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Does galvanic vestibular stimulation decrease spasticity in clinically complete spinal cord injury?

Radoje D. Čobeljić[a], Ksenija Ribarič-Jankes[b], Antonina Aleksić[c], Lana Z. Popović-Maneski[d], Laszlo B. Schwirtlich[a] and Dejan B. Popović[d,e]

[a]Department of Neuro-Orthopedic Rehabilitation, Clinic for Rehabilitation 'Dr. Miroslav Zotović', [b]Euromedik Hospital, [c]School of Electrical Engineering, University of Belgrade, [d]Institute of Technical Sciences of the Serbian Academy of Science and Arts, Belgrade, Serbia and [e]Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

The aim of this study was to determine changes in clinical and biomechanical measures of spasticity after administering galvanic vestibular stimulation in patients with a complete spinal cord injury (SCI). The spasticity in the lower limbs was assessed using the Modified Ashworth Scale and the pendulum test in seven SCI patients (grade A on the ASIA Impairment Scale) before (0^-), immediately after (0^+), and at 5 and 30 min after the real versus sham galvanic vestibular stimulation (15 s each, anode over the right mastoid). Overall, the changes in spasticity were not significantly different between the real and sham galvanic vestibular stimulation. However, the Modified Ashworth Scale and the pendulum test indicated a reduction in spasticity in two out of seven patients. The results suggest that galvanic vestibular stimulation may modify spasticity in some patients with complete SCI, presumably through the residual vestibulospinal influences. Future studies should determine clinical and neurophysiological profiles of responders versus nonresponders and optimize parameters of galvanic vestibular stimulation.

Introduction

Spasticity is a motor disorder caused by an imbalance between inhibitory and excitatory supraspinal inputs controlling the segmental network (Trompetto *et al.*, 2014). Spasticity is present in about 65% of patients with a traumatic spinal cord injury (SCI) at the time of rehabilitation discharge (Holtz *et al.*, 2017) and increasing over time to 85% (Jorgensen *et al*., 2017; DiPiro *et al*., 2018). About 35–55% of SCI patients take some antispasticity medication (Holtz *et al.*, 2017; DiPiro *et al*., 2018) and the majority report that the spasticity negatively affects daily functioning (van Cooten *et al*., 2015) and quality of life (Adams and Hicks, 2005). Many treatments exist for spasticity, including physical therapy modalities,

pharmacological interventions, botulinum toxin injections, intrathecal drug delivery, and finally, surgery (Elbasiouny *et al.*, 2010). However, the treatment of spasticity remains a significant concern both for patients and for doctors (Kita and Goodkin, 2000).

Galvanic vestibular stimulation (GVS) applied to the mastoid processes activates afferent fibers of the vestibular nerve. The activation proceeds to the vestibular nuclei and then to the vestibuloocular and vestibulospinal output pathways (Goldberg, 2000). Vestibulospinal neurons converge on spinal interneurons subserving inhibitory or excitatory actions. Coats and Stoltz (1969) described the changes in natural body sway caused by GVS in healthy individuals and the associated medium latency responses in the soleus muscle have been identified (Britton *et al.*, 1993; Watson and Colebatch, 1998). GVS may also affect the tone of postural muscles, causing hypotonia with the anodal and hypertonia with the cathodal stimulation (Iles and Pisini, 1992). Kennedy and Inglis (2001) reported that GVS may modulate the soleus H-reflex in healthy prone human participants even when the muscle is not being used posturally. We also confirmed the modulation of H-reflex in prone healthy participants using 10 successive short GVS pulses (Čobeljić *et al.*, 2016).

Previous studies in patients with SCI have shown that GVS can elicit medium-latency responses in the soleus muscle with prolonged latencies (Iles *et al.*, 2004; Liechti *et al*., 2008) and amplitudes that correlate negatively with the severity of lesion (Iles *et al.*, 2004). We also applied a binaural GVS (Ribarič-Jankes *et al.*, 2006) and found a reduction in spasticity in five out of nine chronic SCI patients (six complete, three incomplete), ranging from 1 to 2 points on the Ashworth scale (Ashworth, 1964).

