Single-Pulse Transcranial Magnetic Stimulation Reset the Rhythm of Essential Tremor But Not Heart Beat

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Key Words
cardiac rhythm; essential tremor; heart rate; transcranial magnetic stimulation

Background. Human oscillator is observed in and outside the nervous system. Cardiac rhythm is generated by heart itself but can be modulated by brain. Using the technique of transcranial magnetic stimulation (TMS) and resetting index, we studied if single-pulse TMS could reset the cardiac rhythm and help differentiate oscillator of neurogenic or non-neurogenic origin.

Methods. In addition to the study of 4 patients with essential tremor, car diac rhythm was studied in 6 normal subjects. The magnetic intensity was initiated from motor threshold of hand muscle, and then with an increment of 10% up to the maximal output of magnetic stimulator. We used the resetting index in dex (RI) to quantify the influence of the TMS.

Results. The resetting phenomenon was observed in essential tremor (RI = 0.92) but not in cardiac rhythm (RI = 0.02).

Conclusions. Single-pulse TMS is able to reset the rhythm of essential tremor but not heart beat. The pacing mechanism is different between essential tremor and heart beat. The cardiac rhythm is regulated chiefly by heart itself. Essential tremor should not share the same mechanism with heart beat.

[Chin Med J (Taipei) 2001;64:271-276]
Methods

The study included 6 normal subjects (6 male, aged 30-65 years) and 4 patients with essential tremor (3 male and 1 female, aged 55-64 years).

Transcranial magnetic stimulation

The re setting method was based upon our previous study on palatal tremor. Transcranial magnetic stimulation (TMS) was delivered with a magnetic stimulator (Magstim 200) with a figure-of-eight coil. The coil was held with the handle posterior and oriented sagittally. For hand tremor, the precise coil position was adjusted to give a maximal response in the target muscle at a given stimulus intensity. For cardiac rhythm, the coil to reset cardiac rhythm was placed over the frontal, parietal and temporal areas bilaterally (International 10-20 system; Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz). The intensity to reset tremor was initiated at motor threshold of hand muscle with each increment of 10% to the maximal output of 100%. The motor threshold was defined as the intensity to provoke muscle potentials with peak-to-peak amplitude at least 50-100 µV at least 5 times of 10 trials. The stimulus intensity for motor threshold began at 30% of maximal output and was incremented with 5% steps. The interval between stimuli was about one minute.

Cardiac rhythm

The effect of TMS on cardiac rhythm was studied in 6 normal subjects and 4 patients with essential tremor. Cardiac rhythm was recorded with surface electromyography (EMG) at left anterior chest wall, crossing the mid-clavical line and the 7th intercostal space.

Essential tremor (ET)

We studied 4 male patients with clinical diagnosis of classic familial essential tremor. The patients had postural tremor that was most pronounced in the upper limbs. They all had a positive family history of a similar disorder. In the outstretched arms, the essential tremor had a frequency of 5-9 Hz. All patients were taking β-blocker for their tremor: the medication was withheld for at least 2 days before the study.

Data analysis

At least 30 trials were recorded for each test of rhythm re setting of heart beat and essential tremor. The car diac rhythm was quite regular. Twenty trials were chosen for the off-line analysis rejecting those with irregular or non-sustained rhythms before TMS, non-sustained tremor after TMS, or voluntary or involuntary muscle activity during the trial. Accord ing to the method of Lee and Stein, RI was used to quantify the mod ula tion of rhythm. We measured the peak time of the last five oscillator bursts preceding the transcranial stimulus. The time between peaks was defined as cycle length. We calculated the average age of oscillatory cycle length from the interpeak interval for these five oscillatory bursts. We measured the time of the transcranial stimulus from the peak time of the last oscillator burst preceding the transcranial stimulus. The time between peaks was defined as cycle length. We calculated the predicted time for the five oscillator bursts following the transcranial stimulus on the basis of the time of the last oscillator burst preceding the stimulus and the average cycle length. We then measured the actual peak times of the first five oscillator bursts following the transcranial stimulus plotted against the time of the stimulus (%cl). We calculated the predicted time for the five oscillator bursts following the transcranial stimulus. The time of the stimulus varied randomly across trials, and putting the plotted points for all trials with a given stimulus condition (i.e. stimulus in intensity) allowed us to calculate the linear regression, one for each of the first five oscillator bursts following the transcranial stimulus. The time of the stimulus varied randomly across trials, and putting the plotted points for all trials with a given stimulus condition (i.e. stimulus in intensity) allowed us to calculate the linear regression, one for each of the first five oscillator bursts following the transcranial stimulus. The time of the stimulus varied randomly across trials, and putting the plotted points for all trials with a given stimulus condition (i.e. stimulus in intensity) allowed us to calculate the linear regression, one for each of the first five oscillator bursts following the transcranial stimulus.
Using the Wilcoxon rank sum test, nonparametric comparison between groups was analyzed. A p-value less than 0.05 was defined as statistically significant. Simple linear regression analysis was used to evaluate the correlation between RI and the stimulus intensity. For the purpose of visual display, we averaged the rectified signals to the transcranial stimulus. Because the stimuli were delivered randomly in the oscillator cycle, the oscillator bursts preceding the stimulus would be averaged out. However, if the stimulus of TMS has an effect on the oscillator, the signal following the stimulus will show the modulation.\(^9\)

