

Dear Lian-Sheng Ma, Jin-Lei Wang, and the reviewer 1,

I wish to give my hearty thanks to all of you for outstanding, high-quality comments on my manuscript. According to the comments of all of you, I did my best to revise my manuscript point by point.

#1 Dear Lian-Sheng Ma,

Please provide and upload the approved grant application form(s).

>>>They are uploaded into the electronic system.

Would you like to keep only one address?

>>> I would like to keep both addresses.

Under the heading of Case Presentation, the following seven aspects must be presented in this order.

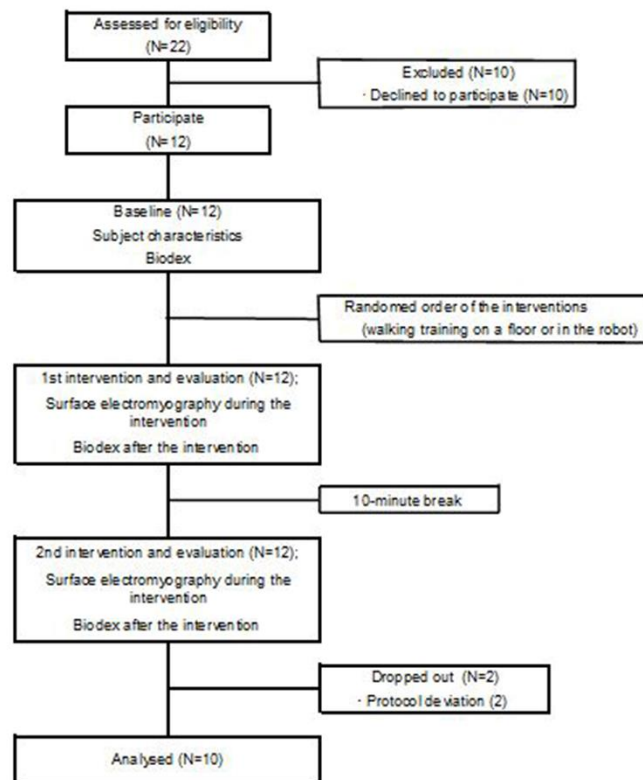
>>>In case of medical journals, it is very important to keep manuscripts being published in the very organized order as your recommendation. However, as you can see that, my manuscript is a case series, not a classical case report, including 12 patients. So, would you mind my requesting of keeping the current format of the case series? It will contribute to the enhanced readers' comprehension on my study. However, if you think it should be changed, I am sure to revise the case series presentation section according to the suggested order by you.

Please add or move the related information under those subtitles.

>>>Because of the same reason (case series of 12 patients focusing on cross-sectional comparisons of intervention efficacy), the related information is difficulty being filled up. However, if you think it should be added, I am ready to do that.

We found that the content of the figures cannot be edited by our staff. Authors have to provide the figures as separate electronic files. Please upload the figures in the following vector or bitmap formats so that we will be able to edit them:

>>>That figure is uploaded in the Bitmap formats (TIFF) as followed.



#2 Dear Jin-Lei Wang,

What are the original findings of this manuscript?

>>>The original findings are described in the first paragraph of the discussion section as followed.

“... muscles were compared. The keys findings were 1) PT of the dominant knee flexor and extensor muscles significantly improved 10 minutes after both of the five-minute interventions, and the degree of improvement was significantly larger in the gait robot than on the floor; and 2) the real-time EMG activities of the dominant thigh and shank muscles were much more lower in the gait robot than those for the floor.”

What are the new hypotheses that this study proposed?

>>>The new hypotheses are described in the introduction section as followed.

“... concept approval. Author supposed that an end-effector type gait robot could provide patients with a training condition that was specific enough to activate rapid cortical plasticity and spinal motor neuron excitability, leading to immediate muscle strengthening throughout the legs.”

What are the new phenomena that were found through experiments in this study?

>>>The new phenomena are that just 5-minute EEGR training induced immediate strengthening of the knee flexors and extensors, despite reduced muscular use. The effect was maintained for 10 minutes. They are described in the conclusion section as followed.

