Modulation of Lower Limb Withdrawal Reflexes During Gait: A Topographical Study

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Spaich, Erika G., Lars Arendt-Nielsen, and Ole K. Andersen. Modulation of lower limb withdrawal reflexes during gait: a topographical study. J Neurophysiol 91: 258–266, 2004. First published September 10, 2003; 10.1152/jn.00360.2003. The aim of this study was to investigate the modulation and topography of the nociceptive withdrawal reflex elicited by painful electrical stimulation of the foot sole during gait. Fifteen healthy volunteers participated in this study. Cutaneous electrical stimulation was delivered on five locations of the foot sole after heel-contact, during foot-flat, after heel-off, and during the mid-swing phase of the gait cycle during treadmill walking. Reflexes were recorded from muscles of the ipsilateral and contralateral legs. Furthermore, the kinematic responses in the sagittal plane of the ipsilateral ankle, knee, and hip joints were recorded. Reflexes in the distal muscles showed a site-dependent modulation. The largest responses in tibialis anterior were evoked at the arch of the foot and the smallest at the heel ($P < 0.05$). The largest soleus responses were also elicited at the arch of the foot ($P < 0.04$). The EMG responses in flexors and extensors of the knee and extensors of the contralateral leg were generally not dependent on the stimulation site. The response at the three joints showed site dependency, especially during the swing phase where maximal flexion was obtained by stimulation at the arch of the foot ($P < 0.05$). The withdrawal reflex was modulated during the gait cycle and presented distinctive characteristics for the different muscles studied. Minimal kinematic responses were observed during stance in contrast to swing phase. Modulation of the reflex probably ensures an appropriate withdrawal but primarily secures balance and continuity of movement.

INTRODUCTION

The flexion reflex was first described in detail by Sherrington (1910) as a general excitatory response of flexor muscles and inhibitory response of extensor muscles to stimulation of the cutaneous afferents and deep nerves. Sherrington (1910) also defined the reflex receptive field (RRF) as the assemblage of receptive points that might evoke a particular reflex movement when suitably stimulated. Eklund et al. (1959), Hagbarth (1960), Kugelberg et al. (1960), and Grimby (1963) found indications of a more complex organization of the human withdrawal reflex. For instance, Grimby (1963) observed ankle dorsiflexion as a result of stimulation of the medial, distal sole of the foot, ankle extension after stimulation of the plantar surface of the heel, inversion following stimulation of the medial side of the foot sole, and eversion after stimulation of the lateral side of the foot sole. These findings reveal a complex response tendency to withdraw the stimulated area from the noxious source.

Schouenborg and Kalliomiäki (1990), Schouenborg et al. (1994), and Levinsson et al. (1999) found indications of highly organized cutaneous nociceptive fields for different limb muscles in the cat and rat. They proposed a modular organization of the withdrawal reflex consisting of functionally separated reflex pathways to different muscles or small groups of synergistic muscles. Furthermore, each muscle group has a separate cutaneous RRF that corresponds to the skin area withdrawn by a contraction of the particular muscle group (Schouenborg et al. 1994). Andersen et al. (1999) and Sonnenborg et al. (2001) provided evidence for a modular organization of the human withdrawal reflex in resting condition. Responses in ankle and knee flexors and extensors and ankle invertors and evertors were evoked depending on the stimulus location on the sole or dorsum of the foot, resulting in a proper withdrawal of the affected area from the noxious source.

The nociceptive withdrawal reflex has been shown to have some degree of plasticity. The reflex varies as a function of the stimulation site (Andersen et al. 1999; Grimby 1963; Levinsson et al. 1999; Schouenborg et al. 1994); the position of the limb (Hagbarth and Finer 1963); the load applied to the limb (Rossi and Decchi 1994); and the stimulation intensity (Andersen et al. 2001; Kugelberg et al. 1960; Willer 1977). The withdrawal reflex is also modulated during the execution of cyclical movements, such as pedaling (Andersen et al. 1995; Brown and Kukulka 1993) and locomotion (Crenna and Frigo 1984; Duyzens et al. 1990a, 1992). Stimulation of an entire nerve bundle was commonly used to study the reflex modulation during these cyclical tasks. Therefore the afferent barrage consisted of a local skin component and likely components from afferents innervating receptors in joint capsules, deep structures, distal skin, and excitatory and inhibitory RRF for the muscles being activated. In contrast, localized cutaneous stimulation, which secures a well-defined stimulus location and minimizes other input components, has only been applied in human studies in relaxed condition (Andersen et al. 1999; Sonnenborg et al. 2001).

