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Abstract:	Electrical stimulation (EStim) refers to the application of electrical current to muscles or nerves in order to achieve functional and therapeutic goals. It has been extensively used in various clinical settings. Based upon recent discoveries related to the systemic effects of voluntary breathing and intrinsic physiological interactions among systems during voluntary breathing, a new EStim protocol - Breathing-controlled electrical stimulation (BreEStim) has been developed to augment the effects of electrical stimulation. In BreEStim, a single-pulse electrical stimulus is triggered and delivered to the target area when the airflow rate of an isolated voluntary inspiration reaches the threshold. BreEStim integrates intrinsic physiological interactions that are activated during voluntary breathing and has demonstrated excellent clinical efficacy. Two representative applications of BreEStim are reported with detailed protocols: management of post-stroke finger flexor spasticity and neuropathic pain in spinal cord injury.
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Breathing-Controlled Electrical Stimulation (BreEStim) for Management of Neuropathic Pain and Spasticity

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Short Abstract: The purpose is to present a new method, breathing-control electrical stimulation – BreEStim, for management of neuropathic pain and spasticity.

Long Abstract

Electrical stimulation (EStim) refers to the application of electrical current to muscles or nerves in order to achieve functional and therapeutic goals. It has been extensively used in various clinical settings. Based upon recent discoveries related to the systemic effects of voluntary breathing and intrinsic physiological interactions among systems during voluntary breathing, a new EStim protocol – Breathing-controlled electrical stimulation (BreEStim) has been developed to augment the effects of electrical stimulation. In BreEStim, a single-pulse electrical stimulus is triggered and delivered to the target area when the airflow rate of an isolated voluntary inspiration reaches the threshold. BreEStim integrates intrinsic physiological interactions that are activated during voluntary breathing and has demonstrated excellent clinical efficacy. Two representative applications of BreEStim are reported with detailed protocols: management of post-stroke finger flexor spasticity and neuropathic pain in spinal cord injury.

Introduction

Electrical stimulation (EStim) refers to the application of electrical current to muscles or nerves in order to achieve functional and therapeutic goals. It has been extensively used in various clinical settings, e.g., transcutaneous electrical nerve stimulation (TENS) for pain management[1], peroneal nerve stimulation for foot drop[2], neuromuscular electrical stimulation (NMES) for activation and strengthening of paralyzed or weakened muscles[3]. When NMES is used to achieve a functional task, it is termed functional electrical stimulation (FES)[4]. Electromyogram (EMG)-triggered neuromuscular stimulation has been used to augment effectiveness of electrical stimulation in motor recovery [5-14] and spasticity reduction after stroke [7, 15]. In this paper, a new EStim protocol – Breathing-controlled electrical stimulation (BreEStim), is introduced, according to recent research findings on the systemic effect of voluntary breathing[16, 17].

Transcutaneous electrical nerve stimulation (TENS) is a non-pharmacological modality for pain management[1]. TENS is noninvasive, inexpensive, safe and easy to use[18]. TENS is usually applied at varying frequencies, intensities, and pulse durations of stimuli for a prescribed treatment time. TENS has been applied to a variety of pain conditions, including neuropathic pain. The clinical effectiveness of TENS is controversial, particularly in spinal cord injury (SCI) and amputation (see Reviews [1, 19, 20]). The possible mechanisms are the gate control theory [21] and the release of endogenous opioids [22, 23]. Acupuncture from Traditional Chinese Medicine is another non-pharmacological modality for pain management. It has been well accepted in Western Medicine[24]. In modern acupuncture, the traditional acupuncture needle has been replaced by a surface electrode (or equivalent). A specialized electrode is place over traditional acupoints and an electrical stimulation is delivered. This modification has been termed electroacupuncture[25, 26]. Needle acupuncture and electroacupuncture are both effective in analgesia via the release of endogenous opioids [27, 28]. The effect of electroacupuncture is usually reliable, however the effect is dependent on intensity and frequency of delivered electrical stimulation. Different frequencies of electrical stimulation generate different endogenous opioids, and the analgesic effect is naloxone-reversible [26, 27]. Recently, it has been found that repetitive painful stimulation (aversiveness) leads to significant pain attenuation. The induced pain attenuation is not naloxone-reversible [29]. Integrating of these pain coping mechanisms (acupuncture, electrical stimulation, aversiveness) into a possible new intervention could improve its clinical efficacy.

