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The Effects of EMG Based Fatigue-Controlled and Forced Exercise on Motor Function Recovery: A Pilot Study

Yuchen Xu, Kedi Xu, Hao LYU, Stephanie NG, Wai Sang Poon, Shaomin Zhang*, Xiaoling Hu*, Yongping Zheng

***Abstract*—Post-stroke physical training resulting in fatigue may affect motor rehabilitation. In this study, we compared the effects of fatigue-controlled and forced treadmill running on motor recovery based on a rat intracerebral hemorrhage (ICH) model. Twelve Sprague-Dawley rats with ICH received electromyography (EMG) electrodes implantation in the gastrocnemius muscle in the affected hindlimb. They were randomly distributed into three groups: control (n=4), forced exercise (n=4) and fatigue-controlled (n=4) groups. The training intensity in the fatigue-controlled exercise was monitored by calculating the real-time mean power frequency (MPF) of EMG. The training intervention started from forty-eight hours after ICH surgery. Modified neurological severity score was applied daily during the following 13-day intervention to evaluate motor recovery. The results showed that fatigue-controlled group achieved the best motor recovery compared with the other two (P <control 0.05) .**

I. Introduction

Stroke is a leading cause of disability [1]. Spontaneous intracerebral hemorrhage (ICH) is common stroke subtype with a high mortality and morbidity [2][3]. ICH appears suddenly without warning, unlike ischemic strokes that are often preceded with a transient ischemic attack [4]. Motor recovery after ICH is associated with the initial severity of the bleeding [4], and is highly relied on the post-stroke rehabilitation [2][3]. However, with up to 40% of survivors not expected to recuperate independence from severe disablements [5]. One of the possible reasons is that overloaded physical training in early stage after stroke may exaggerate the brain lesion and result in limited motor recovery [5].

The traditional understanding on effective motor restoration depends on repeated and intensive limb practices as early as possible after stroke [8]. Treadmill running has been applied widely as a rehabilitation scheme in both clinical studies and animal models in early stroke rehabilitation [9][10]. Intensity is a key factor in treadmill training [11]. Since previous studies found that moderate treadmill training could upregulate brain-derived neurotrophic factor (BDNF)， which is related to neuroplasticity contributing to motor learning, recovery, and neural rehabilitation after stroke [12]. Overloaded exercises with high intensities (self-forced, or followed in a batch treatment) have been found to cause additional stress and release corticosterone, which could down regulate BDNF level in hippocampus and affect the post-stroke rehabilitation process [13][14]. Therefore, it is important to explore an optimized training intensity for individuals after stroke to obtain the maximized motor outcome with minimized brain lesion in early stroke rehabilitation.

Physical exercise inevitably will introduce fatigue to persons after stroke with individualized fatigue tolerance, due to diverse physical and psychological conditions. However, the conventional arrangements routine offig physical treatments on inpatients usually are uniformly administrated in batch for easy management. Currently, there is no effective method to quantify the fatigue level of stroke individual during post-stroke physical training. It could lead to varied rehabilitation outcomes, when the individual fatigue is unknown and treated with a uniform intensity to all patients [11]. Fatigue level during muscular exercise can be assessed by electromyography (EMG), since fatigue will lead to a shift in EMG spectral density towards lower frequencies and an increase or unchange in EMG amplitude **Error! Reference source not found.**, symbolized by a decrease in the mean power frequency (MPF) [16].

In this work, we developed an EMG based fatigue-controlled model with ICH rats, with the purpose to investigate the rehabilitation effects of treadmill training with a moderate fatigue level in individual subjects in early stage after stroke, compared with the conventional forced batch training and the control, i.e., without training.

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Yuchen Xu is with the Qiushi Academy for Advanced Studies, and the Department of Biomedical Engineering and Instrument Science, Zhejiang University, Hangzhou, China

Kedi Xu is with Qiushi Academy for Advanced Studies, Zhejiang University, Hangzhou, China.