The aim of this study was to investigate the topographical distribution of the cutaneous receptive field of the withdrawal reflex elicited from the foot sole and recorded from lower limb muscles during gait. The specific questions addressed were as follows. 1) What is the topography of the withdrawal reflex receptive fields during the gait cycle? 2) Is the amplitude of the reflex elicited from different foot sole locations modulated during the gait cycle? The experimental paradigm was adopted from the previous study of reflex modulation during sitting position (Andersen et al. 1999).
METHODS

Fifteen healthy volunteers (9 male and 6 female; mean age, 25.1 yr; age range, 22–33 yr) participated in the study. The Declaration of Helsinki was respected, and local ethics committee approval was obtained. All subjects gave written informed consent.

Stimulation

Electrical stimulation was delivered on five locations of the right foot sole through self-adhesive electrodes (15 x 15 mm, Ag-AgCl, Medicotest, Oelstykke, Denmark). The stimulation sites were carefully selected to prevent direct nerve stimulation. The electrodes were placed on the first and fifth metatarsophalangeal (MP) joints, the arch of the foot, the mid-lateral foot, and the heel (Fig. 1, inset). A large common anode was placed on the dorsum of the foot (7 x 10 cm electrode, Pals, Axelgaard Ltd., Fallbrook, CA). The stimulation paradigm consisted of a train of five constant current rectangular pulses, each lasting 2 ms and delivered at 200 pulses per second (Stimulator Neuromatic 2000 C, Disa, Skovlunde, Denmark), giving a total stimulus duration of 22 ms. Similar stimulation paradigms were employed earlier by other authors (Decchi et al. 1997; Duysens et al. 1992; Grimby 1963; Meinck et al. 1985). The stimulation intensities were set as a factor of the individual pain thresholds (PThrs) at each stimulation site. Stimulation was delivered at the five locations according to a preprogrammed randomized sequence.

Gait cycle

Stimulation was delivered in four different moments of the gait cycle: 10 ms after heel-contact, during the foot-flat phase (detailed description follows), 10 ms after heel-off, and during the mid-swing phase. To determine the onset of the stimulation during the foot-flat and swing phases, the duration of the heel-contact/heel-off phase and the total stride duration were assessed during 30 s of unperturbed gait using the signal provided by a heel-switch placed inside the right shoe. Based on these measurements, the onset of stimulation during the mid-swing phase was computed as the 80% of the gait cycle. The onset of stimulation during the foot-flat phase was calculated as the middle of the heel-contact/heel-off interval, and lied characteristically between weight acceptance and the vertical passage of the center of mass over the foot.

EMG recordings

The EMG of tibialis anterior (TA), soleus (SOL), vastus lateralis (VL), and biceps femoris (BF) of the right leg were recorded. EMG of SOL (cSOL) and VL (cVL) of the contralateral leg were also recorded. The recordings were obtained using surface electrodes (Medicotest, Oelstykke, Denmark) in a bipolar configuration (2 cm inter-electrode distance), amplified, band-pass filtered (5–500 Hz, 2nd order), sampled at 2 kHz, displayed on a computer screen, and stored for later analysis.

Goniograms

Three goniometers (type XM180, Biometrics Ltd., Gwent, UK) were mounted on the lateral side of the ankle, knee, and hip joints of the right leg to record movements in the sagittal plane at these three joints. The goniometers were sampled at 2 kHz, displayed, and stored together with the EMG recordings.

Experimental protocol

The volunteers were requested to sit while recording electrodes and goniometers were attached to the legs. The stimulation electrodes were carefully placed testing each site to prevent direct nerve stimulation. In case a motor response was observed or the volunteer described a radiating sensation instead of a sharp prick, the electrode was slightly moved and the site was tested again. A series of electrical stimuli, starting at low intensities and reaching levels usually regarded as painful, was delivered to familiarize the subjects with electrical stimulation. Afterward, the following four steps experimental protocol was used.

1) The PThrs for the different stimulation sites were determined using a staircase method, consisting of series of increasing and decreasing stimuli. The procedure was repeated at least twice at each stimulation site to corroborate the determinations. Afterward, the sensations evoked at the different stimulation sites and described by the volunteers were compared, and when necessary, the stimulation intensity was adjusted to make sure the level of perceived pain was the same at the different stimulation sites. The entire procedure was performed with the volunteers in standing position.

2) The duration of the gait cycle and the heel-contact/heel-off phase were calculated by averaging heel-switch signals recorded during 30 s of treadmill walking at 3 km/h. In addition, EMGs and goniograms were recorded during 30 steps of unperturbed gait to generate a control profile.

