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Changes in Input-Output Relations in the Corticospinal Pathway to the Lower Limb Muscles during Robot-Assisted Passive Stepping

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Abstract—**We investigated input (stimulus)-output (response) relations of the corticospinal pathway in the lower limb muscles during passive stepping using a robotic driven gait orthosis. Nine healthy adult subjects passively stepped with 40% body weight unloading (ground stepping) and 100% body weight unloading in the air (air stepping). During passive stepping, the motor evoked potentials (MEPs) of the lower limb muscles elicited by transcranial magnetic stimulation (TMS) were recorded at late-stance, early-, and late-swing phases of 2 stepping conditions. The input-output relation at each phase of the stepping conditions was obtained by increasing stimulus intensity in 5% increments from 40% to 70% of maximal stimulator output. The slopes of input-output relations were steeper at the early-swing phase in the rectus femoris muscle and at the late-stance and late-swing phases in the biceps femoris muscle in both stepping conditions. There were no significant differences in the MEP responses of the rectus femoris and biceps femoris muscles at each phase between the 2 conditions. Low muscle activity was seen at the late-stance phase of ground stepping in the soleus muscle and the MEP amplitude at this phase became larger. The slopes in the tibialis anterior muscle were steep at the early- and late-swing phases of ground stepping. There was a significant difference in the MEPs of the tibialis anterior muscle between the late-swing phases in ground and air stepping. The present study indicates that corticospinal excitability to the lower limb muscles is modulated by sensory inputs elicited by passive stepping.**

I. INTRODUCTION

It has been reported that patients with locomotor dysfunction have a greater chance of recovering walking ability through conventional overground locomotor therapy and body weight-supported treadmill therapy [1]–[3]. A computer-controlled, driven gait orthosis (DGO) for locomotor training has been developed recently, which helps to provide appropriate physiological walking patterns, increase total training duration, and reduce labor-intensive interventions by therapists [4]–[6]. The key concept of these training paradigms is that sensory feedback information elicited by stepping effectively activates the spinal neural circuitry underlying locomotion.

Applying the robotic DGO to healthy subjects makes it possible to impose passive stepping. While the subject experiences near-normal sensory inputs from the lower limb movements in passive stepping, descending commands from the higher brain centers for the stepping might be substantially reduced. Therefore, changes to the excitability in a certain neural pathway during passive stepping are considered to be due to peripherally mediated sensory inputs [7]–[9].

Transcranial magnetic stimulation (TMS) to the motor cortex is used in human subjects as a noninvasive method to investigate the excitability of the corticospinal pathway [10]. TMS applied over the motor cortex activates corticospinal cells either directly close to the cell soma or indirectly through the activation of fibers or neurons projecting onto corticospinal cell. The corticospinal excitability is assessed by the amplitude of a motor evoked potential (MEP) elicited by the TMS in the target muscle. Several TMS studies have demonstrated modulation of corticospinal excitability to the lower limb muscles during normal walking [11]–[14]. However, it was unclear to what extent sensory inputs induced by walking contribute to this modulation of corticospinal excitability. Therefore, in a previous study, we investigated the effect of sensory inputs on the corticospinal excitability to the tibialis anterior (TA) muscle during passive stepping [8]. The results revealed that the MEPs of the TA muscle were facilitated at the early-swing phase and swing-stance transition during passive stepping with body weight loading. In the study, although the MEPs in the lower leg muscles except the TA muscle were recorded, the stimulus intensity of the TMS targeted to the TA muscle was too weak to examine changes of the MEP amplitudes in the other muscles. The MEP recorded at single stimulus intensity may not be sufficient for proper assessment of the corticospinal pathway. If the MEP amplitude is small, it is not possible to detect inhibitory effects to the MEP reliably because of floor effect. Instead, investigation of the input (stimulus intensity)-output

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(MEP response) relation is proposed to measure the excitability of the corticospinal pathway as a whole [15]. In this method, the effects of the step phase during passive stepping on the MEPs in the lower limb muscles might be demonstrated clearly since stimuli at stronger stimulus intensities are applied to enable recording of larger MEP responses. Therefore, this study aimed to identify the input-output relations of the corticospinal pathway to lower limb muscles during passive stepping using a robotic DGO.