“Five-minute end-effector type robot-assisted gait training with non-weight bearing on their feet and 100% guidance force might induce immediate strengthening of the dominant knee flexor and extensor muscles which was maintained for 10 minutes and accompanied by the simultaneous reduction of the usage of the thigh and calf muscles.”

What are the hypotheses that were confirmed through experiments in this study?

>>>It was confirmed through the current study that the EEGR could provide patients with a training condition, leading to immediate muscle strengthening throughout the legs.

What are the quality and importance of this manuscript?

>>>The quality and importance of this manuscript are described in the core tip as followed.

“... calf muscles. It may be a useful tool to strengthen the leg muscles in the elderly or in patients with musculoskeletal injuries. As for its underlying mechanism, author...”

What are the new findings of this study?

>>>The new findings are that just 5-minute EEGR training induced immediate strengthening of the knee flexors and extensors, despite reduced muscular use and the effect was maintained for 10 minutes.

What are the new concepts that this study proposes?

>>>The new concepts are that EEGR may be useful to non-CNS injured, elderly or deconditioned patients as well as CNS-injured patients. They are described in the introduction section as followed.

“Various kinds of gait robots have been developed for rehabilitation of various conditions. Their clinical application has been mostly focused on stroke[1] and spinal cord injury patients.[2] In case that patients cannot walk due to paralysis of the lower legs, long-term brain plasticity can be evoked if patients with injuries of the central nervous system (CNS) can walk repeatedly with the help of gait robots.[3] Meanwhile, a significant number of patients who cannot walk themselves show different underlying causes such as

deconditioning in the very elderly, restricted weight bearing of the legs due to musculoskeletal injuries, or poor muscular activation from pain rather than paraparesis. Gait robots can control patients' weight bearing and leg movement as well as provide body support for the deconditioned elderly patients to stand. However, there are few reports on whether gait robots could contribute to strengthening the muscles of the lower legs in able-bodied patients, who are different from those with CNS injuries."

What are the new methods that this study proposed?

>>>The new method is the EEGR training for leg strengthening. It is described in the case series presentation section as followed.

"... comfortable pace [control] or in the end-effector type gait robot [Morning Walk[®], Hyundai Heavy Industry, South Korea] with non-weight bearing, with 100% guidance force at the speed of 2.1 km/hour [case])."

Do the conclusions appropriately summarize the data that this study provided?

>>>I am sure. However, if you think more adding is needed, please let me know. I am ready to do that.

What are the unique insights that this study presented?

>>>The new unique insights are that EEGR can induce immediate muscle strengthening throughout the legs, through the rapid brain and spinal plasticity in theory.

What are the key problems in this field that this study has solved?

>>>The solved key problems are that a significant number of patients who cannot walk themselves due to deconditioning status, very advanced age, restricted weight bearing of the legs by musculoskeletal injuries, or poor muscular activation from pain may participate in rehabilitation easier with the help of EEGR than the classical training on a floor. They are described in the discussion and conclusion section as followed.

"It is well-known that muscle volume declines with aging or during prolonged bed rest. The decrease in muscle mass and the inappropriate muscle strength contribute to the deficient physical performance. Moreover, such age-related decline can occur in the region-specific manner as well as between muscles.^[29] That kind of differential atrophy can be also noticed during medical deconditioning state.^[30] Meanwhile, knee extensors are significantly related with leg performance,^[31] and the greatest atrophy is noticed in the calf musculature, followed

by the knee extensors and flexors in deconditioning-induced atrophy.^[30] Taken into consideration of two aforementioned reports, it may be clinically significant that increased muscle strength of knee flexor and extensor was noticed in the current trial. However, muscle strength is closely related to the muscle balance in frail or elderly people.”

“... usage of the thigh and calf muscles. It may be a useful tool to strengthen the leg muscles in the elderly or in patients with musculoskeletal injuries.”

What are the limitations of the study and its findings?

>>>The limitations are described in the discussion section as followed.