EMG-triggered neuromuscular stimulation has been used for many years to facilitate post-stroke motor recovery of finger extension impairments [5-10, 12-14, 34]. Recovery of hand function is important for stroke patients, and yet is very challenging. Roughly one third of all people who experience a stroke will have some residual impairment of the upper extremity [30-32], with major impairments in hand function [33]. The EMG-triggered NMES intervention protocol involves initiation of a voluntary contraction of extensor muscles for a specific movement until the muscle activity reaches a threshold level. As soon as the EMG activity reaches a target threshold, an assisting electrical stimulus begins to facilitate the movements. This intervention protocol is superior to regular NMES in motor recovery[6, 7]. Chae and Yu [35] stated that all

randomized controlled studies reported improvement in motor function using this intervention protocol, with mild to moderately impaired patients improving the most. It is most likely that this intervention takes advantage of active engagement of patients (by setting a target EMG threshold) and this results in measureable changes in recovery as well as documented changes in the cortex[6, 7]. This is supported by a recent functional MRI study that showed a significant increase in cortical intensity in the ipsilateral somatosensory cortex after treatment in the NMES group, as compared with the control group[36]. Furthermore, electrical stimulation may also help to reduce spasticity after stroke[7, 15], but the effect is short-lasting, about 30 minutes after EStim[37]. In contrast, our recent invention of breathing-controlled electrical stimulation (BreEStim) has a long-lasting effect on spasticity reduction, even after a single session of treatment [16].

Human breathing is a very unique motor act. It can be controlled reflexively (automatic breathing), e.g., during sleep, and also voluntarily when needed (voluntary breathing), e.g., singing, speech, etc. During voluntary breathing, humans need to voluntarily suppress autonomic control of breathing through voluntary cortical activation (the “cortical respiratory center”) [38, 39]. Brain imaging studies [40-51] have demonstrated extensive respiratory-related involvement of cortical areas bilaterally, including the primary motor cortex (M1), the premotor cortex, the supplementary motor area, the primary and secondary somatosensory cortices, the insula, the anterior cingulate cortex and amygdala, and the dorsolateral prefrontal cortex. The insula is known to have strong connections to brainstem centers and is involved in pain processing [52]. During autonomic breathing, inspiration is active while expiration is passive, mainly relying on recoil force of the chest wall. Similarly, volitional inspiration activates more respiratory-related cortical and subcortical areas when compared to volitional expiration [46]. These cortical and subcortical areas activated during voluntary breathing are also involved in different functions [53], such as muscle tone, pain, posture, mood, speech, etc. Therefore, it is not unreasonable to associate interactions in breathing with modulation of other functions.

Recently, we have discovered that there exist interactions between respiratory and motor systems during voluntary breathing. Specifically, there is a finger extension-inspiration coupling [16, 54-56]. When electrical stimulation is delivered to the finger extensors during the inspiratory phase of voluntary breathing, a long-lasting effect of reduction in finger flexor spasticity (muscle tone) in chronic stroke patient is observed [16]. In another study [17], shooting phantom pain in a patient with an above-the-knee amputation disappeared after the BreEStim treatment, but re-appeared 28 days later after receiving a sustained electrical stimulation accidentally. This case study provides a unique opportunity to understand that the affective component of noxious stimuli of neuropathic pain (shooting phantom pain) has been modified by the BreEStim treatment, but then re-triggered by an accidental stimulation. These observations of tone and pain reduction have demonstrated that voluntary breathing, inspiration in particular, could be integrated into an electrical stimulation paradigm to improve its efficacy in neuropathic pain management and post-stroke spasticity management.

Case presentations

Case 1: Post-stroke spasticity management

The patient was a 69 years-old male who had right hemiplegia secondary to a stroke 22 months ago. He was medically stable and had been discharged from outpatient physical and occupational therapy programs. No brain imaging results were available at the time of experiments. He had weakness on his right side but was able to walk independently without an assistive device. He had residual voluntary finger flexion and extension, but with limited active range of motion at his right metacarpophalangeal (MCP) joints, from 90˚ to 70˚ of MCP flexion, i.e., not able to sufficiently open his hand and fingers for functional use. Muscle tone of his right finger flexors was moderately increased. Modified Ashworth Scale (MAS) was 1+. Sensation of his right hand and fingers, however, was intact to light touch. He received approximately a 30-min BreEStim to the finger extensors. His finger flexor spasticity decreased to minimum (MAS=0) and voluntary finger extension became nearly normal immediately after the treatment. This patient regained his hand function as well. He reported that he could cut meat with a knife and button shirts using his impaired hand. More strikingly, the recovery retained at least 8 weeks during follow-up visits (Figure 1).