Interestingly, in our previous study, the MEP facilitation in the TA muscle occurred during passive stepping with body weight loading was not observed during passive stepping with 100% body weight unloading in the air (completely body weight unloaded passive stepping), which suggested the corticospinal excitability to the TA muscle is facilitated by load-related sensory inputs [8]. Hence, we also investigated the effect of load-related sensory inputs on input-output relations in the lower limb muscles at different body weight-unloading conditions during passive stepping.

II. Methods

A. Subjects

Nine healthy adult subjects with no history of neuromuscular disorders participated in this study. This study was conducted with an ethical approval from the local ethics committee. Each subject provided informed consent for the experimental procedures as required by the Declaration of Helsinki.

B. Passive stepping

Passive stepping was conducted by an exoskeletal DGO (Lokomat®, Hocoma AG, Switzerland). Detailed information of the DGO is provided elsewhere [4]. Briefly, the DGO provides drives for the physiological hip and knee joint movements. The DGO was secured to the subject by straps across the pelvis and chest. The lower limb parts of the DGO were attached to the subject with straps around the thigh and shank. For the ankle joint, a passive foot lifter (a spring-assisted elastic strap) was attached to the foot for dorsiflexion during the swing phase.

The speed of passive stepping was 1.5 km/h. Two body weight-unloading conditions were defined to investigate the effect of the loading on corticospinal excitability during passive stepping. One was passive stepping on a treadmill with 40% unloading of body weight (ground stepping). The other stepping condition was full body weight unloading, where the subject was suspended in the air so that there was no contact between his/her feet and the treadmill during passive stepping (air stepping). A parachute harness connected to counter weights performed the body weight unloading. During passive stepping, the subject was instructed to relax and not prevent the lower limb movements imposed by the DGO.

C. Measurements

Electromyographic (EMG) activities from the rectus femoris (RF), biceps femoris (BF), soleus (Sol), and TA muscles of the right leg were recorded with surface bar-electrodes (inter-electrode distance: 10 mm) placed over the muscle bellies. The EMG signals were amplified (1,000×) and band-bass filtered (15–1,000 Hz) using a bioamplifier (MEG-6108, Nihon Kohden, Japan). The angles at the hip and knee joints of the DGO were provided by potentiometers on the orthosis. Ground contact of the heel during ground stepping was detected by a pressure-sensitive sensor (PH-463, DKH, Japan) placed under the heel. All signals were sampled at 2 kHz using an A/D converter (WE7000, Yokogawa Co., Japan) and stored for later analyses.

D. TMS

TMS was applied over the left motor cortex using a magnetic stimulator (Magstim 200, Magstim Co., UK) to record input-output relations in the right lower limb muscles. A double cone coil was positioned in the best location on the motor cortex (slightly left of the midline) for eliciting MEPs in the lower limb muscles. The details of coil fixation to the cortex have been described in a previous study [8].

The input-output relations were recorded at 3 phases, namely late-stance, early-swing, and late-swing during passive stepping. An output signal from the Lokomat® system was used as a trigger signal for the TMS at 3 predetermined phases of a step cycle. The stimulation was randomly delivered at 1 of 3 phases at intervals greater than 5 s. At each phase of both stepping conditions, the TMS intensity was increased from 40% to 70% of the maximal stimulator output (MSO) in increments of 5% MSO for each subject. Five MEP responses were recorded at each intensity.

E. Data analysis and statistics

Peak-to-peak amplitude of the MEP response was assessed off-line for the MEP analysis. Five MEP amplitudes for each stimulus intensity were averaged at each phase of the 2 stepping conditions in each subject. The background EMG levels were determined as the root mean square values of the EMG signals for 50 ms before stimulation to assess the excitability of the alpha-motoneurons at the instant of stimulation. The data are shown as mean ± SEM.

For statistical analysis, all MEP responses recorded at stimulus intensities of 40%–70% MSO were averaged at each phase of the 2 stepping conditions in each subject. The averaged MEPs for each muscle were analyzed using a two-way repeated ANOVA with factors of loading (ground and air stepping) and phase (3 phases in a step cycle). When the assumption of sphericity by Mauchly's test was violated, Greenhouse-Geisser adjustments were applied to adjust the degrees of freedom. When statistical significance was detected by the ANOVAs, post-hoc multiple comparisons (Tukey) were used to identify significant differences. The significance level was set at $P < 0.05$.

