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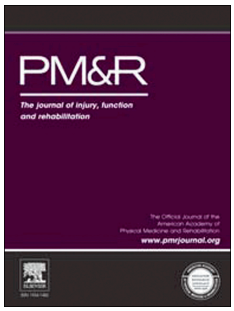

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Who may benefit from Armeo®Power treatment? A neurophysiological approach to predict neurorehabilitation outcomes.

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Who may benefit from Armeo Power® treatment? A neurophysiological approach to predict neurorehabilitation outcomes.

ABSTRACT

Background: The Armeo Power® is a rehabilitation exoskeleton that allows early treatment of motor disabilities providing intelligent arm support in a large 3D workspace to perform intensive, repetitive and goal oriented exercises. This device could efficiently induce new connections and plasticity phenomena potentiation. Therefore, the knowledge of the potential brain plasticity reservoir following brain damage constitutes a prerequisite for an optimal rehabilitation strategy.

Objective: To identify potential neurophysiological markers predicting the responsiveness of stroke patients to upper limb robotic treatment.

Design: Prospective, cohort study.

Setting: Behavioral and Robotic Neurorehabilitation Laboratory of IRCCS Centro Neurolesi Bonino-Pulejo, Messina, Italy

Patients: We enrolled thirty-five stroke patients suffering with unilateral hemiplegia following a first-ever ischemic supra-tentorial stroke, at least 2 months before their enrolment.

Methods or Interventions: All patients underwent forty 1h Armeo Power® training sessions (i.e. five times a week for 8 weeks).

Main Outcome Measurements: We assessed the spasticity and the motor function of upper limb by means of Modified Ashwort scale and Fugl-Meyer assessment, respectively. Moreover, we evaluated the cortical excitability and plasticity potential of the bilateral primary motor areas in response to repetitive paired associative stimulation

paradigm using the transcranial magnetic stimulation, and Armeo Power® kinematic parameters.

Results: The patients showing significant repetitive paired associative stimulation after-effects at baseline, exhibited an evident increase of cortical plasticity in the affected hemisphere (motor evoked potential amplitude increase p=.03), a decrease of inter-hemispheric inhibition (affected hemisphere cortical silent period duration decrease, p=.01; unaffected hemisphere cortical silent period duration increase, p=.004; repetitive paired associative stimulation aftereffect increase, p=.008). Such findings were paralleled by clinical (Fugl-Meyer, p=.04) and Armeo Power® kinematic (elbow flexion/extension, p=.02; shoulder range of movement p=.002) improvements.

Conclusions: Our data suggest that the Armeo Power® practice may improve upper limb motor function recovery predicted by reshaping of cortical and trans-callosal plasticity, according to the baseline cortical excitability.

KEYWORDS: Armeo Power; neural plasticity; repetitive paired associative stimulation; robotic rehabilitation; upper limb paresis.

INTRODUCTION

Stroke represents the leading cause of disability in the industrialized world[1]. Severe upper limb (UL) paresis, usually involving the scapulothoracic, shoulder, or elbow joint, may result in no or very limited voluntary UL movements, thus seriously impairing the quality of life and the ability to perform even simple daily-life tasks[2-3].

Upper limb movement usually recovers within the first six months after stroke onset, then decreasing in the chronic phase[4]. Therefore, the optimal neurorehabilitative strategy aimed at recovering voluntary UL movement and functionality is a major concern. Recent clinical trials have shown significant advances in UL recovery by using different sensory-motor techniques, including intensive repetitive movements[5], constraint-induced movement therapy[6], functional electrical stimulation treatment[7], the use of virtual reality[8], and robot-assisted therapy[9]. To this end, modern concepts of rehabilitation support the use of intensive, repetitive, and task-oriented approaches aimed to restoring UL disability by means of robotic devices, including the Armeo Power® (AP)[10], which is a rehabilitation exoskeleton with an intelligent arm supported in a large-3D workspace.

Growing evidence suggests that brain neural plasticity plays a crucial role in reshaping brain microstructures, and improving motor performances following stroke[11-13]. Conceivably, partial structural and functional impairment likely recovers through a potentiation and extension of residual brain areas, whereas complete lesions require a substitution by functionally-related systems. Peri-infarct activation is one of the potential mechanisms involved, as suggested by experimental animal stroke models[14].