3) To determine the stimulation intensity necessary to evoke a reflex response, the stimulation intensity at the arch of the foot was gradually increased above the PThr. Steps of 5% of the PThr were added until the reflex, defined as an increment of the EMG activity of ≥100% in the interval 60–200 ms after stimulation compared with the prestimulus condition, was elicited in TA and/or SOL EMG. The stimulation intensity for the other stimulation sites was set by adding the same percentage to the corresponding PThrs. The entire procedure was performed with the volunteers in standing position.

4) A computer-controlled randomized stimulation sequence was generated, and five recordings of the reflex for each stimulation site and phase of the gait cycle were obtained during treadmill walking. Therefore the total of 100 stimulation trains were applied. The interstimulation interval was between 8 and 12 s.

Data analysis

The rectified and low-pass filtered (Butterworth, 40 Hz, 10th order, no phase lag) EMG recorded during unperturbed gait was averaged to generate a control profile for each muscle. The reflex recordings were rectified, low-pass filtered, and averaged for each stimulation site and phase of the gait cycle. The averaged EMG reflex recordings and control profiles were normalized by the peak value of the corresponding EMG control profile to decrease the inter-subject variability (Yang and Winter 1984). The EMG reflex responses were assessed by the difference between the mean poststimulation EMG and the corresponding mean EMG activity in the control profile. The time-window analysis for TA, VL, and BF of the stimulated leg and SOL and VL of the contralateral leg was the interval of 60–200 ms. The SOL reflexes in the stimulated leg were analyzed in two time windows: a short reflex loop (SRL) in the interval of 60–120 ms and a long reflex loop (LRL) in the interval of 120–200 ms poststimulation (see RESULTS for details on these intervals).

The onset latency of the reflex EMG activity was calculated by custom-made software. A response was considered excitatory if the EMG signal was facilitated more than 100% with respect to the control profile during unperturbed gait and the facilitation lasted ≥5 ms. A response was considered inhibitory if the EMG signal was suppressed more than 40% with respect to the control profile and the inhibition lasted ≥5 ms. If the criteria were fulfilled, the latency was calculated as the time from the stimulation onset until the first point where the EMG was facilitated or suppressed. Visual inspection was used to verify all the assessments. Latencies shorter than 50 ms and longer than 200 ms were discarded.

The goniograms recorded during unperturbed gait were low-pass

J Neurophysiol • VOL 91 • JANUARY 2004 • www.jn.org
filtered (Butterworth, 25 Hz, 6th order, no phase lag), averaged to generate the control profiles, and normalized in amplitude to the maximum range of motion occurring within the step cycle. The recordings performed after stimulation were similarly filtered, averaged for each stimulation site and phase of the gait cycle, and normalized to the corresponding range of motion measured during unperturbed condition. The angle changes were determined as the difference between the maximum angle variation in the goniograms recorded after stimulation and the control profiles in the interval ranging from 125 to 200 ms poststimulation. This analysis window comprises the interval in which the peak mechanical change is expected to happen. A similar analysis window was used earlier by Zehr et al. (1997), and Duysens et al. (1992).

**Statistics**

The EMG recorded after stimulation was compared with control EMG profiles to detect the presence of reflex responses. Student’s paired t-test was used if the data were normally distributed, otherwise Wilcoxon signed rank test was applied. Two-way repeated measure ANOVA was used to analyze the effect of stimulation site and phase of the gait cycle on the evoked responses. Student-Newman-Keuls (SNK) test was used for posthoc pairwise comparisons. $P < 0.05$ was considered statistically significant.

## RESULTS

The reflex responses at the different muscles and joints are presented in the following manner: first, the general characteristics of the response are described, then the stimulation site dependency is detailed, and finally the variations during the gait cycle are presented.

### Stimulation intensity

The mean PThr across all subjects and stimulation sites was 20.8 ± 8.1 mA; the minimum PThr was observed at the arch of the foot (14.6 ± 5.8 mA), and the maximum at the heel (26.9 ± 7.9 mA). To elicit the withdrawal reflex, the stimulation intensity was increased between 40 and 110% of the PThr (average increment among subjects: 67%). The individual PThrs and stimulation intensities applied at each stimulation site are presented in Table 1. All subjects described the stimuli as producing a sharp, pinprick pain sensation coming specifically from the stimulation sites at the foot sole and lasting less than 1 s. None of them reported any sensation on the dorsum of the foot.

