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1-Hz Repetitive Transcranial Magnetic Stimulation Increases Cerebral Vasomotor Reactivity: A Possible Autonomic Nervous System Modulation

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ABSTRACT

Background: Neuromodulation techniques, i.e. repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), can modify cerebral hemodynamics. High frequency rTMS appeared to decrease cerebral vasomotor reactivity (VMR), while there is still poor evidence about the effect of low frequency (LF) rTMS on cerebral blood flow (CBF) and VMR.
Hypothesis: The present study aimed to test if LF rTMS decreases CBF and increases cerebral VMR. Monolateral or bilateral hemispheric involvement and duration of the effect were considered. A possible role of autonomic nervous system in CBF and VMR modulation was also investigated.
Methods: Twenty-four right-handed healthy subjects underwent randomly real (12) or sham (12) 20-min 1-Hz rTMS on left primary motor cortex. Mean flow velocity and VMR of middle cerebral arteries were evaluated by means of transcranial Doppler before (T0), after 10 min (T1) and after 2 (T2), 5 (T3) and 24 h (T4) from rTMS. Heart rate variability (HRV) was studied within the same timing interval, assessing low frequency/high frequency (LF/HF) ratio as index of autonomic balance.
Results: After real rTMS compared with sham stimulation, MFV decreased bilaterally at T1 ($F = 3.240$, $P = .030$) while VMR increased bilaterally ($F = 5.116$, $P = .002$) for at least 5 h (T3). LF/HF ratio decreased early after real rTMS ($F = 2.881$, $P = .040$).
Conclusion: 1-Hz rTMS may induce a bilateral long-lasting increase of VMR, while its effect on MFV is short-lasting. Moreover, HRV changes induced by rTMS suggest a possible autonomic nervous system modulation.

Introduction

Neuromodulation techniques, i.e. repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), can modify cortical activity. High frequency (HF) rTMS and anodal tDCS (a-tDCS) are able to enhance the excitability of the stimulated hemisphere, while low frequency (LF) rTMS and cathodal tDCS (c-tDCS) can suppress it [1,2].

rTMS and tDCS are also reported to impact cerebral blood flow (CBF). Rollnik et al. [3] first demonstrated that LF rTMS on dorsolateral prefrontal cortex may temporarily decrease CBF velocity (CBFv) in the ipsilateral middle cerebral artery (MCA) as detected by transcranial Doppler (TCD). Other neuroimaging studies showed local and transient CBF decrease after LF rTMS [2,4]. Otherwise, there is evidence that HF rTMS and a-tDCS induce a localized and transitory CBF increase [5–7].

Neuromodulation techniques resulted also to influence cerebral vasomotor reactivity (VMR), which is the capability of cerebral vessels to dilate after a stimulus [8]. A significant VMR decrease was found in healthy subjects and stroke patients after HF rTMS [9]. Moreover, c-tDCS was demonstrated to increase cerebral VMR, while a-tDCS to decrease it [10]. These VMR changes resulted to be long-lasting (up to 2 h) and appeared to be induced by autonomic nervous system (ANS) modulation, as assessed by Heart Rate Variability (HRV).

There is still poor evidence about the time course of LF rTMS-mediated modulation of cerebral hemodynamics, as well as the net effect on cerebral vasomotor reactivity [11].

The present study aimed to test if 1-Hz rTMS applied on motor cortex decreases MCA CBF as detected by TCD and increases

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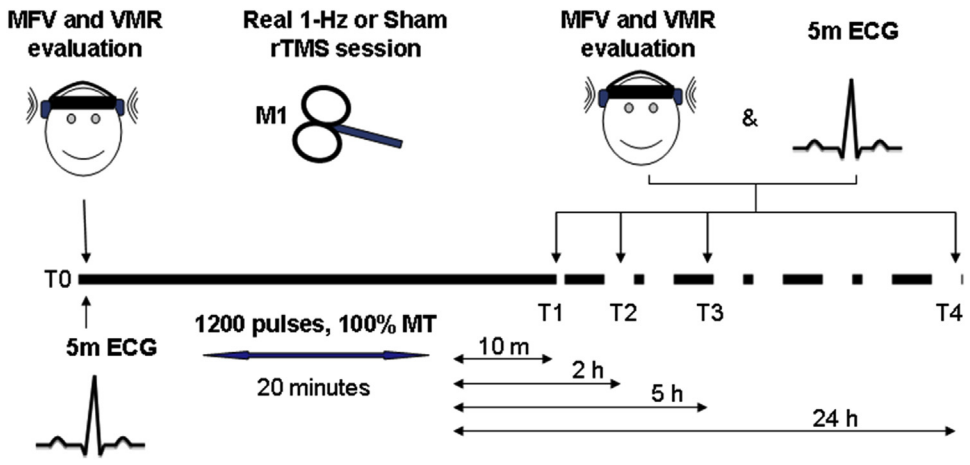

Figure 1. Time-schedule of the experimental design including: real or sham repetitive transcranial magnetic stimulation (rTMS) on primary motor cortex (M1); basal mean flow velocity (MFV) and vasomotor reactivity (VMR) in middle cerebral arteries evaluated by means of transcranial Doppler before (T0), after 10 min (T1) and after 2 (T2), 5 (T3) and 24 h (T4) from rTMS. Heart rate variability (HRV) was studied by 5-min (5m) electrocardiogram with the same timing intervals.

cerebral VMR as evaluated by CO_2 inhalation test. Time course and mono- or bilateral hemispheric involvement were investigated. Moreover, in order to explore if autonomic nervous system modulation could be responsible of cerebral blood flow changes induced by rTMS, HRV was calculated within the same time interval of cerebral hemodynamics variables.