Noteworthy, robotic devices, including AP, could efficiently induce new connections and plasticity phenomena potentiation within either damaged or unaffected brain areas[9]. Therefore, the knowledge of the potential brain plasticity reservoir following brain damage constitutes a prerequisite for an optimal rehabilitation strategy. The aim of our study was to identify possible plasticity markers predicting the responsiveness of chronic post-stroke patients to AP treatment, by means of a neurophysiological approach. In addition, we evaluated whether AP treatment could be useful in improving motor performances in chronic post-stroke condition.

MATERIALS AND METHODS

Participants

We enrolled 35 stroke patients (13 women; mean age 51.1± 11) who met the following inclusion criteria: i) unilateral hemiplegia secondary to a first-ever ischemic supra-tentorial stroke (confirmed by MRI scan) at least 2 months before their enrollment; ii) no history of concomitant neurodegenerative diseases or brain surgery; iii) no severe cognitive impairment (Mini-Mental State Examination score >24points); and iv) no transcranial magnetic stimulation (TMS) contraindications[15]. Clinic-demographic characteristics are presented in table 1. All of the patients gave their written informed consent. The study was approved by our local Ethics Committee.

Clinical assessment

All patients were clinically evaluated using the Modified Ashwort Scale (MAS), Fugl-Meyer Assessment of UL motor recovery after stroke (FMA), Functional Independence

Measure (FIM), The Short Form (36) Health Survey (SF36), and Hamilton rating scale for depression and anxiety (Ham-D and Ham-A, respectively), both at baseline (T_{PRE}) and following the AP training (T_{POST}).

MAS is the main clinical measure of muscle spasticity in patients with neurological conditions[16], subjectively measuring muscle resistance during passive soft-tissue stretching. It consists of a 5-point nominal scale ranging from zero, i.e. no tone increases, to 4, i.e. severe spasticity. An additional grade (1+) was added to enhance sensitivity and accommodate hemiparetic patients who typically graded at the lower end of the scale. FMA is used to evaluate recovery in post-stroke hemiplegic patients by means of a performance-based impairment index, including UL motor, sensation, and joint domains[17]. The FIM scale assesses physical and cognitive impairment, and focuses on the level of disability indicating the burden of caring for patients[18]. The SF-36 questionnaire can be used as a self-administered functional assessment, and provides information on patient's physical, psychological, social, and role functions[19]. The Ham-D is the most widely used clinician-administered depression assessment scale, pertaining to symptoms of depression experienced over the past week, whereas Ham-A is a validated tool for measuring the severity of a patient's anxiety[20-21].

Armeo-Power intervention

The AP (Hocoma AG, Volketswil, Switzerland) is a rehabilitation exoskeleton allowing early treatment of motor abilities and providing intelligent arm support in a large-3D workspace. As a part of the sustainable Armeo Therapy Concept [22-24], the AP is designed for individuals who suffered from stroke, traumatic brain injury, and other neurological disorders resulting in UL impairment. The suspension system is an

123 exoskeleton that supports subject's UL from the proximal to distal region, and
124 magnifies any residual active movement of the paretic UL in a 3D space. System
125 sensitivity can be adjusted depending on patient's condition. Virtual reality settings are
126 designed to provide different levels of difficulty (direction of movement, velocity,
127 moving area) and a functional approach to the task. The system allows calibrating the
128 working space and the level of task difficulty, according to patient's active mobility.
129 Moreover, it provides information about specific movement parameters (resistance,
130 strength, range of motion, and coordination).
131 Patients underwent an intensive UL rehabilitative program, consisting of forty 1 hour
132 training sessions (i.e. five times a week, from Monday to Friday, for 8 consecutive
133 weeks). During the first session, the device was adjusted for patient's arm size and
134 angle of suspension. Once the UL had been fitted to the system, the working space and
135 the exercises were selected. The working sessions were supervised by a skilled
136 physiotherapist who modified the exercise programs according to each patient's
137 progress. While patients were undergoing AP training, the therapists provided
138 additional exercises that did not target the arm.
139 *Transcranial magnetic stimulation*
140 Transcranial Magnetic Stimulation (TMS) is a non-invasive means of electrically
141 stimulating neurons in the human cerebral cortex. This technique allows modifying
142 neuronal activity locally and at distant sites[25-26], thus extending the knowledge of
143 intracortical physiology, corticospinal tract function, motor system plasticity, and motor
144 control[27]. Single-pulse TMS is commonly applied over the primary motor cortex in
145 order to activate contralateral target muscles, inducing motor evoked potential (MEP).
146 The latter provides quantifiable attributes in terms of corticospinal plasticity and