Case 2: Neuropathic pain management

The patient was a 40 years-old male who suffered a spinal cord injury 4.5 years ago in a motor vehicle accident, resulting in T8 ASIA A spinal cord injury. The patient complained of neuropathic pain at the injury level, while he had no other active medical issues. He had been stable on a pain regime for 2 weeks prior to the treatment. He received EStim (one session per day for five consecutive days) first, waited 1 week as a washout, and then received BreEStim with the same dose (one session per day for 5 consecutive days). Each treatment session consisted of 120 stimuli (EStim or BreEStim). Surface electrodes were placed on acupoints (Neiguan and Weiguan) of the right forearm. Modified Visual Analogue Scale (mVAS) was used to compare the effect of each intervention (EStim and BreEStim). As shown in Figure 2, BreEStim had a greater pain reduction effect than EStim, except for Day 2 during BreEStim when the patient had a urinary tract infection (UTI) which was successfully treated with antibiotics. The intensity of electrical stimulation was similar between EStim and BreEStim (Figure 2). He tolerated both interventions well (maximum output intensity from the stimulator was used), even during the UTI. During the entire experimental period (4 weeks), the subject maintained the same dose and schedule of pain medications. Both BreEStim and EStim treatment sessions were performed at the same time of the day (between 11Am to Noon), such that changes in the pain rating could possibly be attributed to stimulation effects and not diurnal variation.

Protocol: The following BreEStim protocol could be applied for both finger flexor spasticity and neuropathic pain management. The main difference lies in surface electrode placement and adjustment of stimulation intensity. These differences are explained in detail for each application.

1. Subject preparation and setup

    1.1. Seat the subject comfortably. Place the arms and hands comfortably on the treatment table.

    1.2. Identify and localize the area of interest for surface electrode placement.

        1.2.1. For spasticity management, palpate the muscle belly of finger extensors and confirm with electrical stimulation.

1.2.2. For pain management, locate acupuncture points of Neiguan and Weiguan on the forearm[24] ipsilateral to the side of interest, e.g., amputation[17], or on the side with more symptoms, e.g., SCI. Neiguan is located about 3-finger width above the wrist crease on the volar side and in the middle between medial and lateral boards of the forearm (i.e., distal 1/6 of the forearm)[24] (Figure 3). Weiguan is the counterpart of Neiguan, located in the dorsal aspect of the forearm[24].

1.3. Trim each self-adhesive electrode to about a 2cm x 2cm square to provide focal and isolated electrical stimulation.

1.3.1. For spasticity management, place the cathode over the finger extensor muscle belly (Figure 4). Attach the anode to a site 1~2 cm distal to the cathode. Optimize the sites for the anode and cathode when eliciting the largest and isolated finger extension response with a minimal wrist response.

1.3.2. For pain management, place the cathode electrode on Neiguan, and the anode electrode on Weiguan.

1.4. Connect surface electrodes to the electrical stimulator (Digitimer DS7A, UK, www.digitimer.com).

1.5. Place and secure facemask. Select the size of facemask carefully to fit individual's face to prevent air leakage and to provide comfort of wearing the mask (Figure 5).

1.6. Connect facemask to a pneumotach system (Series 1110A, Hans Rodolph Inc; Kansas City, Missouri; http://www.rudolphkc.com).

2. Instruction on voluntary breathing

Voluntary breathing, particularly voluntary inhalation, plays a critical role in this intervention. Voluntary inhalation is defined as effortful deep and fast inhalation. Instruct the subject to take a single isolated deep breath, similar to routine deep breaths, but faster and stronger. There is no need to perform voluntary exhalation preceding forced inhalation in a breathing cycle. Allow the subject to have 8~10 practice trials to understand the instructions.

3. Electrical stimulation settings

3.1. Set a single electrical stimulus as a single square-wave pulse with 0.1ms duration. The intensity of electrical stimulation is different for different applications. Since a single electrical stimulus is delivered each time, there is no need to set frequency parameter.