Hao LYU, Stephanie NG and Wai Sang Poon are with Division of Neurosurgery, Department of Surgery, Prince of Wales Hospital, The Chinese University of Hong Kong, ShaTin, NT, HongKong, China.

Shaomin Zhang is Qiushi Academy for Advanced Studies of Zhejiang University, Key Laboratory of Biomedical Engineering of Ministry of Education, Zhejiang Provincial Key Laboratory of Cardio-Cerebral Vascular Detection Technology and Medicinal Effectiveness Appraisal, Hangzhou, Zhejiang, China; (corresponding author, Phone: +86 571 87952838; Fax: +86 57187952865; e-mail: shaomin@zju.edu.cn).

Yongping Zheng is with Dept. of Biomedical Engineering, The Hong Kong Polytechnic University, Hong Kong.

Xiaoling Hu is with Dept. of Biomedical Engineering, The Hong Kong Polytechnic University, Hong Kong. (Co-corresponding author; e-mail: xiaoling.hu@polyu.edu.hk)

II. Materials and Methods

A. *EMG electrodes implantation*

Twelve young male Sprague Dawley rats weight from 270g to 310g were used in this study. Rats were housed in a 12h light/dark cycle with free access to food and drink throughout the experimental period. Each rat was trained through an accommodation stage of 500 m treadmill running per day and lasted for three consecutive days before surgery. Rats were anesthetized with propofol (10mg/Kg, 10 ml/Kg body weight). Then the Teflon-coated stainless steel wires (AW633, Cooner Wire, USA) were implanted in the gastrocnemius muscle in the affected hindlimb. Biopolar electrodes were made by peeling insulation off the end of the wires with 2.5 cm. Cut a 2 cm long incision on the hindlimb, looping two electrodes around the muscle belly of medial gastrocnemius (MG) muscle and then passing them hypodermically from the incision to the exposed skull. Five 1 mm diameter holes were drilled on skull, settled a 3 pin connector on skull using five screws, four at the edge of parietal bone, and one at the post fontanelle, also used as ground. Two electrodes and a ground electrode were connected to the connector, by stabilizing the connector and screws on the skull with dental cement **Error! Reference source not found.**, the illustration of electrode implantation

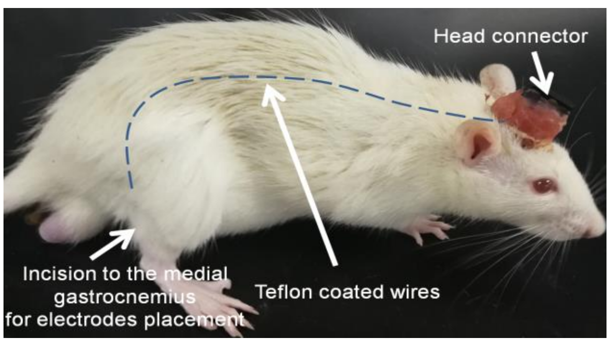

Fig. 1 Graphical illustration of the electrode implantation.

is shown in Fig. 1.

B. *ICH model*

After the EMG electrodes implantation, the rats received the ICH surgery. A hole above the striatum (0.2 mm anterior, 3.0 mm lateral to the bregma) was drilled on the skull [17]. A 26-G needle was inserted 6.0 mm deep over 5 minutes, and started infusion 5 minutes later for brain shape recovery. 1200 nL type IV collagenase (Sigma, C5138 0.25 U in 1000 nL NaCl 0.9%) was infused into the striatum over 6 minutes through micro infusion pump at a speed of 200 nL/min. After infusion, the needle was kept still for 15 minutes before withdraw to prevent backflow. Then remove the needle at a speed of 1.2mm/min. The hole was sealed with bone wax, the incision was closed, and the animals were kept warm and allowed to recover.

