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Effect of intrathecal baclofen on gait control in human hereditary spastic paraparesis

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Abstract

The covariation between thigh, shank and foot elevation angles during locomotion was analysed by means of orthogonal planar regression in a patient with pure hereditary spastic paraparesis before and after an intrathecal bolus of baclofen and in seven healthy subjects. The size, shape and spatial orientation of the loop defining patient's planar covariation (thigh angle vs. shank angle vs. foot angle) significantly differed from the controls' before baclofen, whereas these features resumed normal characteristics after baclofen injection. This shows that alteration of the control of phase coupling for the co-ordination of lower limb segments in human gait by increased spinal reflexes can be reversed by intrathecal baclofen injection.

Keywords: Human; Locomotion; Co-ordination; Planar covariation; Baclofen; Hereditary spastic paraparesis

As a $GABA_B$ agonist [14], baclofen reduces the release by primary afferent terminals in laminae II and III of excitatory neurotransmitters onto ventral horn motoneurons in the spinal cord [5,17]. Although intrathecal baclofen (ITB) is becoming a standard treatment of spinal origin spasticity [15], its effect on locomotor control is unclear. A recent approach has revealed a specific covariation of elevation angles of the lower limb segments along an attractor plane during locomotion in healthy humans [2–4,10]. The plane orientation and the shape of the loop that defines it reflect the phase relationships between these angles and therefore intersegmental co-ordination, on which postural stability with respect to gravity and dynamic equilibrium for forward progression depend. Recently, the features of this covariation in Parkinson's disease before and after therapeutic intervention gave insights into basal ganglia function [11]. In this study, we analysed this covariation in a patient with uncomplicated autosomal dominant hereditary spastic paraparesis (HSP) [9] before and after an ITB bolus.

The studied patient, aged 41, has normal muscle power, increased tone and reflexes in the lower limbs, extensor plantar responses and a spastic gait. Seven healthy subjects (aged 38.2 ± 4.6) participated as controls.

Using the ELITE system [8], four sessions of ten trials of the patient's self-paced locomotion over ten meters were recorded with a 100 Hz sampling rate, respectively before ITB of 75 μg (0.77 μg/kg) via lumbar puncture and 2, 4 and 6 h after it. Ten trials were recorded for each control subject. Markers over the anterior-superior iliac spine, trochanter, lateral knee condyle, lateral malleolus and 5th metatarsal, defined the segments of the thigh, shank and foot.

Statistical analysis of the angle covariation was based on principal component (PC) analysis (see [2]). PCs were computed by pooling the sample of time-varying angles after subtracting the mean. PCs are linear combinations of variates which are the covariance matrix eigenvectors. The ith PC is given by: $PCi = u_i^T \alpha$ where u_i is the eigenvector and α the variates. The normal vector of a particular plane corresponds to the 3rd eigenvector (u_3). The angular orientation of the covariation planes for different sets of data was computed using: $\theta(\text{set}) = \arccos u_3(\text{set}).\overline{u_3(\text{controls})} / |u_3(\text{set})|.|\overline{u_3(\text{controls})}|$, where u_3(set) is the 3rd eigenvector of the plane for the considered set of data and u_3(controls) is the mean 3rd eigenvector of the controls' planes.

Fig. 1 shows the lower limb kinograms of one representative step of the patient before (A) and after ITB (C,E), and