To expand on our previous observations in a more rigorous way, the aim of this study was to determine whether the binaural GVS alters clinical and biomechanical measures of spasticity in SCI patients classified as a grade A on the ASIA Impairment Scale (AIS-A) (Maynard *et al.*, 1997). We applied real versus sham GVS in a full cross-over design and assessed the effects by the Modified Ashworth score (MAS, Bohannon and Smith, 1987), and the Pendulum test goniogram, tachogram, and pendulum test (PT) score (Bajd and Vodovnik, 1984; Popović-Maneski *et al.*, 2018). The inclusion of clinically complete SCI patients was prompted by the presence of the erector spinae responses recorded below the level of lesion in two out of nine AIS-A patients following binaural GVS (Iles *et al.*, 2004) and also by the presence of vestibular-evoked myogenic potentials in the soleus muscle in two out of 16 patients with motor-complete SCI following a series of high-intensity, short-tone burst acoustic stimuli (Squair *et al.*, 2016). In contrast to the acoustic stimulation, which activates only a small part of the vestibular apparatus (saccule), the galvanic stimulation excites the

entire vestibular nerve, that is, the afferents originating from the semicircular canals and the otoliths. The modification of spasticity (muscle hypertonia) following GVS would suggest a possible existence of the residual vestibular (vestibulospinal) influences over the spinal network below the level of clinically complete SCI.

Patients and methods

Patients

The inclusion criteria for this study were (i) AIS-A SCI above the Th12 level; (ii) stable neurological and medical status; (iii) no cognitive impairments; (iv) no autonomic dysreflexia, and (v) no history of hearing or balance disorders. The sample was drawn from a pool of 22 inpatients and outpatients screened at the Clinic for Rehabilitation 'Dr. Miroslav Zotović' in Belgrade, of whom seven fulfilled the inclusion criteria. The Ethics Committee of the Clinic for Rehabilitation approved the study and all patients signed the informed consent before entering the study. The patients were asked to skip the morning dose of the prescribed antispasticity medications and the study was carried out in the early afternoon after they completed the daily conventional therapy.

Procedure and instrumentation

Each patient was transferred from a wheelchair to the exam bed by two therapists. A firm mattress was placed behind the back to support the patient in a semi-reclined position (trunk–hip angle of about 135°). The head was supported by a firm pillow (Fig. 1).

The knee joint was positioned about 5 cm over the edge of the bed, allowing the shank to swing freely in the sagittal plane. The thigh and shank were secured by soft cuffs to the pendulum test apparatus consisting of two lightweight aluminum rods connected by a hinge joint (Fig. 1). The hinge joint was instrumented with a Hall-effect angular encoder. Inertial sensors, attached to the aluminum rods, measured acceleration and the angular rate of the thigh and shank movements during the pendulum test. All sensors were connected to the laptop using a 12-bit analog-digital converter with the sampling rate of 100 Hz (for more details, see Popović-Maneski *et al.*, 2018). Before commencing the study, sufficient time was allowed to ensure that the patient was comfortable and relaxed.

For GVS, the anode and the cathode were placed over the right and left mastoid process, respectively (3 × 3 cm self-adhesive, disposable BF-2Bio-Flex electrodes; Bio- Medical

Instruments, Warren, Michigan, USA). The electrodes were connected to a custom-built stimulator capable of producing monophasic pulses ranging from 1 to 10 mA. In the case of real GVS, the examiner increased the intensity until observing the right turn of the head and torso (typically 4 mA). A total of 10 pulses (1 s each separated by 0.5 s) were delivered over 15 s using a manual control (for more details, see Čobeljić *et al.*, 2016). For the sham GVS, the intensity was maintained at 0mA. The sham GVS was administered 2 h after the real GVS in patients 1–3, whereas in patients 4–7, the sham and real GVS were performed on different days.