C. *Treadmill training.*

Forty-eight hours after ICH and electrodes implanted surgery, twelve rats were randomly divided into three groups, i.e., fatigue-controlled, forced training and control. We evaluated the motor impairments by modified Neurological Severity Scale (mNSS) everyday (from post stroke day 2 to post stroke day 14). The speed of the treadmill for the forced training group was 16m/min with duration of 30 min every day [18]. For the fatigue-controlled group, rats ran at an adaptable speed with the maximum of 16m/min. MPF represents the fatigue level, it declines when fatigue level increases [19]. We set 89% of the initial MPF (i.e., no fatigue) as the lower threshold in the work. We turned off the treadmill for 3 min if the MPF dropped to the MPF lower threshold, so the rats could have a rest, and started running again after recess, total duration was 30 min. No treadmill exercise was conducted in the control group, the detailed experiment procedures are shown in Fig. 2.

All surgery and experimental procedures conformed to the Guide for The Care and Use of Laboratory Animals (China Ministry of Health) and were approved by the

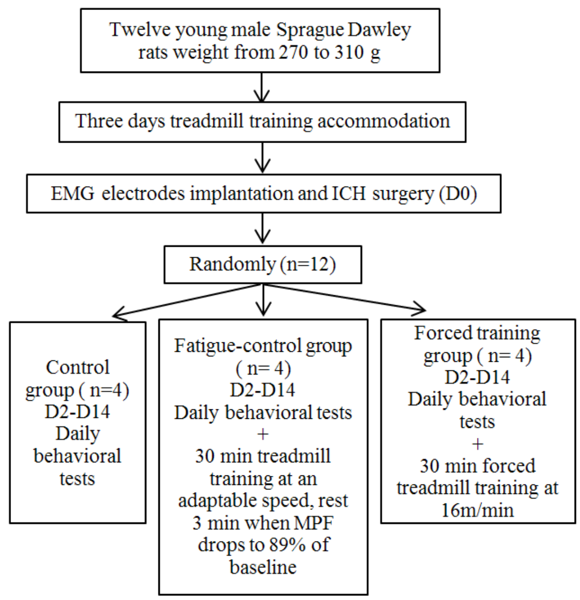

Fig. 2 The flow chart of the experiment procedure. All rats were accommodated to treadmill exercises for 3 days. EMG electrodes implantation and ICH surgery were conducted on D0. Treadmill exercise intervention was delivered to fatigue-controlled and forced training group from D2 to D14. Motor functions were evaluated daily.

Animal Care Committee of Zhejiang University, China.

D. *EMG processing*

EMG from MG was recorded by neural data acquisition system (Plexon Inc., USA), using a sampling rate of 20 kHz. The signals were segmented into 5s fragments and band-pass filtered (4th order Butterworth filter, 60-2000 Hz) in Matlab

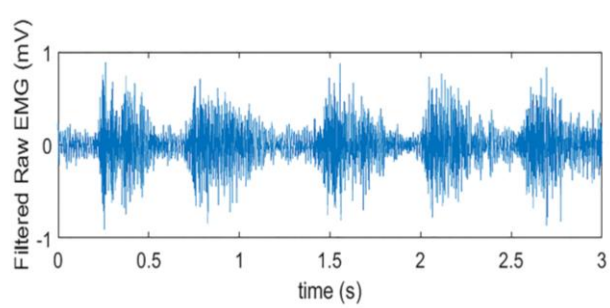

Fig. 3 The raw EMG signal during treadmill running, filtered by band-pass filter (4th order Butterworth filter, 60-2000 Hz).