### Ankle joint

**TA response.** The TA EMG activity recorded after stimulation was significantly different from the activity during unperturbed gait ($P \leq 0.007$, paired t-test or Wilcoxon signed rank test). The TA response consisted of a burst of excitatory activity (Fig. 1A), starting at the same mean latency after heel-contact, during foot-flat, and after heel-off ($87.8 \pm 19.4$ ms) and at $74.6 \pm 9.5$ ms during the swing phase (average across all stimulation sites). The latencies of the evoked responses decreased when stimulating at the arch of the foot after heel-contact and after heel-off ($P \leq 0.001$, SNK compared with all other stimulation sites). No differences in the latencies of the responses evoked at the different stimulation sites were found during the foot-flat and swing phases. During the gait cycle, the shortest latencies were found during the swing phase ($P \leq 0.025$, SNK) at all stimulation sites except the arch of the foot, which resulted in constant latencies irrespective of the phase of the gait cycle.

Stimulation at the arch of the foot elicited the largest reflexes in TA ($P < 0.05$, SNK; Fig. 1B). Stimulation at the heel evoked the smallest reflexes during swing and after heel-contact ($P < 0.02$, SNK). During foot-flat and after heel-off, smallest reflexes were also evoked by stimulation of the heel ($P < 0.02$, SNK) compared with stimulation of the first MP joint and the arch of the foot.

The TA withdrawal reflex was modulated during the gait cycle when stimulation was applied in the mid-foot sole, i.e., arch and mid-lateral stimulation sites, the largest TA reflexes were obtained after heel-contact ($P \leq 0.013$, SNK) compared with heel-off and swing phases.

**SOL response.** The SOL response had two different patterns. During the swing phase, after heel-contact, and during foot-flat, the response was excitatory (Fig. 2A) with latencies of $85.9 \pm 18.4$, $116.2 \pm 32.3$, and $139.2 \pm 24.5$ ms, respectively (average across all stimulation sites). While after heel-off, it consisted of an inhibitory component, with a latency of $71.2 \pm 6.2$ ms, followed by an excitatory response with a latency of $136.0 \pm 25.7$ ms (average across all stimulation sites). No differences in the latencies among stimulation sites were found.

Due to the characteristics of the evoked responses, the results will be presented separately for the SRL (60–120 ms) and LRL (120–200 ms). In the SRL, both excitatory and inhibitory responses were observed compared with SOL activity during unperturbed gait (Fig. 2B). SOL SRL excitatory responses were evoked at all stimulation sites during the swing phase ($P \leq 0.003$, paired t-test), with the largest SOL SRL reflexes evoked by stimulation at the arch of the foot ($P \leq 0.004$, SNK). SOL SRL excitatory responses were also observed after heel contact when stimulating the arch and first MP joint ($P < 0.05$, paired t-test), with the largest SOL SRL reflex evoked at the arch of the foot ($P \leq 0.006$, SNK). SOL SRL inhibitory responses were recorded after heel-off when stimulating at all stimulation sites ($P < 0.05$, paired t-test), the size of the inhibitory component did not differ among stimulation sites. The largest SOL SRL responses were observed during swing and after heel-contact compared with foot-flat and heel-off ($P \leq 0.002$, SNK).

In the LRL, only SOL excitatory responses were recorded (Fig. 2B). The SOL EMG was significantly different from the activity during unperturbed gait ($P < 0.05$, paired t-test) at all stimulation sites and phases of the gait cycle. The largest LRL

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**TABLE 1. Pain thresholds and stimulation intensities at the different stimulation sites**

<table>
<thead>
<tr>
<th>Stimulation Site</th>
<th>Pain Threshold [mA]</th>
<th>Stimulation Intensity [mA]</th>
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<tbody>
<tr>
<td>First MP joint</td>
<td>19.5 ± 4.5</td>
<td>32.6 ± 8.3</td>
</tr>
<tr>
<td>Fifth MP joint</td>
<td>22.6 ± 8.0</td>
<td>38.3 ± 17.4</td>
</tr>
<tr>
<td>Arch of the foot</td>
<td>14.6 ± 5.8</td>
<td>24.6 ± 11.5</td>
</tr>
<tr>
<td>Mid-lateral foot</td>
<td>20.6 ± 8.8</td>
<td>34.6 ± 16.4</td>
</tr>
<tr>
<td>Heel</td>
<td>26.9 ± 7.9</td>
<td>44.9 ± 14.2</td>
</tr>
</tbody>
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Values are means ± SD. *Significantly smaller stimulation intensity compared with the fifth MP joint and heel sites ($P < 0.05$).
FIG. 1. Tibialis anterior (TA) EMG response to electrical stimulation at the specified stimulation sites and phases of the gait cycle. A: grand mean of response, computed across all subjects, is plotted in bold. Grand mean of background activity is plotted with a thin line. Responses are shown from 10 ms before stimulus onset. B: responses (mean ± SE) are presented as a proportion of the EMG peak activity of the control profile. TA EMG peak of the average (across subjects) control profile: 96 μV. Significant differences (P < 0.05) compared with all the remaining stimulation sites at each phase of the gait cycle are indicated. Inset: position of the stimulation electrodes: 1, first metatarsophalangeal joint; 2, fifth metatarsophalangeal joint; 3, arch of the foot; 4, mid-lateral foot; 5, heel.