Outcomes measures

All assessments were performed on the right leg before ($t = 0^-$), after ($t = 0^+$), and at 5 and 30 min after GVS. To assess the muscle tone according to MAS, the examiner ranged the knee joint at the angular velocity of about 14 rpm and assigned the score from 0 (normal tone) to 5 (segment rigid in extension) for the resistance perceived during the knee extensors stretch. For the pendulum test, three repetitions were performed after a pause of 15 s. From the averaged data, seven parameters were estimated: R_{2n} is the normalized relaxation index, N is the number of sways, φ_{max} is the maximum angle from the goniogram after the limb drop, ω_{max} and ω_{min} are the absolute maximum and minimum lower limb angular speed as defined by Bajd and Vodovnik (1984), f is the frequency of oscillations, and $|P^+–P^-|$ is the relative difference between the positive and the negative area of the goniogram. The PT score was calculated from the goniogram and tachogram data (Fig. 2) according to the following formula (Popović-Maneski *et al.*, 2017):

$$PT_i = \left|\frac{\left(R_{2n_i} - \hat{R}_{2n_H}\right)}{7 \times \hat{R}_{2n_H}}\right| + \left|\frac{\left(N - \hat{N}_H\right)}{7 \times \hat{N}_H}\right| + \left|\frac{(\varphi_i - \hat{\varphi}_H)}{7 \times \hat{\varphi}_H}\right| + \left|\frac{(\omega_{max_i} - \hat{\omega}_{max_H})}{7 \times \hat{\omega}_{max_H}}\right| + \left|\frac{(\omega_{min_i} - \hat{\omega}_{min_H})}{7 \times \hat{\omega}_{min_H}}\right| + \left|\frac{\left(f_i - \hat{f}_H\right)}{7 \times \hat{f}_H}\right| + \left|\frac{\left(\left|\frac{P^+ - P^-}{P_{total}}\right|_i - \left|\frac{\widehat{P^+ - P^-}}{P_{total}}\right|_H\right)}{7}\right|,$$

where i denotes a patient, H is used for healthy individuals, − represents a mean value of three

trials in the same patient, and ^ represents the mean value for the healthy individuals (R_{2n}= 1.05, N = 7.39, φ_{max}= 0.69, ω_{min} = − 4.78, f = 0.96, $|P^{+}- P^{-}|$= 0.06). For the normalization of PT, each part of the equation was divided by the total number of parameters used for calculating PT (for instance seven parameters). Typical values of the PT score for healthy individuals are less than less than 1. More details can be found in Popović-Maneski *et al.* (2017, 2018).

Results

Figure 3 shows the MAS results before ($t = 0^{-}$), immediately at the end ($t = 0^{+}$), and at 5 and 30 min after sham and real GVS for each individual patient along with the group averages.

The average MAS decreased from about 2.7 to 1.7 after real GVS, whereas the change after sham GVS was small. When the changes over time were examined (slope), the overall decrease was steeper after real than sham GVS, but the difference was not significant (*t*-test for two independent samples, t = 1.19, P = 0.11).

Figure 4 shows the pendulum test goniograms before, immediately at the end, and at 5 and 30 min after sham and real GVS, indicating three different behaviors: flexor spasticity (patient 5, Fig. 4, top panel), low spasticity (patient 6, Fig. 4, middle panel), and pronounced extensor spasticity (patient 7, Fig. 4, bottom panel).

A switch from tonic to phasic spasticity was found in patient 5, with the faster change after real than sham GVS. Patient 6 showed increasing number and longer duration of oscillations after real GVS. Patient 7 showed a gradual change from tonic to phasic extensor tone after real GVS, with the minimal change in the goniogram trace after sham GVS.

Figure 5 shows the individual and group results for the PT score before, immediately at the end, and at 5 and 30 min after sham and real GVS.

The PT score variably decreased in patients 1, 3, 4, 5, 6, and 7 at different time-points after real GVS, whereas at the comparative time points after sham GVS, it either decreased to a lesser degree (patient 5), remained about the same (patients 2, 3, 6, and 7), or even increased (patients 1 and 4). In patient 2, surprisingly, the PT score increased after real GVS. As a result of inconsistent changes in terms of the magnitude and timing among all patients, the overall difference in the PT score was not statistically significant between real and sham stimulation.