“This trial is a cross-sectional, non-randomized, single-center study. The recruited subjects were young to middle ages with relatively healthy status. In a further trial, some elderly patients should be recruited for study because they will be the target for potential application. It also needs to be applied in different groups of patients with musculoskeletal injuries in comparison to healthy adults. Even though preemptive calculation on the number of participants was performed, the small sample size is a major limitation in the present study. Instead of the within-patients comparison, an appropriate control group should be included. Regarding the study about the muscle strength, the data of body composition that is important for basic information, especially for such development of new device, should be included. Walking speed may affect the EMG activities of the lower leg muscles.^[34] Cortical activation measured by spectroscopy and lower leg muscles activities measured by surface electromyography were proportionally increased as gait speed increased in the exoskeleton robot (from 1.5 to 3.0 km/hour and 2.7 to 6.2 km/hour) in healthy people.^[19, 34] Although no change of muscle activities was also reported in the range of 1.5 to 2.7 km/hour in healthy people,^[22] it is uncertain if 2.1 km/hour of gait speed could be ideal for the current evaluation. Additionally, the different number of steps and the different walking speed between the two interventions could affect the current findings. Although the ground reaction forces in end-effector robots are changeable in different gait conditions,^[35] this factor was not evaluated. Furthermore, rapid CNS plasticity was not evaluated in terms of electrical evoked potential, H-reflex, or spectroscopy.”

What are the future directions of the topic described in this manuscript?

>>>The future directions of the topic are the approval of EEGR-induced rapid brain and

spinal plasticity. They are described in the discussion section as followed.

“... was not evaluated. Furthermore, rapid CNS plasticity was not evaluated in terms of electrical evoked potential, H-reflex, or spectroscopy.”

What are the questions/issues that remain to be solved?

>>>They are whether EEGR can induce the rapid brain and spinal plasticity in the elderly or in the patients with musculoskeletal injuries. They are described in the discussion section as followed.

“... single-center study. The recruited subjects were young to middle ages with relatively healthy status. In a further trial, some elderly patients should be recruited for study because they will be the target for potential application.”

What are the questions that this study prompts for the authors to do next?

>>>It is whether the rapid brain and spinal plasticity can be approved, using multi-modality-mediated evaluations. They are described in the conclusion section as followed.

“... musculoskeletal injuries. To prove the rapid brain and spinal plasticity in therapy as it's underlying mechanism, author has been conducting an electrophysiology-, biomechanics-, computer tomography-based randomized, controlled trial using the end-effector type gait robot, based on the literature review.”

How might this publication impact basic science and/or clinical practice?

>>>This paper will be of interest to the readership because major interest of your journal's readers is its clinical application on an emerging field; rapid CNS neuroplasticity can be tried into immediate peripheral neuro-muscular strengthening strategies in safety.

#3 Dear the reviewer 1,

This manuscript reported an interesting study on the application of EEGR to improve the strength of knee flexors and extensors immediately after 5 min training program. It may be a potential application for the elderly patients in the future to prevent frailty. However, this study needs more evidence to achieve such a conclusion. More issues are needed to be addressed before considering for publication in World Journal of Clinical Cases.

1. The recruited subjects were young to middle ages with relatively healthy status. Regarding the study about the muscle strength, the data of body composition is important for basic information, especially for such development of new device. In addition, some elderly patients should be recruited for study because they will be the target for potential application.

>>>I am totally agreed with your opinion. The basic data of weight and height is incorporated in the manuscript in the form of Table 1 as followed.

Subjects	Age (years)	Sex	Weight (kg)	Height (cm)	Evaluated Side	Walking speed on a floor (km/hour)	Protocol deviation
001	34	M	81.3	176.8	Right	2.3	+
002	38	F	70.0	163.1	Right	2.4	
003	27	M	78.0	177.9	Right	2.1	
004	34	M	85.0	172.9	Right	2.8	
005	28	M	85.0	186.1	Right	2.6	
006	30	F	50.3	160.5	Right	2.1	
007	22	F	54.0	156.2	Right	2.5	
008	24	F	70.0	169.8	Right	2.4	
009	35	M	74.0	178.0	Left	2.9	
010	24	M	70.0	180.1	Right	3.1	
011	49	M	60.0	174.9	Left	2.8	
012	45	F	63.0	174.0	Right	2.0	+

>>>The current trial was a prospective one and was approved from the IRB, based on the current design. As for getting more details of the body composition such as BMI, I am not permitted to call patients in and conduct further evaluations. Instead, I inserted your opinions in the limitation section as followed.