FIG. 2. Soleus (SOL) EMG response to electrical stimulation at the specified stimulation sites and phases of the gait cycle. A: grand mean of response, computed across all subjects, is plotted in bold. Grand mean of the background activity is plotted with a thin line. Responses are shown from 10 ms before stimulus onset. B: responses (mean ± SE) are presented as a proportion of the EMG peak activity of the control profile. SOL EMG peak of the average (across subjects) control profile: 71 μV. Significant differences (P < 0.004) compared with all the remaining stimulation sites at each phase of the gait cycle are indicated.
SOL reflexes were evoked at the arch of the foot ($P \leq 0.04$, SNK, compared with fifth MP joint). The LRL SOL reflex response was maximum during foot-flat ($P \leq 0.01$, SNK; Fig. 2B).

**KINEMATICS.** The main movement evoked at the ankle joint was dorsiflexion (Fig. 3). Hence, ankle dorsiflexion was observed when stimulation was applied at all stimulation sites after heel-contact, during foot-flat, and during swing ($P < 0.05$, paired t-test). No significant kinematic changes were observed when the stimulation was applied immediately after heel-off compared with the control recordings. A mean maximal dorsiflexion of $4.3 \pm 3.8^\circ$ was obtained during the swing phase by stimulating the arch of the foot. Minimal dorsiflexion ($1.5 \pm 1.4^\circ$) was observed after heel-contact, as a response to heel stimulation.

The mechanical response depended both on the stimulation site and the phase of the gait cycle in which the stimulation was applied (Fig. 4). Regarding the stimulation site, maximal angle change was obtained by stimulation of the mid- and forefoot ($P \leq 0.04$, SNK, compared with heel stimulation). Concerning the gait cycle, significantly larger responses were obtained after heel-contact, during foot-flat, and swing phases ($P \leq 0.02$, SNK) compared with the responses evoked after heel-off.

**FIG. 3.** Average kinematic responses ($n = 5$) at the ankle, knee, and hip joints for a single subject. Responses evoked by stimulation of the arch of the foot (continuous line) and heel (dotted line) are shown starting at stimulation onset and superimposed over corresponding control goniograms. Moments of heel-contact and heel-off and stimulation onsets are indicated. Time windows in which kinematic analysis was carried out are represented by vertical, hatched bars. Abbreviations: d. flex., dorsiflexion; p. flex., plantar flexion; flex., flexion; ext., extension.

**FIG. 4.** Kinematic responses at the ankle, knee, and hip joints during the gait cycle. Angle changes induced by electrical stimulation at specified electrode locations are averaged across all subjects.
Knee joint

VL RESPONSE. The reflex response evoked in the VL muscle consisted of a burst of excitatory activity starting at the same mean latency in the four phases studied (133.0 ± 14.9 ms, average across all stimulation sites). The shortest latencies (129.9 ± 15.1 ms) were observed following stimulation of the forefoot and arch of the foot, while the longest latencies (137.8 ± 13.2 ms) were observed following stimulation of the mid-lateral foot and heel (P < 0.05, SNK).

Only the response evoked by stimulation at the arch of the foot after heel-contact was significantly larger than the responses evoked at all other stimulation sites (P < 0.03, SNK). During the other phases of the gait cycle, the VL responses did not depend on the stimulation site (Fig. 5).

The amplitude of the VL reflex response was modulated during the gait cycle, and minimal responses were observed when the stimulation was applied after heel-off, compared with swing and heel-contact phases (P < 0.03, SNK, arch of the foot and mid-lateral stimulation sites) and compared only with the swing phase when the stimulation was applied at the fifth MP joint and heel (P < 0.05, SNK; Fig. 5).