Discussion

The overall result of this study is that the spasticity (muscle hypertonia) in the thigh muscles did not change significantly between the real and sham GVS when examined across all seven patients with clinically com- plete SCI. The reason for this result lies in large inter- individual differences in response to GVS on both MAS and the PT score (Figs 3 and 5). A large variability of individual results may be because of spontaneous fluctuations of spasticity within and between the days, which makes the assessment complex (Biering-Sørensen *et al.*, 2006). To minimize these confounds, we performed all assessments in the same manner and at the same time of the day, used both real and sham GVS in an attempt to isolate the true effects, and followed the recommendation by Bajd and Vodovnik (1984) to have an interval of 15 s between two pendulum trials. Thus, the apparent inter- individual differences in responsiveness to GVS are more likely because of distinct features of spasticity and other characteristics of underlying SCI among the patients recruited for this study. Some of the differences are discussed below.

In patient 7, the outcome measures suggest that real GVS reduced spasticity. Namely, MAS decreased for one point (from 3 to 2) immediately after GS and remained the same for 30 min (Fig. 3), the pendulum goniograms showed a gradual change from tonic to phasic extensor tone (Fig. 4), and the PT score was reduced (Fig. 5). In contrast, this was not found after sham GVS. Similarly, none to minimal changes after sham GVS were observed in patient 6, whereas the MAS score decreased by one point starting at 5 min after real GVS (Fig. 3), which was preceded by the decrease in the PT score starting immediately after real GVS (Fig. 5). The goniograms for patient 6 (Fig. 4, middle panels) also provide supportive results.

Another subset of patients showed a different pattern of results – reduced spasticity after both types of GVS. First, a comparably greater decrease in spasticity was seen in patient 5 after real than sham GVS. This patient showed a two-point versus a one-point drop on MAS (Fig. 3), switch from tonic to phasic spasticity on the goniogram (Fig. 4), and a decrease in the PT score (Fig. 5) after sham and real GVS. The decrease in spasticity even after sham GVS may be associated with repeated knee joint excursions during the assessment. Indeed, repetitive movements may decrease stretch–reflex amplitude because of mechanical alterations in muscle structure (Hagbarth *et al.*, 1985) and stretch–reflex habituation (Turpin *et al.*, 2016).

The remaining patients showed somewhat inconsistent results between different outcomes and real versus sham GVS, for example, no change in MAS, but a small yet progressive decrease in the PT score after real GVS (patient 3), or change in MAS accompanied by a similarly fluctuating pattern of changes in the PT score for both the real and sham GVS (patient 1).

Our results support and extend the previous observations suggesting some degree of

vestibulospinal preservation in cases of clinically complete (AIS-A) SCI. However, the reported changes in spasticity after GVS in two out of seven SCI patients reported here are in contrast to the lower prevalence of medium latency responses in the erector spinae muscles below the level detected by Iles *et al.* (2004) in only two of nine patients or the presence of vestibular-evoked myogenic potentials reported by Squair *et al.* (2016) in two of 16 AIS-A patients. Thus, the accumulated evidence is consistent with broader neuro-physiological observations suggesting traces of somato-sensory (Finnerup *et al.*, 2004; Awad *et al.*, 2015; Wrigley *et al.* 2018) and motor preservation (Sherwood *et al.,* 1992; McKay *et al.*, 2004; Dimitrijević *et al*., 2015; Mayr *et al*., 2016) is patients classified as having the AIS-A injury, which is also supported by the autopsy studies (Kakulas and Kaelan, 2015).

Our results raise the question as to whether GVS may be used for treating the spasticity. Larger studies are necessary for defining the optimal set of parameters of GVS (intensity-duration), distinguishing the responders from nonresponders, and assessing the duration of treatment effect.

Conclusion

The results of this preliminary sham-controlled cross- over study indicate that GVS may modify spasticity (muscle hypertonia) in selected patients with AIS-A SCI.