147 excitability, including resting and active motor threshold (RMT and AMT), and MEP
148 amplitude and latency[26-28]. These parameters represent measures of corticospinal
149 excitability. Stroke often causes an increase in motor excitability threshold, MEP
150 alterations with delayed latencies, reduced amplitudes, and abnormal morphology, and
151 asymmetry of the cortical motor maps between affected and unaffected hemisphere[29].
152 These changes usually occur at maximum degree within few months following stroke,
153 and then become stable in the chronic stage[30-32].
154 Motor cortex excitability was tested through monophasic TMS pulses delivered by a
155 high-power Magstim 200 stimulator (Magstim, Dyfed, UK). We used a figure of eight-
156 coil with an external loop diameter of 9cm. The centre of the coil was located over the
157 "motor hot spot" for the contralateral flexor radialis carpi muscle (FRC) from each
158 hemisphere (i.e. the optimum scalp position which consistently elicited the largest MEP
159 with the steepest initial slope in the relaxed FRC muscle at 120% of resting motor
160 threshold -RMT). The handle of the coil pointed 45° postero-laterally. The coil current
161 flowed toward the handle during the rising phase of the magnetic field. Thus, the
162 induced current in the cortex flowed in a posterior-to-anterior direction. The
163 monophasic magnetic stimulus had a rise time of approximately 100μs, decaying back
164 to zero over approximately 800μs.
165 First, we determined the RMT and AMT. RMT was defined as the minimum intensity
166 evoking a peak-to-peak MEP amplitude of 50μV in at least 5 out of 10 consecutive
167 trials in the relaxed FRC[25]. AMT was defined as the minimum intensity that elicited a
168 reproducible MEP of at least 200μV in the tonically contracted FRC in at least 5 out of
169 10 consecutive trials[25]. The AMT was normalized according to the contraction strength
170 exerted by the patient, which was ensured through oscilloscope and loudspeakers. Then,

171 we delivered 10 supra-threshold monophasic pulses (120% RMT) in order to elicit
172 MEP, whose peak-to-peak amplitude was calculated and averaged. In addition, we
173 registered 10 MEP during tonic contraction of the FRC of the affected and unaffected
174 side, and measured the cortical silent period (CSP) duration, which is a period of
175 electromyographic (EMG) silence following a MEP when a TMS pulse is given to the
176 motor cortex during tonic contraction of target muscle. The duration of the CSP
177 depends on the recovery of motor cortical excitability from gamma-amino-butyric-
178 acidergic inhibition following TMS pulses, and it is used as a measure of excitability
179 concerning cortical inhibitory circuits[33-35]. For CSP duration measurements, EMG traces
180 were rectified, but not averaged. The duration of CSP was defined as the time from the
181 onset of the MEP to reappearance of sustained EMG activity, measured in each trial[36],
182 and normalized according to the contraction strength exerted by the patient.
183
184 *Rapid paired associative stimulation (rPAS)*
185 rPAS is an experimental method used in order to investigate Hebbian principles of
186 neural plasticity in humans[37]. Briefly, a single electrical stimulus is directed to a
187 peripheral nerve before TMS pulse is applied on the contralateral M1. The repeated
188 pairing of such stimuli over time may increase or decrease the excitability of
189 corticospinal projections in a long-term potentiation/depression (LTP/LTD)-like
190 plasticity manner[38-40]. Therefore, the assessment of cortical responses to rPAS paradigm
191 may represent an estimate of neural plasticity properties that can be addressed by brain
192 networks in order to restore a function that has been lost[41-44].
193 rPAS consisted of 600 pairs of stimuli, which were continuously delivered on the M1
194 of the affected hemisphere at a rate of 5Hz for 2min. Each pair of stimuli consisted of an

electrical stimulus given to the contralateral median nerve followed by a biphasic TMS stimulus (at an individually adapted inter-stimulus interval, 23ms on average) given to the M1 of the affected hemisphere. We chose this inter-stimulus interval since a former study showed that PAS at 25 ms and very low frequency produced long-lasting facilitation of motor cortical excitability[45].