BF RESPONSE. The BF response consisted of an excitatory component starting at the same mean latency in the four phases studied (116.7 ± 29.8 ms, average across all stimulation sites). The longest latencies were observed when stimulating the heel after heel-contact and during swing (P < 0.05, SNK, compared with arch of the foot and forefoot).

No significant variation between the size of the responses evoked at the different stimulation sites and phases of the gait cycle was found (Fig. 5).

KINEMATICS. Flexion of the ipsilateral knee was the predominant movement recorded in response to painful stimulation of the foot sole and was observed after stimulation at all stimulation sites in all phases of the gait cycle (P = 0.005, paired t-test or Wilcoxon signed rank test, compared with knee kinematics of control steps; Fig. 3). A maximal flexion of approximately 20° was obtained during the swing phase.

Maximal knee flexion was observed after stimulation of the arch of the foot and the mid-lateral foot sole (P < 0.04, SNK). The magnitude of the evoked knee movement was also modulated during the gait cycle; maximal responses were obtained after heel-off and during swing, compared with heel-contact and foot-flat (P < 0.05, SNK; Fig. 4).

Hip joint

KINEMATICS. The main hip joint response to electrical stimulation of the foot sole was flexion (Fig. 3); this response differed significantly from the kinematics of the unperturbed steps (P < 0.008, paired t-test or Wilcoxon signed rank test). The largest hip flexion was obtained during swing (9.1 ± 5.1°).

The size of the response varied as a function of both the stimulation site and the phase of the gait cycle (Fig. 4). Regarding the first variable, the largest hip flexion was evoked at the medial aspect of the foot (arch and mid-lateral position) compared with the first MP joint (P < 0.05, SNK). During the gait cycle, the flexion response observed after heel-off and during swing was significantly larger than the responses after heel-contact and during foot-flat, at all stimulation sites (P ≤ 0.04, SNK).

BF RESPONSE. The BF response consisted of an excitatory component starting at the same mean latency in the four phases studied (133.0 ± 14.9 ms, average across all stimulation sites). The shortest latencies were observed following stimulation of the forefoot and arch of the foot, while the longest latencies (137.8 ± 13.2 ms) were observed following stimulation of the mid-lateral foot and heel (P < 0.05, SNK).

Only the response evoked by stimulation at the arch of the foot after heel-contact was significantly larger than the responses evoked at all other stimulation sites (P < 0.03, SNK). During the other phases of the gait cycle, the BF responses did not depend on the stimulation site (Fig. 5).

The amplitude of the BF reflex response was modulated during the gait cycle, and minimal responses were observed when the stimulation was applied after heel-off, compared with swing and heel-contact phases (P < 0.03, SNK, arch of the foot and mid-lateral stimulation sites) and compared only with the swing phase when the stimulation was applied at the fifth MP joint and heel (P < 0.05, SNK; Fig. 5).

KINEMATICS. The main hip joint response to electrical stimulation of the foot sole was flexion (Fig. 3); this response differed significantly from the kinematics of the unper-
profile during unperturbed steps). No differences in the latencies among stimulation sites were found. During the gait cycle, the latency of the cSOL response was statistically longer during stance than during swing of the stimulated leg ($P \leq 0.001$, SNK) at all stimulation sites.

When the stimulation was applied at the arch of the foot/heel during the swing phase of the stimulated leg, a maximal reflex response was recorded in cSOL ($P \leq 0.02$, SNK, compared with first and fifth MP joint stimulation sites). The cSOL responses to stimulation of the different sites during stance were similar. Modulation of the responses during the gait cycle was found, with the largest cSOL reflexes being evoked at all stimulation sites during the swing phase of the stimulated leg ($P \leq 0.02$, SNK, compared with heel-contact and foot-flat; Fig. 5).

cVL RESPONSE. The cVL response to painful electrical stimulation of the contralateral leg was excitatory ($P \leq 0.02$, paired t-test or Wilcoxon signed rank test, compared with cVL EMG profile during unperturbed steps). The mean latency of the reflex response was 113.1 $\pm$ 22.6 ms in the four phases studied.

The size of the cVL response was independent of the stimulation site and phases of the gait cycle (Fig. 5).

**DISCUSSION**

In general, the amplitude of the nociceptive reflex, as recorded from different muscles of the lower limb and elicited by localized stimulation of the foot sole, depended on the position of the stimulation electrode (topographical organization) and on the phase of the gait cycle in which the stimulation was delivered (phase dependant modulation). Furthermore, the kinematic response to electrical stimulation also had a stimulus site and phase dependency related to that of the muscles producing the movements.