III. RESULTS

The duration of a step cycle was approximately 2,750 ms during passive stepping at 1.5 km/h. Since hip and knee trajectories of the robotic DGO were under direct computer control, there were few differences in the hip and knee joint angles between ground stepping and air stepping. There were no visible EMG activities in the RF, BF, and TA muscles across the step cycle under both stepping conditions. Therefore, the background EMG levels in those muscles were unchanged at 3 phases in the 2 passive stepping conditions. In the Sol muscle, low EMG activity was observed at the stance phase of ground stepping in some subjects.

Fig. 1(a) illustrates a typical example of MEP waveforms in the TA muscle recorded at 3 phases of ground stepping in a single subject. The MEP waveforms were the average of 5 responses to each stimulus intensity. In this subject, MEP latency from stimulation to the onset of response was approximately 30 ms. Increased MEP amplitudes were observed at the 3 phases as stimulus intensity increased. However, despite the same stimulus intensity, there were differences in the MEPs among the 3 phases of ground stepping. Fig. 1(b) represents the input-output relations of the MEP data in the Fig. 1(a). The mean peak-to-peak MEP amplitude from 5 responses was plotted against the corresponding TMS intensity. The differences among the 3 phases were apparent in the maximal MEP amplitudes and the slopes of the resulting input-output relations.

Fig. 2 illustrates group data of input-output relations in each muscle at the 3 phases of ground and air stepping from 9 subjects. In the RF muscle, the slopes and maximal MEP amplitudes in the input-output relations increased at the early-swing phase compared to those at the late-stance and late-swing phases. Since it was obvious that the MEP amplitudes increased when stimulus intensity was increased from 40% to 70% MSO, the averaged amplitude of all MEP responses elicited by stimuli of 40%–70% MSO in each phase was used for statistical processing. For the RF MEPs, the two-way ANOVA [loading (2 stepping conditions) × phase (3 different step phases)] tests demonstrated a significant main effect of phase ($F_{1,8} = 4.06$, $P < 0.05$), but the main effect of loading and the interaction of loading × phase were not significant. Thus, the MEPs in the RF muscle were different among step phases, but not between the 2 unloading conditions of passive stepping. The post-hoc test demonstrated that the RF MEPs were significantly increased at the early-swing phase compared to the late-stance and late-swing phases ($P < 0.01$). Contrary to the steeper slopes at the early-swing phase in the RF muscle, the slopes of the BF muscle at the late-stance and late-swing phases were steeper than those at the early-swing phase. In addition, the input-output relations at 3 step phases in the BF were not influenced by body weight loading during passive stepping. For the averaged MEP responses of the BF muscle elicited by all stimulus intensity, no significant effects of loading, phase,

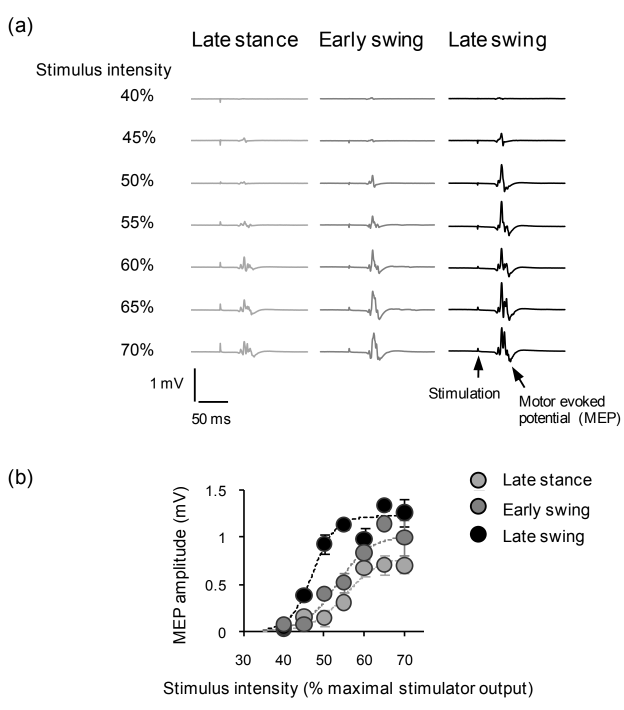

Fig.1. (a) Averaged motor evoked potentials (MEPs) of the tibialis anterior (TA) muscle at late-stance, early-swing, and late-swing phases of ground stepping in a subject. (b) Relations between stimulus intensity and MEP amplitude of the TA muscle during the ground stepping illustrated in the Fig. 1(a).