Error! Reference source not found., typical EMG signals during treadmill running are shown in Fig. 3. The power spectrum density (PSD) was computed first by fast Fourier Transform (FFT), and the mean power frequency (MPF) during treadmill exercise was:

$$MPF = \frac{\int_0^\infty f \cdot m(f)df}{\int_0^\infty m(f)df} \quad (1)$$

where f is the frequency, $m(f)$ is the PSD of EMG signal. The MPF baseline was calculated through the first minute data, and the drop rate of MPF was related to the real-time MPF:

$$MPF\ drop\ rate = \frac{MPF_{Baseline} - MPF_{Real-time}}{MPF_{Baseline}} \cdot 100\% \quad (2)$$

E. Statistical analysis

The behavioral tests were carried out by experimenters who were blinded to the group identity. The baselines of three groups were compared by one-way ANOVA with an insignificant statistical difference (P > 0.05). We evaluated the motor recovery among three different groups by two-way analysis of covariance (ANCOVA). The independent factors were groups (i.e., fatigue-controlled, forced training, and control groups) and behavioral scores at different timepoints (i.e., D3 … D14). Take the baseline behavioral score (i.e., assessments on D2) as a covariate. Then we compared the between-group behavioral scores at different timepoints by one-way ANCOVA with Bonferroni post hoc tests, the covariate was mNSS score on D2. Finally, we investigated whether behavioral score showed significant difference at different time points in each group by one-way analysis of variance (ANOVA) with Bonferroni post hoc tests [20]. The levels of statistical significance were indicated at 0.05, 0.01 and 0.001 in this study.

III. Results

Behavioral scores in Fig. 4 indicated motor function recovery for the three groups during the experiment periods (post-stroke D2 to D14). The one-way ANOVA tests with *post hoc* tests implied significant motor function improvements for the three groups, which showed that in the early stage after ICH (subacute period), there was spontaneous motor function recovery (P < 0.001), and both forced and fatigue controlled treadmill intervention led to the motor function rehabilitation.

Significant differences were observed with respect to the factors of groups and time points between the three groups (P < 0.001, Table 1). The *post hoc* tests showed that compared to the control group, the interactions between groups and time points were statistically significant in the fatigue-controlled (P < 0.001, Table 1) and force training groups (P < 0.05, Table 1).

It suggested that the fatigue-controlled group obtained better motor function recovery compared with the forced training group. However, there was no significant difference between fatigue-controlled and forced training group with respect to the interaction of groups and time points (P = 0.196, Table 1).

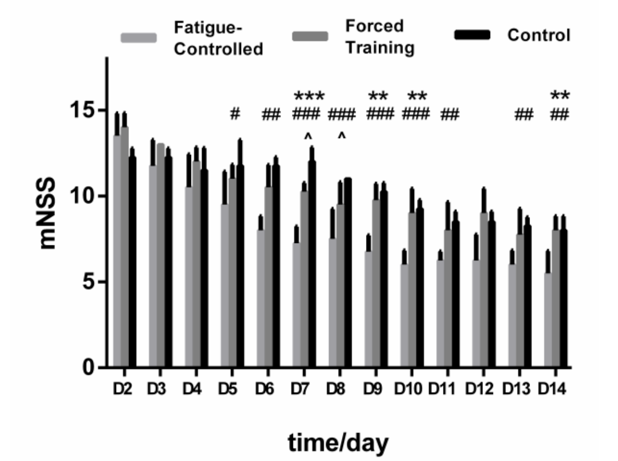

Fig. 4 The behavioral assessments evaluated by mNSS in Fatigue Control, Forced Training and Control groups from post-stroke D2 to D14. Differences with statistical significance are marked with superscripts above daily mNSS scores. (" * " represent significant difference between fatigue control group and forced training group, " # " stands for significant difference between fatigue-controlled group and control group, " ^ " for significant difference between forced training group and control group). Significant levels are indicated as, 1 superscript for < 0.05, 2 superscripts for ≤ 0.01, 3 superscripts for ≤ 0.001.