“... group should be included. Regarding the study about the muscle strength, the data of body composition that is important for basic information, especially for such development of new device, should be included.”

>>>With the same reason, I cannot recruit some elderly patients any more. Instead, I inserted your opinions in the limitation section as followed.

“... single-center study. The recruited subjects were young to middle ages with relatively

healthy status. In a further trial, some elderly patients should be recruited for study because they will be the target for potential application.”

2. The study is a cross-sectional, non-randomized study. In addition, this is an one author article. It means impossible to conduct a single-blinded study. Therefore more studies are needed to be done and proved the effects.

>>>I am absolutely agreed with your opinion. So, that limitation is descried in the limitation section as followed.

“This trial is a cross-sectional, non-randomized, single-center study. Therefore more studies are needed to be done and proved the effects.,,,”

The author needed to explain the criteria of appropirate controls in this study.

>>>To be a more qualified trial, it is essential that an appropriate control group is included, as your comments. However, our trial is a case series in which within-individual change was compared between before and after the intervention such that no criteria for control group could be explained. To make it clear, revision was made in the case series presentation and limitation section as followed.

“... Medical band, during the intervention (five-minute walking training on an even floor at a comfortable pace [control] or in the end-effector type gait robot [Morning Walk[®], Hyundai Heavy Industry, South Korea] with non-weight bearing, with 100% guidance force at the speed of 2.1 km/hour [case]). Each order of the two consecutive interventions was determined randomly and then both interventions were provided to the same patients.”

“... limitation in the present study. Instead of the within-patients comparison, an appropriate control group should be included.”

Some parameters may need be revised for optimal or better outcomes. This preliminary data may be more valuable and supported by a well-designed study.

>>>I am totally agreed with your comments in principle. However, the peak torque and the maximal ratio of torque development in the table 2 were standardized using body weight of each subject. The real-time EMG findings in the table 3 may need be revised, as your comments. However, the real-time EMG data (mean amplitude, peak amplitude, mean value of AUC, and total value of AUC) are not the raw ones. The method with which they were selectively collected and were standardized was described in the case presentation section as followed. Nonetheless, if you let me know another method for data standardization, I am sure to try to fit it into our EMG data.

“... electromyography (WEMG-8, LAXTHA, Republic of Korea). The moving average of smoothed electrical signals that lasted for at least one second was determined and divided by the baseline amplitude of CMAP to obtain the standard value.”

3. Regarding the mechanisms, the author has been conducting an electrophysiology-, biomechanics-, computer tomography-based randomized, controlled trial using the end-effector type gait robot to prove the rapid brain and spinal plasticity as it's underlying mechanism. This may also need time and research designs.

>>>Of course, the more well designing, the better. We are glad to be conducting the RCT, as your suggestion. To make it clear, the followings were described in the core tip section and the conclusion section.

“... with musculoskeletal injuries. As for its underlying mechanism, author supposes the rapid brain and spinal plasticity **in theory.**”

“... musculoskeletal injuries. To prove the rapid brain and spinal plasticity **in theroy** as it's underlying mechanism, author has been conducting an electrophysiology-, biomechanics-, computer tomography-based randomized, controlled trial using the end-effector type gait robot, **based on the literature review.**”

4. Muscle strength is closely related to the muscle balance. The clinical significance of increased muscle strength of knee flexor and extensor should be discussed, expecially no effects of study on other muscle groups. The authors also should provide an effective way to control a proper muscle balance.

>>>According to your comments, I inserted a new paragraph in the discussion section and related references in the references section as followed.