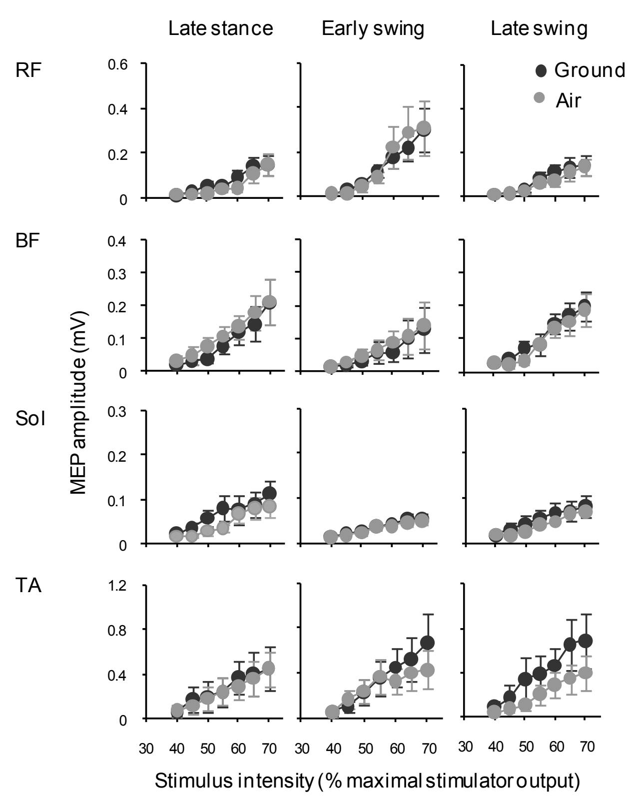

Fig.2. Group data of input-output relations in the rectus femoris (RF), biceps femoris (BF), soleus (Sol), and tibialis anterior (TA) muscles at late-stance, early-swing, and late-swing phases of ground and air stepping with the Lokomat® in 9 subjects.

and interaction were observed. In the Sol muscle, slight EMG activity was observed at the late-stance phase of ground stepping. Similarly, the slope and maximal MEP amplitude of the input-output relation in the Sol muscle were greater at the late-stance phase during ground stepping. However, the ANOVA tests demonstrated no significant effects of loading, phase, and interaction where the averaged Sol MEPs at each phase for the statistical analysis were concerned. In the TA muscle, the slopes and maximal MEP amplitudes of early- and late-swing phases were greater during ground stepping than air stepping. The ANOVA test of the averaged MEPs in the TA muscle revealed a significant interaction with loading × phase ($F_{2,16}$ = 3.98, P < 0.05), suggesting that the loading effect to increase the MEP amplitude of the TA muscle differed among the step phases during passive stepping. The post-hoc test demonstrated that the averaged MEP at the late-swing phase increased significantly during ground stepping compared to air stepping (P < 0.05).

IV. Discussion

The aim of this study was to clarify the excitability of the corticospinal pathway to the lower limb muscles during passive stepping by using input-output relations. In addition, the effects of the load-related sensory inputs on corticospinal excitability were investigated. Therefore, MEP responses to increasing stimulus intensity at 5% MSO intervals from 40% to 70% MSO were recorded at 3 phases in 2 passive stepping conditions involving different body weight unloading (40% and 100% unloading).

In the present study, passive stepping was conducted using Lokomat® in healthy adult subjects who were required to keep their lower limb muscles relaxed during stepping. Indeed, other than the EMG activity of the Sol muscle at the late-stance phase of ground stepping, no EMG activity in the RF, BF, and TA muscles was observed in both passive stepping conditions. These EMG activation patterns were similar to previous findings from passive stepping with the same DGO [16], [17]. Despite no EMG activity in the RF and BF muscles at the 3 predetermined phases of passive stepping, changes in the slopes of the input-output relations were observed (Fig. 2). The slope of the input-output relations was considered a general measure of excitability in the corticospinal pathway. In the RF muscle, the MEP amplitudes at the early-swing phase were significantly larger than those recorded at the late-stance and late-swing phases, whereas the MEPs in the BF muscle tended to increase at the late-stance and late-swing phases compared to the early-swing phase (Fig. 2). Since the DGO imposed joint movements of the lower limb during passive stepping, descending commands for the movements might be substantially reduced. Therefore, it appears that corticospinal excitability during passive stepping is modulated by peripheral sensory inputs associated with locomotor-like movements. Similarly, it has been speculated that modulations in the corticospinal excitability to forearm muscles during passive wrist movement are primarily related to the Ia afferent inputs [18]. In the present study, since background EMG activities were not observed in the RF, BF, and TA muscles, changes in the subliminal fringe of the alpha-motoneurons during passive stepping were unknown. Hence, postsynaptic effects on the MEP modulation cannot be excluded in the present study.