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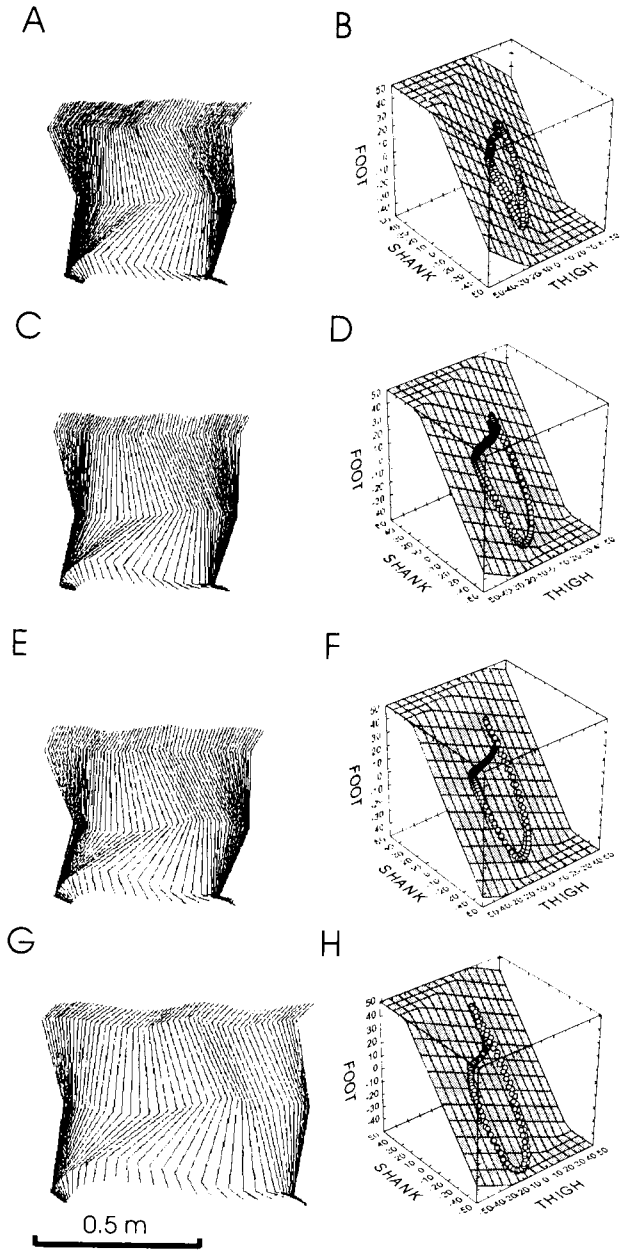

Fig. 1. Left: Stick diagrams representing the movement of the lower limb during one representative step of the patient before baclofen (A), 2 h (C), and 6 h after injection (E), and one step of a normal subject (G). Right: Planar covariation of elevation angles of the thigh, shank and foot over two successive gait cycles the patient before baclofen (B), 2 h (D), and 6 h after injection (F), and a normal subject (H).

one step of a normal subject (G), illustrating differences in speed, step length and span of the joints. The planar covariation of the corresponding elevation angles of the thigh, shank and foot are illustrated in Fig. 1B,D,F,H. The progression of the quasi-elliptic loop paths follows the counterclockwise direction, with the heel strike and toe-off corresponding approximately to the top and bottom of the loop, respectively. The shape of the loop path markedly differed from the physiological aspect before ITB and then gradually tended towards it. Namely, the ellipse short axis and, at a lesser extent, its long axis were smaller, the ellipse lower extremity more pointed and the top-right appendix which is typical of physiological gait was virtually absent before ITB. Fig. 2 shows the orientation of the patient's covariation plane before and after ITB. The plane angle was computed using the mean u_3 value of the controls, whose components were $u_3\alpha_t = 0.223 \pm 0.092$; $u_3\alpha_s = -0.772 \pm 0.026$; $u_3\alpha_f = 0.587 \pm 0.042$, α_t, α_s and α_f being the elevation angles of the thigh, shank and foot, respectively. This orientation significantly differed from controls before baclofen ($P < 0.001$) but not after ITB. The percentage of variance of u_3, which is the eigenvector orthogonal to the plane, was close to zero in all the sets of data, indicating that the orthogonal planar regression accounted for more than 99.2% of the data variance (Fig. 3). The percentage of variance of u_1 gradually increased after ITB while that of u_2 decreased, tending towards physiological values. Before ITB, the patient's speed and stride length significantly differed from the controls (Table 1). These parameters increased after ITB, becoming significantly different from the initial values 2 h after the injection. However, they remained significantly lower than the control values 6 h after ITB. The patient's cadence and cycle duration did not significantly differ from the controls either before or after ITB, but they were significantly higher 4 and 6 h after the injection than before it.