TMS biphasic pulses at 90% AMT were given through a standard figure-of-eight-coil connected to a Magstim Rapid stimulator (Magstim Company, Whitland, Dyfed, UK). Concerning the repetitive electric nerve stimulation (rENS) we applied square-wave pulses through a bipolar-electrode montage (Digitimer D-160 stimulator; Digitimer Ltd, Welwyn Garden City, Herts, UK) to the median nerve at the elbow contra-lateral to the TMS stimulated hemisphere. The cathode was located proximally and the pulse width was 500μs.

Study Protocol

At baseline (T_{PRE}), we measured the following electrophysiological parameters from the affected and unaffected FRC: RMT (RMT_{aff} and RMT_{unaff}), AMT (AMT_{aff} and AMT_{unaff}), peak-to-peak MEP amplitude (MEP_{aff} and MEP_{unaff}), CSP duration (CSP_{aff} and CSP_{unaff}), and MEP peak-to-peak amplitude induced by rPAS on the affected hemisphere ($rPAS_{aff}$ and $rPAS_{unaff}$). In addition, we measured AP kinematic parameters (i.e. the range and the force of movement of scapulothoracic, shoulder, elbow, and wrist of the affected side) and clinical scores (MAS, FMA, FIM, SF-36, Ham-D, and Ham-A). Then, patients performed the AP rehabilitation protocol. Thus, the clinical, electrophysiological, and kinematic parameters were assessed after the end of the AP training (T_{POST}).

Statistical analysis

The effects of AP on each clinical, kinematic, and electrophysiological parameter were assessed by means of two-way repeated measure ANOVA with *time* (two levels: T_{PRE} and T_{POST}) and *side* (two levels: affected and unaffected) as within-subject factors. Hierarchical multiple regression analyses were conducted to determine the variables that predicted the clinical, kinematic, and electrophysiological changes after the AP intervention. When a significant difference was observed, the Bonferroni procedure was used to conduct *post-hoc* paired *t*-tests. A p-value <.05 was considered significant. Correlation analyses for changes in motor function, baseline motor impairment, and cortical excitability were performed using the Spearman test.

RESULTS

At baseline, all of the patients showed a mild-to-severe UL motor impairment, as shown by FMA data, low AP force, and reduced joint excursions, besides MAS, SF-36, and FIM scores (table 1). In addition, patients showed a mild mood depression and anxiety mainly focused on their health conditions. The MRI patterns documented a T2-weighted and FLAIR hyper-intensity lesion involving the territory of the left (13 patients) or right (22) middle cerebral artery. Those clinic and kinematic findings were paralleled by low MEP_{aff} and long CPS_{aff}, mild $rPAS_{aff}$ increase, and marked $rPAS_{unaff}$ increase. After AP training, we observed a CSP_{aff} decrease, and a CSP_{unaff}, MEP_{aff}, and $rPAS_{aff}$ increase. Instead, $rPAS_{unaff}$ after-effects were not significant (fig. 1). These findings were paralleled by an increase of elbow flexion-extension force and shoulder intra-

extrarotation range of movement (ROM) (fig. 2), and an UL function amelioration (fig. 3). In particular, patients improved in the self-care functions **on** the FIM scale (from moderate to minimal assistance), and at the FMA concerning flexor synergies, coordination and speed, passive joint motion and joint pain, sensation and shoulder and elbow proprioception. Statistical data are reported in table 2.

In addition, CSP_{unaff} duration, MEP_{aff} amplitude, and $rPAS_{aff}$ and $rPAS_{unaff}$ after-effects predicted the clinical and kinematic improvement following AP practice (table 3 and 4).

DISCUSSION

There are two main findings from our work: i) the effectiveness of AP treatment in chronic stroke patients in improving UL motor function by means of synaptic plasticity remodeling the bilateral primary motor areas; and ii) the usefulness of electrophysiological assessment by means of TMS in identifying plasticity markers that could predict the neurorehabilitation outcome.