**Methodological aspects**

The evoked response is composed of a withdrawal from the potentially tissue-damaging stimulus and balance correction reactions. Subsequently, the locomotor pattern is resumed by additional motor corrections. It is difficult to separate the pure reflex response from the motor corrections during a complex movement such as gait. In the present work, the reflex size was measured as the difference between the mean poststimulation EMG and the corresponding control EMG in an early time window, implying an additive model where the reflex response is superimposed on the ongoing EMG pattern. It is assumed therefore that the observed results are produced by site dependant modulation of the withdrawal reflex circuits. However, a possible site dependant modulation of gait motor programs cannot be discarded.

Electrical stimulation has commonly been used to elicit withdrawal reflexes (Duyssens et al. 1990a; Grimby 1963; Shahani and Young 1971) and shown appropriate to outline the cutaneous receptive fields of different muscles (Andersen et al. 1999; Grimby 1963; Hagbarth 1960; Sonnenborg et al. 2000). However, other stimulation modalities are also available and have been used to elicit the nociceptive withdrawal reflex, for instance, heat (Campbell et al. 1991; Willer et al. 1979) and mechanical stimulation (Schouenborg and Kalliomäki 1990).

Electrical stimulation seems to be the best choice when cutaneous reflexes are evoked during gait (Bastiaanse et al. 2000; Duyssens et al. 1990a,b; Yang and Stein 1990), especially from the toes or foot sole (Belanger and Patla 1987; Decchi et al. 1997; Rossi and Decchi 1994).

The stimulus intensity was determined as a factor of the individual pain thresholds at each stimulation site to obtain as equal afferent input at all stimulation sites as possible, allowing the comparison of the reflexes across stimulation sites. Alternatively, the detection thresholds could have been used as normalization method. Detection thresholds are related to the pain thresholds (Andersen et al. 2001) and lie outside the nociceptive range; therefore the pain thresholds were preferred. The withdrawal reflex thresholds were discarded since they would mask the reflex sensitivity to stimulation at different sites. Identical stimulation intensities at different positions on the foot sole evoked different compound action potentials at the tibial nerve (Andersen et al. 2001), suggesting an effect of the skin thickness and/or neural innervation of the foot sole. Thus calibration based on the pain thresholds seemed most appropriate.

The electrode configuration used in this study ensured that the evoked sensation originated from well-localized positions on the foot sole, as was confirmed by all the volunteers who participated in the study (see RESULTS). Although special care was taken to prevent direct nerve stimulation, activation of the intrinsic foot muscles and/or proprioceptive afferents cannot be completely discarded. Electrical stimulation of the skin primarily evokes muscle reflex responses mediated by small diameter myelinated and nonmyelinated fibers. In this study, the pain sensation evoked by the stimuli and described by all the volunteers (sharp, pinprick) corresponds to Aδ afferent inflow (Birder and Perl 1994; Gardner et al. 2000). To our knowledge, no previous studies reported the electro-receptive fields of Aδ nociceptors in the human foot sole; however, different animal models provide some measurements: areas of 5 cm$^2$ in monkey skin (Peng et al. 1999) and 0.1 cm$^2$ in rabbit corneal epithelium (MacIver and Tanelian 1993) have been reported. Considering the size of the electrodes used in this study and their location on the foot sole (Fig. 1, inset), nerve endings from different nociceptive units were likely excited, and in consequence, the variation in the responses was probably due to central and not peripheral mechanisms.

**RRFs**

The RRF had different characteristics for proximal and distal muscles. The results revealed that TA RRF was located in the medial, distal foot in agreement with previous reports in humans (Andersen et al. 1999; Grimby 1963; Hagbarth 1960; Kugelberg et al. 1960) and animal models (Levinsson et al. 1999; Schouenborg and Kalliomäki 1990). The latencies of the TA responses to stimulation of the sural or tibial nerve during gait (Duyssens et al. 1990a,b) and stimulation of the foot sole during free standing (Decchi et al. 1997) are comparable to our findings. The latency of the TA reflex decreased when the stimulation site was the arch of the foot; previous works (Grimby 1963; Schouenborg and Kalliomäki 1990) reported increasing latencies toward the border of the receptive field in human and rat, likely due to an increment of the sensitivity in the focus of the RRF.
The excitatory SOL RRF in the SRL was located in the arch of the foot, while in the LRL, it seemed to cover the entire foot sole (cf. Andersen et al. 1999). A SOL RRF covering most of the plantar aspect of the foot was also observed during symmetrical stance (Andersen et al. 2003). In contrast, the SOL RRF in relaxed condition is well defined and located in the proximal, medial side of the foot (Andersen et al. 1999; Grimby 1963; Hagbarth 1960). The enlarged SOL RRF during gait most likely reflects a change in reflex gain mediated by descending motor commands and proprioceptive inputs (see Schomburg 1990 for a review on multisensory convergence on reflex pathways). The latency of the SOL excitatory response during swing is comparable to that reported in relaxed condition (Andersen et al. 1999).