This suggests that the vestibulospinal influences may be preserved below the level of clinically complete SCI. Future investigations should determine the clinical and neurophysiological profiles of responders vs. nonresponders and optimize parameters of GVS.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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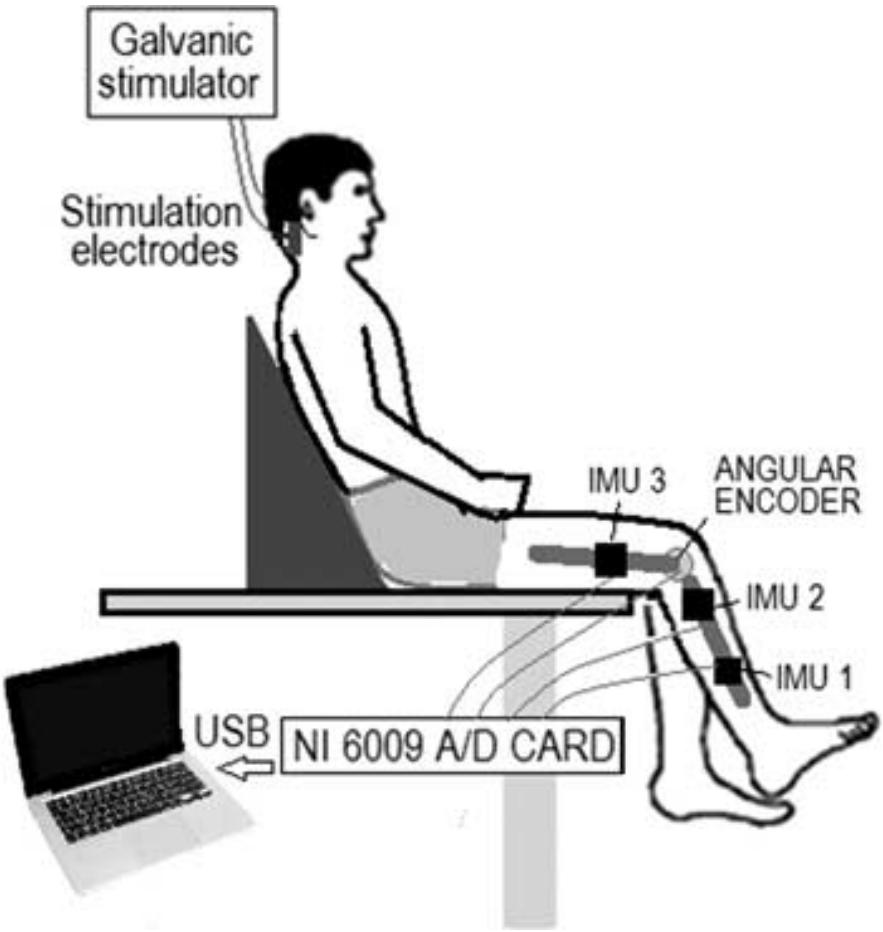

Fig. 1 A sketch of the instrumentation used in the study. The thigh and shank of the right leg were placed in a custom-built pendulum test apparatus.