Robotic devices may efficiently allow active, systematic, and intensive repetition of specific movements, thus providing a setting of sensory-motor integration with a variable degree of attention demand and complexity[5-9]. In particular, such devices may potentiate the plasticity phenomena at cortical and subcortical levels that are responsible for functional restoration of the affected brain areas after brain injury[10-13,46].

To date, only one previous work demonstrated the efficacy of Armeo Spring in the rehabilitative treatment of mild to moderate UL paresis in post-stroke chronic phase[47]. To the best of our knowledge, this is the first report evaluating the AP effectiveness in patients suffering from post-stroke UL impairment.

Synaptic plasticity modeling by AP treatment

The diaschisis between damaged and intact neuronal networks may corrupt the cortical excitability and connectivity patterns within either surrounding (probably via cortico-cortical connections) or remote areas, even in the unaffected hemisphere (via trans-callosal fibers). The degree of motor function deterioration correlates with the level of cortical excitability impairment of the affected area (which also shows a maladaptive plasticity)[48], which in turn depends on either the brain injury or the inhibition from the unaffected hemisphere[49-51]. The consistent finding of bilateral activation abnormalities following stroke suggests that both cerebral hemispheres play an important role in functional recovery and plastic rearrangement of neuronal networks[52-54]. Indeed, our data suggest that AP-induced clinical and kinematic amelioration (flexor synergies, coordination and speed, passive joint motion, joint pain, sensation, and proprioception of shoulder, arm and forearm, self-care functions, mood, and anxiety) could depend on a potentiation of cortical plasticity within the affected hemisphere (as shown by clear rPAS after-effects and MEP amplitude increase), and a reduction of the inhibition exerted by the unaffected on the impaired areas, namely inter-hemispheric inhibition (lack of rPAS after-effects and longer CSP duration). These findings suggest a dis-inhibition of preexisting silent areas nearby the lesion[55]. In addition, they are more consistent with a bimodal balance-recovery model, which includes either inter-hemispheric reshape or exploitation of the functional recovery reservoir in the intact structures, rather than a simple inter-hemispheric competition model (which focuses on unidirectional inter-hemispheric connections)[56].

Although it is widely recognized that most spontaneous behavioral recovery tends to occur within the first 3 months after stroke onset, different patterns of recovery may emerge depending on many complex factors. In our sample, post-stroke recovery was probably due to a combination of natural and mediated processes, at least in those patients with a shorter disease duration (i.e. not really in the chronic stage).

Finally, we did not observe any further increase of the already existing compensatory motor patterns in the unaffected side. In fact, stroke patients often develop a compensatory hyper-reliance on the unaffected side, proximal paretic side, and trunk, in order to perform daily-life tasks[57-60], despite the presence of abnormal motor patterns[61-64]. Thus, our data suggest a remodeling of the maladaptive plasticity within the affected hemisphere, a prevention of the negative effect of non-paretic limb training after stroke, and a facilitation of experience-dependent plasticity in the affected hemisphere.

Electrophysiological markers predicting motor outcome

The patients who got a better clinical and kinematic response to AP treatment showed clearer rPAS after-effects in the affected hemisphere, whereas they were missing in the unaffected one. Such effects were paralleled by a longer CSP_{unaff} duration and a MEP_{aff} amplitude increase. Therefore, these findings may be useful predictors of post-stroke UL functional recovery. In addition, they further suggest that the reduction of inter-hemispheric inhibition from the unaffected to affected side, and the enhanced plasticity within the affected hemisphere play a key role in motor function recovery.

Limitations

The main limitations of our study consisted of the small sample size and the lack of direct inter-hemispheric inhibition measures, since we did not have available focal small-diameter figure-of-eight coils. In addition, the implementation of our rehabilitative protocol could be difficult in a common neurorehabilitation setting, since we used an intensive training and expensive devices. Nevertheless, the inter-hemispheric remodeling of MEP amplitude, rPAS after-effects, and CSP duration may indicate an AP-induced change of the inter-hemispheric inhibition and predict the neurorehabilitative outcome.

Conclusions

Our data underscore the importance of a neurophysiological assessment focusing on a bimodal balance–recovery model in order to more objectively predict the functional motor outcome and personalize the robotic rehabilitation training. This would allow clinicians to optimize timing of recovery, neurorehabilitation strategy, and employment of neurorobotic devices, thus avoiding non-useful intensive neurorehabilitative treatments.