TABLE 1 The statistical probabilities of one-way ANOVA on intra-group motor function increments and two-way ANCOVA on the factors of groups and timepoints.

mNSS	**2-way analysis of covariance**		
	P (Partial η^2)		
	Time point	***Group***	***T*G***
3 groups	*0.000+ + +* *(0.795)*	*0.000+ + +* *(0.705)*	*0.000+ + +* *(0.383)*
Fatigue-controlled Forced training	0.000*** (0.809)	0.000*** (0.519)	0.196 (0.177)
Fatigue-controlled Control	0.000*** (0.829)	0.000*** (0.765)	0.000*** (0.477)
Forced training Control	0.000*** (0.756)	0.000*** (0.242)	0.024* (0.266)

Differences with statistical significance are marked with superscripts besides the P values (" + " for 2-way ANCOVA tests on the group and time point effects with the D2 mNSS scores as the covariate, " * " for post hoc tests for 2-way ANCOVA tests), Significant levels are indicated as, 1 superscript for < 0.05, 2 superscripts for ≤ 0.01, 3 superscripts for ≤ 0.001.

In the between-group comparison, significant decrease in the mNSS score was observed in the fatigue-controlled group from post stroke D5 to D14 (P < 0.05, P < 0.001, Table 2, Fig. 4) excepted D12 (P = 0.175, Table 2, Fig. 4) compared to the control group. It indicated that the fatigue-controlled exercise scheme could improve and accelerate the motor function recovery. In the middle and late stages of the experiments (D7, D9, D10, D14), the fatigue-controlled group showed better motor function recovery in comparison with forced training group (D7: P = 0.001, D9: P = 0.004, D10: P = 0.008, D14: P = 0.01, Table 2, Fig. 4) with statistical significance. It suggested that the training intensity would affect the rehabilitation outcome, and a moderate fatigue level as controlled in this work could achieve better motor improvement than the forced training, where fatigue level was uncontrollable for the individual rats. It was also observed that forced training group showed significant lower mNSS score compared with control group on D7 and D8 ($P < 0.05$, Table 2, Fig. 4) and no significant difference on the following days (D9 - D14). It suggested that the forced training exercise scheme might not be helpful for motor function recovery in long term rehabilitation.

TABLE 2. THE STATISTICAL PROBABILITIES OF ONE-WAY ANCOVA ON ON THE RESPECTIVE TIMEPOINT BETWEEN GROUPS, BY TAKING D2 MOTOR ASSESSMENTS AS THE COVARIATE.

Time point	**1-way ANCOVA**		
	Fatigue-controlled Forced training	***Fatigue-controlled Control***	***Forced training Control***
D5	1.000	$0.040^{\#}$	0.232
D6	*0.102*	$\mathit{0.007}^{\#\#}$	*0.259*
D7	*0.001****	$\mathit{0.000}^{\#\#\#}$	*0.029^*
D8	*0.178*	$\mathit{0.001}^{\#\#\#}$	*0.019^*
D9	*0.004***	$\mathit{0.000}^{\#\#\#}$	*0.081*
D10	*0.008***	$\mathit{0.000}^{\#\#\#}$	*0.062*
D11	0.209	$0.009^{\#\#}$	0.214
D12	0.067	0.175	1.000
D13	0.143	$0.005^{\#\#}$	0.140
D14	0.010**	$0.003^{\#\#}$	0.637

Differences with significance are marked with superscripts beside the P value. (“ * ” represent significant difference between fatigue control group and forced training group, “ # ” stands for significant difference between fatigue-controlled group and control group, “ ^ ” for significant difference between forced training group and control group). Significant levels are indicated

IV. CONCLUSION

In this work, the effects of EMG based fatigue-controlled treadmill training in early stage after ICH were investigated, and compared with those by the forced batch training and with no rehabilitation. The fatigue-controlled group showed a significant improvement in motor function compared to the forced training and control groups. However, the forced training did not show significant improvement compared to the control group, maybe mNSS is not sensitive enough to distinguish between the two groups. Physical training with an intensity of moderate fatigue level would improve and accelerate the motor function rehabilitation. Further studies are needed to explore the rehabilitative effects with more rats, as well as the effects of different fatigue levels on the motor recovery. Besides, the mechanisms of the behavioral results should be explored in molecular level, to figure out the relationship between exercise intensity, neurotrophic factors and stress.

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