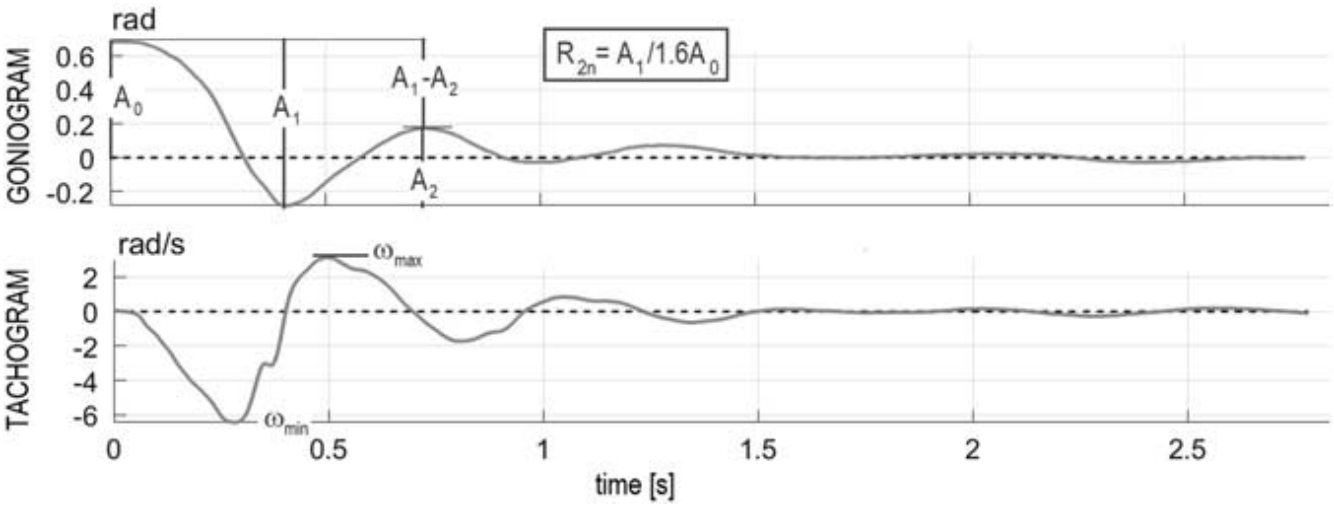

Fig. 2 An example of the goniogram and tachogram with the values used for the calculation of the pendulum test score.

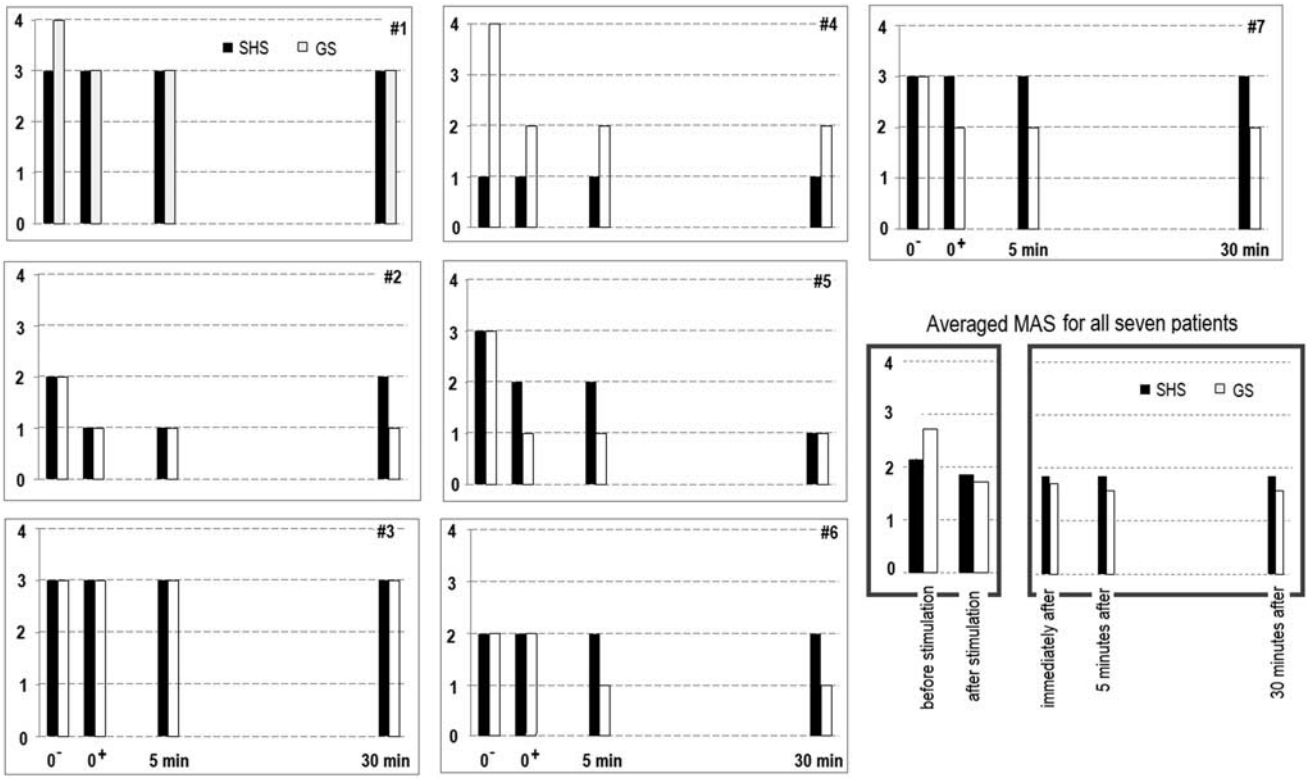

Fig. 3 MAS for sham (black bars) and real (white bars) GVS at different time-points for each patient individually and after averaging across the entire group.