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523 **Table 1.** Baseline clinical, kinematic and electrophysiological findings. Data are
524 expressed as mean±SE.

525

	parameter		UL affected	UL unaffected
electrophysiological	CSP (ms)		61±4	55±6
	MEP (mV)		.3±.05	.6±.05
	rPAS(% unconditioned MEP)		108±5	129±10
	RMT (%)		76±4	57±6
clinical	MMSE	25±.1		
	MAS	2±.2		
	FMA	20±1.5		
	FIM	78±4		
	Ham-D	6±.8		
	Ham-A	7±.6		
	SF-36	30±4		
kinematic		**joint**		
	ROM (°)	E-fl/ex	55±1	
		FA-p/s	125±1	
		S-ab/ad	62±1	
		S-fl/ex	65±.5	
		S-ir/er	87±.5	
		W-fl/ex	123±2	
	Force (N·m)	E-fl/ex	3±.1	
		FA-p/s	1±.1	
		S-ab/ad	13±2	
		S-fl/ex	13±2	
		S-ir/er	10±2	
		W-fl/ex	0	

526

527 Legend: CSP cortical silent period; MEP motor evoked potential; rPAS rapid paired associative
528 stimulation; RMT resting motor threshold; MMSE mini-mental state examination; MAS Modified
529 Ashworth Scale; FMA Fugl-Meyer Assessment; FIM Functional Independence Measure; Ham-A and
530 Ham-D Hamilton scale for depression and anxiety; SF-36 Functional Status; ROM range of movement (E
531 elbow, FA forearm, S shoulder, W wrist, fl/ex flexion/extension, p/s pronation/supination, ad/ad
532 abduction/adduction, ir/er intra-rotation/extra-rotation); UL: upper limb

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535 **Table 2.** Significant RM-ANOVA data concerning AP treatment after-effects.

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parameter		***timeXside*** $\mathbf{F_{(1,34)}, p}$	***time*** $\mathbf{F_{(1,34)}, p}$	$\mathbf{t_{(1,34)}, p}$
electrophysiological	CSP_{aff}	7.2, .009	6.3, .01	-3, .005
	CSP_{unaff}		9, .004	2, .04
	MEP_{aff}	NS	4.7, .03	2.5, .01
	$rPAS_{aff}$	NS	6.6, .008	2.1, .04
clinical	FIM		4.5, .04	2.1, .04
	FM		4.5, .04	2.1, .04
kinematic	F_E-fl/ex		6.4, .02	3.5, .006
	ROM_S-in/ex		4.9, .002	2.9, .005

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538 Legend see table 1

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546 **Table 3.** Significant multiple regression data concerning the electrophysiological
547 parameters predictive of clinic-kinematic improvement.

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parameter	F, p	t, p
CSP_{unaff}	4.5, .04	3, .005
MEP_{aff}	12, <.001	4.5, <.001
$rPAS_{aff}$	19, <.001	2, .04
$rPAS_{unaff}$	10, <.01	4, <.001

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550 Legend see table 1

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560 **Table 4.** Significant correlation data concerning post-AP changes in motor, kinematic,
561 and electrophysiological data.

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F_E-fl/ex ROM_S-in/ex	Z	p
PAS_{aff}	2.4	.01
CSP_{unaff}	4.5	<.001
MEP_{unaff}	-3	.003
$rPAS_{unaff}$	-3.4	.001

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564 Legend see table 1

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578 **FIGURE CAPTIONS**

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580 **Fig. 1** shows the AP-induced electrophysiological modification within the affected and
581 unaffected UL. RMT was unchanged, whereas MEP increased significantly in the
582 affected side but not in the unaffected. Such effects were paralleled by CSP_{aff}
583 shortening, CSP_{unaff} lengthening, $rPAS_{aff}$ potentiation, and $rPAS_{unaff}$ weakening. * refer
584 to significant change ($p<.05$), error bars to SE.

585

586 **Fig. 2** reports the kinematic after-effects. We observed a significant increase of shoulder
587 intra-extrarotation and a force enhancement in elbow flexion/extension. * refer to
588 significant change ($p<.05$), error bars to SE.

589

590 **Fig. 3** reports the clinical after-effects. We observed a significant amelioration of FIM
591 and FMA scores. * refer to significant change ($p<.05$), error bars to SE.