### Results

#### Cardiac rhythm

No arrhythmia was observed throughout the study. In normal subjects, motor threshold of the hand muscles was 30-45% (mean 36.8 ± 4.6%). There was no significant change even the stimulation was at maximal intensity (Fig. 1). RI was close to 0 and ranged from 0.002 to 0.056 (mean 0.02 ± 0.02) despite that the stimuli were applied at either side of hemisphere or at frontal, parietal or temporal areas. There was no resetting phenomenon of cardiac rhythm to single-pulse TMS even at the maximal intensity (100%).

#### Essential tremor

The resetting phenomenon of tremor rhythm to single-pulse TMS was observed in the ET patients. Motor threshold (MT) of their hand muscles was 35-50% (mean 39.3 ± 5.2%). RIs ranged from 0.84 to 0.97 at 100% MT, mean 0.863 ± 0.013; at 110 MT mean 0.873 ± 0.013; at 120 MT, mean 0.878 ± 0.010; at 130 MT, mean 0.888 ± 0.013; at 140 MT, mean 0.893 ± 0.009; at 150 MT, mean 0.910 ± 0.010; at 160 MT, mean 0.925 ± 0.010; at 170 MT, mean 0.930 ± 0.010; at 180 MT, mean 0.940 ± 0.010; at 190 MT, mean 0.948 ± 0.009; at 200% MT, mean 0.955 ± 0.010) for patients with ET. The RI increased along with the increase of TMS in intensity (Fig. 2). The re-

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**Fig. 1.** The rhythm of essential tremor and heart beat to transcranial magnetic stimulation. (A1) and (B1) were data before averaging. (A2) and (B2) were data after averaging. After averaging, the rhythm was clearly reset in essential tremor but not in cardiac rhythm.

**Fig. 2.** In patients with essential tremor, there was a positive correlation between re-setting index and the intensity of magnetic stimulation.
ting of ET was more apparent with increase of magnetic intensity. The resetting of the tremor rhythm was not dependent upon the time when the stimulus was delivered. Using the Wilcoxon rank sum test, non-parametric comparison showed significant difference between the groups of cardiac rhythm and ET.

**Discussion**

Stimulation of the human brain could induce change of heart beat. Tachy cardia is observed when the motor cortex surface is stimulated. The ECG changes may outlast the stimulation for several hours, sometimes leading to ventricular fibrillation. The mechanism of mediating cardiovascular effects from the motosensory cortex is still unknown. Stimulation of the corticospinal tract seems to go through the connection with hypothalamus and lower brainstem and further provoke autonomic response. Single-pulse TMS can not modulate the cardiac rhythm even with the maximal output of the stimuli at frontal, temporal or parietal areas, since its intensity is not sufficient to provoke significant effects, and the sites are away from cortical sites involved in cardiac control. The anatomic site could be embedded in a deeper area so that single-pulse TMS could not reach. The prime cortical sites for modulation of cardiac rhythm were in the brain. Our results were consistent with previous studies and further confirmed the safety of single-pulse TMS in clinical application. The cardiac rhythm is chiefly modulated by the heart itself.

The pathogenesis of ET still remains uncertain. The study of pathology has not showed any evidence of structure lesion in the brain. TMS was able to reset the rhythm of ET but not the heart beat. Also, the pacing mechanism was different between ET and heart beat. Positron emission tomography of patients with ET revealed increased cerebellar activity at rest and during tremor, in indicating that cerebellum has an important role in the generation of ET through the mechanism of oscillation within cerebello-olivary pathways, rephrased by way of the thalamus and motor cortex to the spinal cord. Using the method of RI and transcranial stimulation, the ET is reset by magnetic stimulation but not by electrical stimulation. It emphasizes the role of intracortical structures in the generation of ET. Our findings support the hypothesis that central nervous system has a role in inducing ET. Using RI to quantify the degree of TMS modulation on cardiac rhythm, we concluded that single-pulse TMS would not influence the cardiac rhythm even at the maximal intensity of the magnetic stimulator now available. Sin gle-pulse TMS lasts only a few seconds, but epileptic attacks or emotional events usually last more than a few minutes. If TMS does not produce seizure, then it would not have significant effect on cardiac rhythm. It seemed clear that single-pulse TMS could not produce effective modulation on the heart beat through the machine of magnetic stimulation (Magstim 200). After rapid-rate TMS, transient acceleration of heart rate was noted and lasted for a few seconds. Its mechanism was inferred as an arousal reaction to magnetic stimulation. Thus, our results confirmed the safety of TMS in clinical application.

**Acknowledgement**

The study was supported in part by a grant from National Science Council, R.O.C. (NSC88-2314-B-075-069).

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