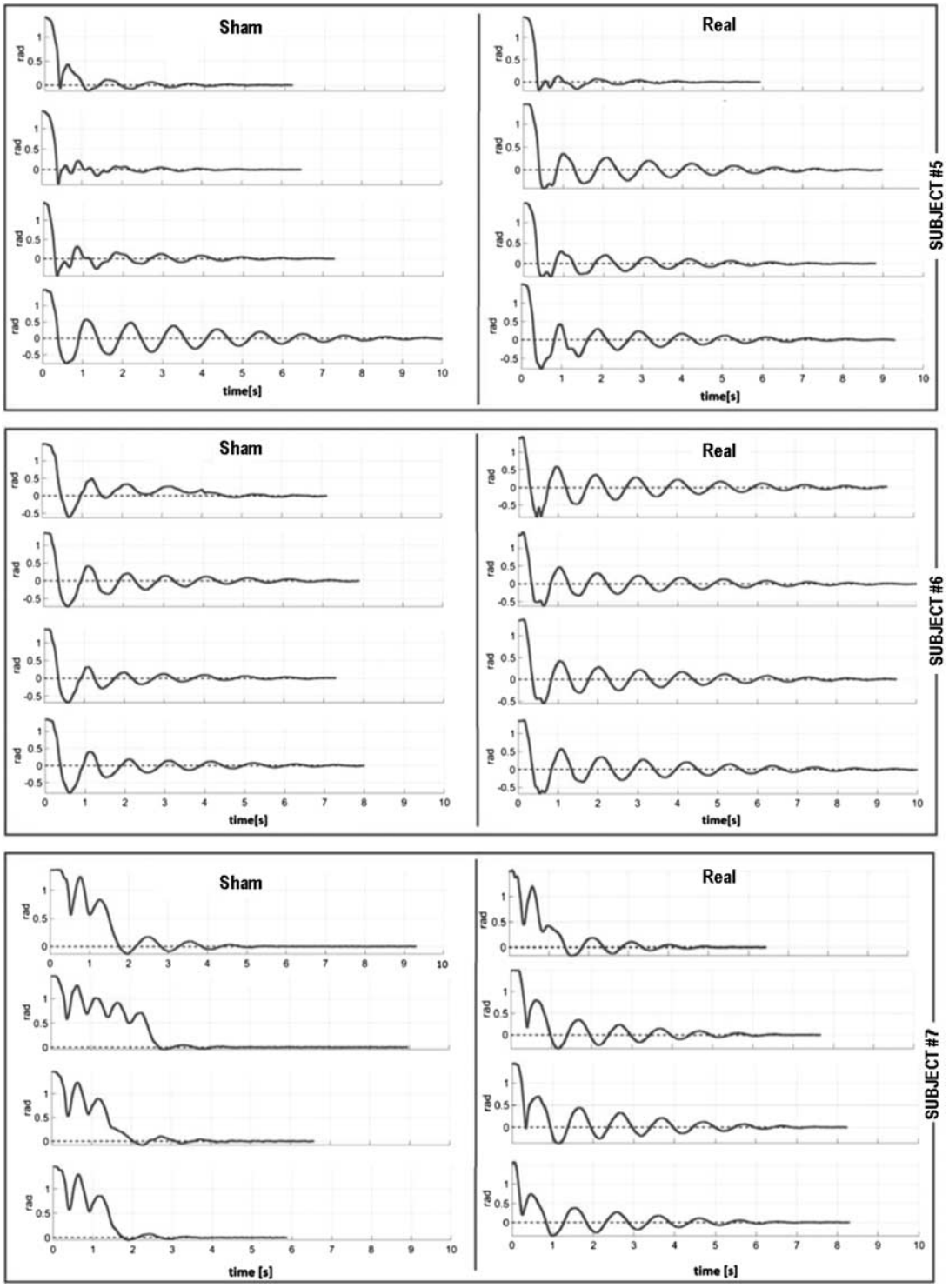

Fig. 4 Pendulum test goniograms in three patients recorded before (top row of each panel), immediately after (second row), and at 5 min (third row) and 30 min (fourth row) after sham (left panels) and real galvanic vestibular stimulation (right panels) indicating different patterns of spasticity (see text for details).