The present study demonstrates a dramatic effect of ITB

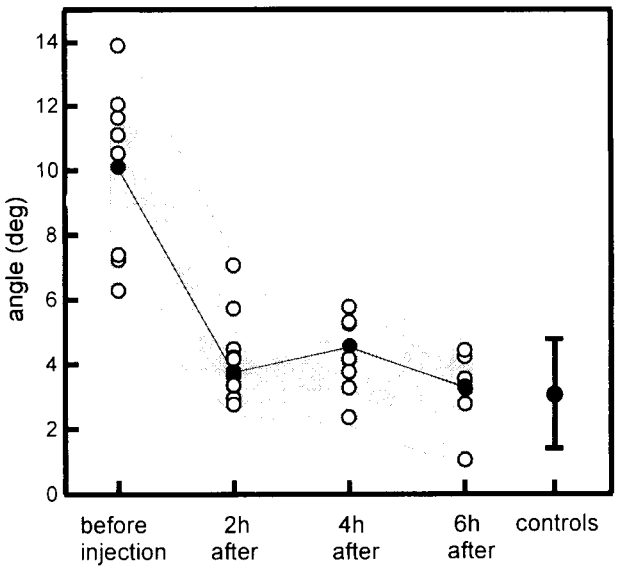

Fig. 2. Effect of intrathecal baclofen on the percentage of variance accounted for by each principal component of the planar covariation. Percentage of variance accounted for by the principal component of eigenvectors u_1 (A), u_2 (B) and u_3 (C). u_1 and u_2 lie on the plane and u_3 is orthogonal to it. All trial values of the patient are shown as open circles. The mean (black dot) and standard deviation of the control subjects are presented in the right part of the figure.

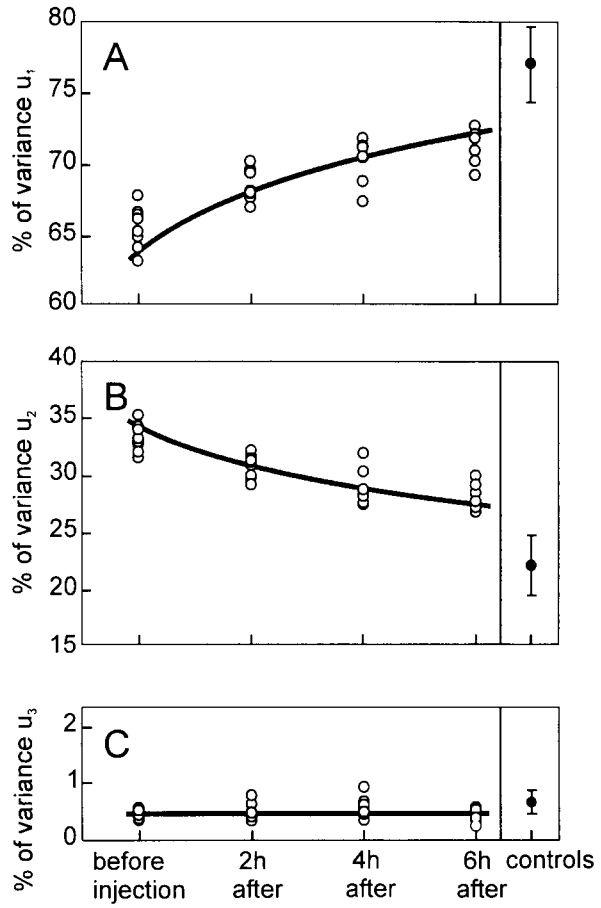

Fig. 3. Effect of intrathecal baclofen on the angular orientation θ of the covariation plane. The black dots represent the mean of each set of data. All trial values of the patient are shown as open circles. The mean and standard deviation of the control subjects are presented in the right part of the figure.

on the lower limb locomotor co-ordination in one HSP patient, indexed by a planar covariation rule recently identified in normal subjects [2]. Despite marked differences in mechanical constraints, this physiological characteristic of human gait is maintained through the swing and stance phases, representing an integration of the dynamic interaction requirements into the motor commands. This covariation is more consistent across trials and subjects than intersegmental angles or EMG patterns [2,10].

