.01$ for 10 Hz infrathreshold stimulation, $p < 0.05$ for all other stimulations). The maximal shift was about 2.3 cm/s to the left MCA during 10 Hz infrathreshold stimulation.

Discussion

Our data suggest that rTMS leads to a mild but significant increase of CBFV. We did not observe any impact of rTMS on general circulatory parameters. This implies that the observed changes of CBFV cannot be related to changes of pulse rate or blood pressure but must be contributed to a direct effect of rTMS on cerebral hemodynamics.

An increase of CBFV as compared to baseline was observed both for the infrathreshold and for the suprathreshold stimulation intensity in the stimulated hemisphere but not for placebo stimulation. For the suprathreshold stimulation, the increase was higher and could even be noted in the not stimulated hemisphere, probably because of an activation via interhemispheric pathways across the corpus callosum and not by a direct effect on the resistance vessels on the contralateral side since the effects of rTMS can only be noted in a distance of about 5 cm. We conclude that the amount of CBFV increase can in part be related to the amount of the magnetic stimulation intensity. The frequency of stimulation, on the other hand, was a less important parameter for changes of CBFV in our study since there were only mild and not significant changes of CBFV by increasing the stimulation frequency. The total amount of magnetic field application (i. e., the product of the time of stimulation and the stimulation frequency) applied in both stimulation frequencies is similar.

The exact mechanisms leading to the observed changes in CBFV cannot be determined definitely by this study. The pulsatility index did not show any changes during rTMS. This suggests that the small resistance vessels are dilated. One of the general mechanisms leading to such a dilatation is an increased oxygen consumption of the smooth muscle tissue in the vessel walls or of the respective brain tissue. A vasoconstriction of the MCA which would also explain an increased CBFV is unlikely because of the unchanged pulsatility index.

We observed a nearly uniform shift of CBFV to the left MCA both during placebo and during verum stimulation (see Fig. 1). We suppose that this interhemispheric shift in favour of the left hemisphere during all stimulation procedures must predominantly be related to the acoustical stimulation by the device itself and not to a direct influence of the magnetic field. This phenomenon of a left hemisphere shift of CBFV during unspecific acoustical stimulation is well-known from the literature (Hartje et al. 1994; Evers et al. 1999), the amount of the shift by about 1–4 % is in concordance with similar studies (Droste et al. 1989; Evers et al. 1999). We did not observe a difference of this shift between the different stimulation frequencies, most probably because the sounds of the 10 Hz and of the 20 Hz stimulation are very similar. Studies on regional cerebral blood flow after rTMS revealed a similar increase not more than that induced by voluntary muscle activation mimicking the motor effects of rTMS (Dressler et al. 1990).

There is evidence from SPECT studies that the regional cerebral blood flow is decreased in the frontal lobe in major depression (Goodwin 1997; Galynker et al. 1998). Interestingly, unilateral stimulation of the left frontal lobe obtains better outcome results in the treatment of depressive patients than stimulation of the right frontal lobe (Pascual-Leone et al. 1996). This finding is the reason why we stimulated the left frontal lobe. Our results of an increase of CBFV predominantly in the stimulated left hemisphere is in concordance with clinical studies. However, the relationship between the therapeutic mechanisms of rTMS and the regional hemodynamic changes remains to be explored.

This study analyzed the impact of rTMS on cerebral hemodynamics under conditions and parameters which are assumed to be of therapeutic efficacy in psychiatric diseases. As compared to previous studies with low frequency rTMS resulting in a CBFV increase between 5 % and 8 % (Sander et al. 1995) in the MCA and about 10 % in the posterior cerebral artery (Sander et al. 1996), we observed a similar increase of CBFV with our high frequency technique. This is in concordance with the study by Niehaus et al. (1999b). However, the respective increase rates of CBFV in ECT studies with a comparable design are exorbitantly higher and may reach more than 100 % (Saito et al. 1995; Vollmer-Haase et al. 1998).

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