Materials and methods

Healthy volunteers were enrolled from departmental staff. The inclusion criterion was right-handedness according to the Edinburgh inventory [12]. Exclusion criteria comprised poor insonation of temporal bone windows, contraindication for rTMS, and any history of cardiovascular, neurological or respiratory diseases. Eligibility criteria for rTMS were defined according to guidelines for the use of transcranial magnetic stimulation [13,14].

A complete ultrasound study of the cerebral vessels, including color-coded duplex sonography of the neck arteries (iU22, Philips Ultrasound, Bothell, WA, USA) and transcranial Doppler (TCD, Multidop X Digital, DWL, Sipplingen, Germany), was carried out to exclude extracranial or intracranial artery diseases.

Real rTMS was applied on the primary motor cortex (M1) of the left hemisphere, with a figure-of-eight coil connected with Magstim Rapid magnetic stimulator (MagStimCo. Ltd., Whitland, Dyfed, UK), as previously described [9]. The "hot spot" and the rest Motor Threshold (MT) of the first dorsal interosseus (FDI) were defined according to the IFCN recommendations, using surface EMG monitoring [13]. Real rTMS consisted of a 20-min train at 1 Hz (1200 pulses in total) with stimulus intensity equal to MT. Sham sessions were performed with the same parameters of the real rTMS but with the coil angled away from the head to reproduce the noise of the stimulation as well as some local sensations [15,37].

Cerebral VMR to hypercapnia was evaluated by means of CO_2 reactivity test [16]. During the experiments, end-tidal expiratory CO_2 was measured and mean arterial blood pressure (mABP) was monitored. The study was carried out in a quiet room, with patients lying in a comfortable supine position, without any visual or auditory stimulation. Subjects were asked to avoid smoking, caffeine/alcohol/drugs consumption, physical exercise, emotional stress, sleep-deprivation the day before and the days of the experiment. Two TCD dual 2-MHz transducers fitted on a headband and placed on the temporal bone windows were used so as to obtain a bilateral continuous measurement of MFV in the MCAs insonated at a depth of 50 ± 4 mm. Once the signals recorded became stable, MFV at rest was obtained through the continuous recording of a 60-s period of normal room air breathing. Hypercapnia was induced by the inhalation of a mixture of 7% CO_2/air, and subjects breathed through the mask until MCA flow velocity became stable. Once equilibrium was reached, a further 30-s recording was made at this stage (plateau period). The maximal vasodilatory range [17] was determined by the percentage increase in MFV occurred during the administration of 7% CO_2 mixture.

Each experiment consisted of three consecutive periods, i.e. a 60-s rest period, the 90-s CO_2 inhalation period – always including for each subject the 30-s plateau period – and, finally, the 90-s recovery period. Each experiment described above was repeated at least three times, at 10-min intervals at least. The MFV baseline value was taken as the average of the rest period (60 s). The MFV CO_2 value was the average of the plateau period of 30 s. VMR values were obtained according to the formula:

$$\mathrm{VMR} = \left\{\frac{\mathrm{MFV\ CO_2} - \mathrm{MFV\ baseline}}{\mathrm{MFV\ baseline}}\right\} \times 100$$

HRV analysis was performed in each subject on consecutive RR-interval series of a 5-min resting electrocardiogram, using standard procedures [18]. HRV was analyzed in the frequency domain using dedicated HRV Analysis Software 2.0 for Windows (Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland) [19]. Power spectral analysis was calculated using autoregressive method. We calculated the total power spectrum (ms^2) resulting from the sum of Very Low Frequency (VLF) power, LF power and HF power. For the analysis we considered an HF component, centered at .15–.4 Hz reflecting mostly vagal activity, an LF component, centered at .04–.15 Hz, and a VLF component (<.04 Hz). The LF/HF ratio was used as an index of sympatho-vagal balance and was calculated on the normalized units of LF and HF power (LFN, HFN), obtained dividing each power component by the total power less the VLF component.

MFV, VMR and LF/HF ratio were evaluated before (T0), after 10 min (T1) and after 2 (T2), 5 (T3) and 24 h (T4) from rTMS (Fig. 1). Subjects, neuro-sonographer and HRV analysis performer were blinded to the type of stimulation.

The institutional review committee approved the study protocol. All subjects gave their informed written consent.