In our previous study [8], small MEPs elicited by single stimulus intensity during passive stepping also demonstrated slight modulations in the similar tendency of the present findings in the RF and BF muscles. These phases with larger MEP amplitudes during passive stepping corresponded to the phases at which EMG activities in the respective muscles were observed during normal walking [19] and active stepping with the DGO [17]. Moreover, it has been reported that TMS to the motor cortex of the leg area increased hip flexion movement at the initial-swing phase during treadmill walking, whereas the stimulation increased the hip flexion movement at the mid-stance phase of the treadmill walking [14]. These results suggest that excitability of the corticospinal pathway in the RF muscle was relatively increased at the initial-swing phase and that corticospinal excitability to the BF muscle was relatively increased at the mid-stance phase, which is consistent with the changes of the input-output relations during passive stepping in the present study.

As for the Sol muscle, weak EMG activity was observed at the late-stance phase during ground stepping. The EMG activity appeared to be reflexively generated because the stepping was performed passively. Since Sol activity was not observed during air stepping, load-related sensory inputs might be required for locomotor EMG activities. Dietz *et al.* [16] demonstrated that as simple rhythmic muscle stretching or body loading alone did not lead to locomotor EMG activities, a combination of locomotor-like sensory inputs would be necessary to evoke locomotor EMG activities. In the present study, the averaged MEP amplitude and slope of the input-output relation at the late-stance phase of ground stepping became greater, as shown in the Fig. 2. This MEP facilitation might be attributed to higher alpha-motoneuron excitability at this phase.

In the TA muscle, steep slopes in the input-output relations were observed at the early- and late-swing phases during ground stepping despite there being no differences in background EMG activity between phases of the 2 stepping conditions (Fig. 2). In addition, a significant difference between ground stepping and air stepping was observed at the late-swing phase for the averaged MEPs in the input-output relations. The result of the MEP facilitation in the TA muscle occurring during ground stepping was similar to that observed during normal treadmill training [11] and that observed in our previous study [8]. The factor facilitating corticospinal excitability of the TA muscle during ground stepping appears to be load-related sensory inputs. On the other hand, there were no differences in the input-output relations at any phases between ground and air stepping in the RF and BF muscles. It is of particular interest that enhancement of corticospinal excitability by body weight loading during passive stepping was not observed in the RF and BF muscles. Further experiments are needed to clarify mechanisms responsible for the difference in the facilitation of the corticospinal pathway among the muscles.

Concerning the effects of load-related sensory inputs on other neural pathways, Bastiaanse *et al.* reported that load-related inputs are involved in phasic modulation of the cutaneous reflex in the leg muscles during normal walking [20]. Moreover, by using the same DGO as in the present study, Nakajima *et al.* identified strong facilitation of the cutaneous reflex in the TA muscle during the late-stance to early-swing phases of passive ground stepping, but not during passive air stepping [7]. Thus, it seems that load-related inputs are also related to modulation of the cutaneous reflex pathway during stepping.

Although much attention has been paid to the changes in spinal neural circuitry by locomotor training, less is known about the changes in corticomotor function. However, it has recently been shown that locomotor training enhances corticospinal excitability to the lower limb muscles [21] and that the corticospinal excitability to the TA is related to locomotor function [22]. In the present study, corticospinal excitability to the lower limb muscles was modulated during passive ground stepping, which is a similar modulation pattern to that of normal walking. The neural mechanisms of locomotor control should be elucidated to indentify a more effective approach to locomotor recovery.

V. Conclusion

In the present study, changes to the slope and averaged MEP in input-output relations were observed during passive stepping. Thus, changes in the excitability of the corticospinal pathway to the lower limb muscles were indicated across step phases during passive stepping. A robotic DGO could be very useful not only for locomotor therapy, but also for neuroscience studies investigating neural control of walking in humans.

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