“It is well-known that muscle volume declines with aging or during prolonged bed rest. The decrease in muscle mass and the inappropriate muscle strength contribute to the deficient physical performance. Moreover, such age-related decline can occur in the region-specific manner as well as between muscles.^[29] That kind of differential atrophy can be also noticed during medical deconditioning state.^[30] Meanwhile, knee extensors are significantly related with leg performance,^[31] and the greatest atrophy is noticed in the calf musculature, followed by the knee extensors and flexors in deconditioning-induced atrophy.^[30] Taken into consideration of two aforementioned reports, it may be clinically significant that increased muscle strength of knee flexor and extensor was noticed in the current trial. However, muscle

strength is closely related to the muscle balance in frail or elderly people. Because no effects was found on other muscle groups, effective way to control a proper muscle balance should be provided. Resistance exercise training is known to alleviate aging-associated type II myofiber atrophy through the increased muscle protein synthesis.^[32] Functional electrical stimulation can modulate characteristics of muscle fibers so that it can be an alternative, especially in those who unable to perform physical activities or elderly people.^[33]”

“29 Watanabe K, Kouzaki M, Moritani T. Effect of aging on region-specific functional role and muscle geometry along human rectus femoris muscle. *Muscle & nerve* 2017; 56(5): 982-986 [PMID: 28044357 DOI: 10.1002/mus.25556]

30 Miokovic T, Armbricht G, Felsenberg D, Belavy DL. Heterogeneous atrophy occurs within individual lower limb muscles during 60 days of bed rest. *Journal of applied physiology* (Bethesda, Md : 1985) 2012; 113(10): 1545-1559 [PMID: 22984243 DOI: 10.1152/japplphysiol.00611.2012]

31 Visser M, Newman AB, Nevitt MC, Kritchevsky SB, Stamm EB, Goodpaster BH, Harris TB. Reexamining the sarcopenia hypothesis. Muscle mass versus muscle strength. Health, Aging, and Body Composition Study Research Group. *Annals of the New York Academy of Sciences* 2000; 904: 456-461 [PMID: 10865789]

32 Liao CD, Tsao JY, Wu YT, Cheng CP, Chen HC, Huang YC, Chen HC, Liou TH. Effects of protein supplementation combined with resistance exercise on body composition and physical function in older adults: a systematic review and meta-analysis. *The American journal of clinical nutrition* 2017; 106(4): 1078-1091 [PMID: 28814401 DOI: 10.3945/ajcn.116.143594]







33 Carraro U, Kern H, Gava P, Hofer C, Loeffler S, Gargiulo P, Mosole S, Zampieri S, Gobbo V, Ravara B, Piccione F, Marcante A, Baba A, Schils S, Pond A, Gava F. Biology of Muscle Atrophy and of its Recovery by FES in Aging and Mobility Impairments: Roots and By-Products. *European journal of translational myology* 2015; 25(4): 221-230 [PMID: 26913160 PMCID: PMC4748978 DOI: 10.4081/ejtm.2015.5272]

34 Hof AL, Elzinga H, Grimmius W, Halbertsma JP. Speed dependence of averaged EMG profiles in walking. *Gait & posture* 2002; 16(1): 78-86 [PMID: 12127190]

35 Tomelleri C, Waldner A, Werner C, Hesse S. Adaptive locomotor training on an end-effector gait robot: evaluation of the ground reaction forces in different training conditions. *IEEE International Conference on Rehabilitation Robotics : [proceedings]* 2011; 2011:

5975492 [PMID: 22275689 DOI: 10.1109/icorr.2011.5975492]”

>>>As for need to take a minor language polishing, I attached the certification of quotation service as followed.

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This document certifies that the paper listed below has been edited to ensure that the language is clear and free of errors. The logical presentation of ideas and the structure of the paper were also checked during the editing process. The edit was performed by professional editors at Editage, a division of Cactus Communications. The intent of the author's message was not altered in any way during the editing process. The quality of the edit has been guaranteed, with the assumption that our suggested changes have been accepted and have not been further altered without the knowledge of our editors.	
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Nikesh Gosalia, Vice President, Author Services, Editage	
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