For proximal muscles, VL and BF, the RRF covered the entire foot sole. Similar results were reported earlier by Andersen et al. (1999) for human plantar stimulation in relaxed condition and by Schouenborg and Kalliomäki (1990) and Levinsson et al. (1999) in rats and cats, respectively. The latencies of the responses were in accordance with those reported by Crenna and Frigo (1984) for VL and BF (late response) during free walking.

**EMG and kinematic responses during gait**

A combined analysis of TA and SOL responses revealed that, during stance, a pattern of activation of TA with no response or suppression of SOL was followed by co-contraction of the antagonistic muscles. The first part of this pattern can be interpreted as a protective mechanism, since the result is an unloading of the foot, and consequently, a reduction of the pressure against the source of painful stimulation (Duyens et al. 1992). The subsequent simultaneous activation of both muscles, present also in the swing phase, is probably intended to stabilize the ankle joint and to prevent from collapsing or stumbling. A similar pattern of co-activation was reported by Belanger and Patla (1987) after painful stimulation of the second digit of the foot during locomotion.

The main resulting movement at the ankle joint was dorsiflexion. Maximal dorsiflexion was achieved stimulating the RRF of TA (the medial, distal foot). The contraction of TA produced dorsiflexion of the foot and, hence, unloading of the TA RRF. During locomotion, dorsiflexion was observed in all phases, except heel-off, where no mechanical response followed the stimulation. A slight plantarflexion, albeit not significant, was observed at heel-off. This is in contrast with results in relaxed condition where plantar flexion was evoked by stimulation at the heel (Andersen et al. 1999; Grimby 1963). Duyens et al. (1992) reported dorsiflexion during early and mid-stance and plantarflexion at late stance and early swing, the latter due to suppression of the TA ongoing activity.

At the knee joint, only VL was modulated during the gait cycle. A similar pattern of modulation was reported earlier by Crenna and Frigo (1984). VL facilitation during swing was also reported by Zehr et al. (1998) and regarded as a safety mechanism since it increases knee stiffness and reduces the possibility of limb collapse.

Flexion was the dominant response at the knee and hip joints, in agreement with the results reported by Kugelberg et al. (1960). The phase-dependent modulation is consistent with the functional task being performed, since a large knee and/or hip flexion at heel-contact or during foot-flat could result in collapse. Thus the highest priority is to maintain posture and to continue the movement.

The phase-related response evoked in cSOL muscle revealed that, when stimulation is delivered during the swing phase, a large reflex response is evoked, probably to ensure support while the other limb is in swing and to facilitate the ongoing forward movement.

Various factors could be responsible for the modulation of withdrawal reflexes during gait. Posture, balance, limb load, and precontraction level of the muscles have been shown to affect the size of the reflex in free standing position (Rossi and Decchi 1994). Cutaneous reflexes are modulated during cycling, but not in static position at matched EMG activity (Brown and Kukulka 1993). They are also unaffected by passive cycling movement (Brooke et al. 1999), revealing that active cyclic movements are needed to obtain phase-modulated cutaneous reflexes. It is conceivable then, that the modulation of the withdrawal reflex occurs at the spinal level as a result of the integration of nociceptive information, afferent inflow providing feedback during locomotion, descending commands, and perhaps spinal motor programs.

The mechanical response observed at the three main joints of the leg depended on the stimulation site on the foot sole. In addition, large knee and hip flexion, accompanied by ankle dorsiflexion (Fig. 4), were achieved by applying distributed electrical stimulation after heel-off and during swing. These two elements make this technique interesting for future applications in rehabilitation programs based on functional electrical therapy and functional electrical stimulation assisted gait.

In conclusion, this study showed that painful stimulation of the foot sole during locomotion evoked distinctive muscle and mechanical responses depending on the stimulus location. The withdrawal reflex site dependency, primarily in distal muscles, extended the modular organization of the human withdrawal reflex for lower limb muscles to this functional task. At the same time, the results showed that the responses were modulated to prioritize maintenance of balance and continuity of locomotion.

**DISCLOSURES**

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**REFERENCES**