Before ITB the covariation differed significantly from the normal pattern. Three aspects of this covariation can be considered separately. Firstly, the planarity, represented by a very small percentage of variance accounted for by the 3rd eigenvector, was already present in the untreated patient. Secondly, the plane orientation significantly deviated from physiological values in the patient before ITB. Changes in plane orientation measured in different dynamic conditions have been correlated with changes in mechanical energy expenditure [4]. After ITB, the orientation rapidly reached physiological values. In contrast the third aspect of the covariation, the shape of the loop path, was more gradual in achieving normal features. In particular, the top-right appendix to the elliptic path, which was absent before ITB, reached physiological proportions (23.6 ± 2.2%) 6 h after injection. This appendix represents in-phase shank and foot forward rotation at the end of the swing phase and backward rotation after the heel strike while the thigh elevation angle remains constant.

Planar covariation may represent an aspect of phase coupling between units of central pattern generators (CPGs) driving the limb segments during locomotion. CPGs are neuronal networks that are able to generate rhythmic signals to muscles, producing organised rhythmic movement [12]. Such rhythmic patterns can be recorded at several levels during walking in mammals, suggesting spinal and supraspinal control [1]. Evidence for a spinal CPG for locomotion has been found in humans [6,7,18]. The tuning of CPG activity relies on multi-level supraspinal control, in such a way that normal rhythmic patterns generated at the spinal level depend on the integrity of the whole system from the cortex to the spinal cord. In the case of HSP, the altered neuronal targets are mainly in the spinal cord. Electrophysiological [16] and neuropathological [13] studies have demonstrated maximal axonal degeneration in the terminal portions of the longest corticospinal tract fibres from the motor cortex pyramidal neurones and fasciculus gracilis from dorsal root ganglia neurones. The beneficial effects of ITB in HSP could therefore be attributed to $GABA_B$-mediated reduction of afferent excitation of alpha motoneurons in the spinal cord. Interaction with cerebral $GABA_B$ receptors is also possible, but probably less significant.

A highly organised CPG, tuned peripherally and

Table 1
Gait parameters in the patient and controls[a]

Trials	Speed (ms^{-1}) mean ± SD	Stride length (m) mean ± SD	Cadence (steps/min) mean ± SD
Before ITB ($n = 10$)	0.730 ± 0.068^{+}	0.802 ± 0.050^{+}	109.08 ± 4.98
2 h after ITB ($n = 10$)	0.878 ± 0.084^{+}*	0.904 ± 0.045^{+}*	116.42 ± 6.71
4 h after ITB ($n = 10$)	0.909 ± 0.092^{+}*	0.898 ± 0.051^{+}*	122.70 ± 8.09*
6 h after ITB ($n = 10$)	0.971 ± 0.039^{+}*	0.938 ± 0.024^{+}*	124.18 ± 2.51*
Controls ($n = 70$)	1.314 ± 0.147	1.397 ± 0.061	121.32 ± 38.64

[a] ITB intrathecal baclofen; $^{+}P < 0.005$ difference with controls; $*P < 0.005$ difference with trials before ITB.

centrally, could also account for the similarities in alterations of planar covariation in this HSP case and patients with Parkinson's disease [11]. These neurological conditions are clearly distinct, both pathophysiologically and clinically. Gait, in particular, is clinically distinctive. However, a planar covariation impairment could be explained by abnormal tuning of the CPG exerted by the basal ganglia loop via the motor cortex in Parkinson's disease and by enhanced spinal reflexes due to decreased inhibition of afferent terminals on motoneurons in HSP.

In conclusion, the orthogonal planar regression analysis of the elevation angles of the lower limb segments consistently revealed abnormal orientation of the covariation plane and abnormal shape of the loop path that defines it in a patient with HSP. ITB restored physiological covariation. Although this does not demonstrate at which level the control of phase coupling for the co-ordination of lower limb segments is normally controlled, it shows that alteration of this control can be reversed by reducing abnormal alpha motoneuron excitability.

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