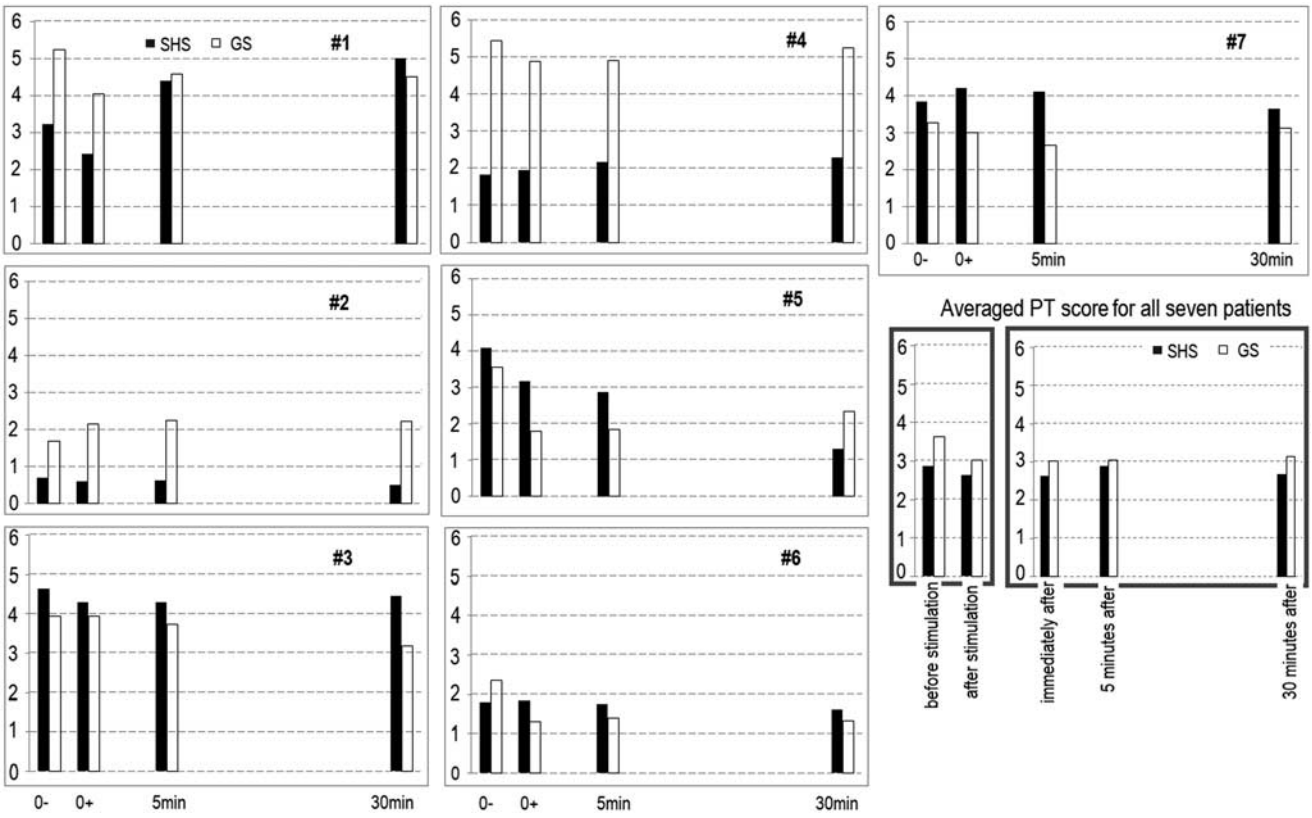

Fig. 5 The pendulum test scores for sham (black bars) and real (white bars) galvanic vestibular stimulation at different time-points for each patient individually and after averaging across the entire group.