3.2. For spasticity management, determine the intensity of electrical stimulation when 1) isolated finger extension responses are elicited with minimal involvement of wrist joint responses; 2) the highest level that the subject could tolerate. The absolute magnitude of stimulation intensity could be different for different subjects. Encourage the highest intensity that the subject could tolerate to achieve the best outcome.

3.3. For pain management, allow the subject to determine incremental changes of the stimulation intensity. The starting intensity is zero. The highest level is the maximal output of the stimulator or the level the subject could tolerate. However, explicitly instruct the subject that discomfort or painfulness, even "aversiveness" of electrical stimulation is part of treatment; therefore, encourage the subject to select the highest level that the subject could tolerate.

4. Control of electrical stimulation

4.1. Write a customized LabView (National Instrument, Austin, TX) program to control delivery of electrical stimulation in two ways: BreEStim and EStim.

4.2. Breathing-controlled electrical stimulation (BreEStim) (Figure 6):

4.2.1. Determine the peak airflow rate during voluntary inhalation, i.e., during the deepest and fast inhalation.

4.2.2. Determine the threshold which is 40% peak airflow rate. Of note, set the threshold higher than the airflow rate during normal breathing to encourage deeper and faster voluntary breathing.

4.2.3. Then set the trigger function. When the instantaneous airflow rate of an isolated voluntary inhalation reaches or beyond the threshold, the LabView program triggers and delivers a single electrical stimulus with preset duration and intensity[16]. Allow the subject to rest upon request.

4.3. Randomly-triggered electrical stimulation (EStim):

4.3.1. Allow the subject breathe normally without specific instructions on breathing.

4.3.2. The LabView program randomly delivers a single electrical stimulus with preset duration and intensity every 4 to 7 seconds. Similarly, allow the subject to rest upon request.

5. Dose of BreEStim

It is recommended that each session of treatment has 100 to 120 BreEStim stimuli. It lasts approximately 30-40 minutes.

6. Recording and monitoring

6.1. Make sure there is no air leakage from the facemask, since voluntary inhalation plays an important role in this protocol.

6.2. Monitor signs of hypoxemia and hyperventilation when the subject wears facemask. Allow rest at the subject's request for this purpose.

6.3. Record any side effect, tolerance of voluntary breathing via a face mask, and any psycho-social effects.

6.4. For pain management, record any reduction of pain, i.e., visual analogue scores (VAS) [57] and duration of the effect. Use the modified VAS (mVAS) to further quantify the effect of pain reduction, i.e., how much pain is reduced and how long it lasts (reduction × hours). Also record the average intensity for each session, since the intensity of electrical stimulation varies during each session of treatment.

6.5. For spasticity management, record the Modified Ashworth Scale (MAS) value of the target muscle and other clinical measurements, including strength, sensation, and range of motion.

Results

Breathing-controlled electrical stimulation (BreEStim) has demonstrated excellent clinical efficacy in management of neuropathic pain in spinal cord injury and post-stroke finger flexor

spasticity. Spasticity reduction after BreEStim treatment depends on the severity of pretreatment conditions. As shown in Figure 1, the finger flexor spasticity was greatly reduced after BreEStim treatment. Finger flexor spasticity has been reduced from MAS 1+ to minimum (MAS=0). The patient is able to open his hand and fingers for functional use. It is important to note that other patients may not have the same degree of spasticity reduction and functional improvement. In a patient with severe finger flexor spasticity (MAS=3) and without residual voluntary finger extension (as shown in Figure 4), finger flexor spasticity was reduced to MAS=1. This makes it easier for the patient to range her fingers, but does not restore functional use of her hand.

BreEStim also demonstrates better and longer pain reduction effects. Figure 2 shows that with similar intensity of electrical stimulation, BreEStim has better outcome than regular electrical stimulation. However, BreEStim did not affect pain scores on Day 2 when the patient had a urinary tract infection. This suggests that BreEStim has no effect on pain reduction when pain is confounded by infection.

Voluntary breathing plays a key role in BreEStim. It is important to choose a facemask that fits the patient (Figure 5) to prevent air leakage. The airflow rate is relatively low during normal breathing (1.6 liter/sec, Figure 6). Forceful voluntary inhalation could greatly increase the airflow rate (about 8 liter/sec). Placement of surface electrodes is also important. As described in detail and shown in Figure 3 and Figure 4, placement for pain and spasticity management is different. It is necessary to note that location of muscle belly of finger extensors may change as a result of atrophy, deformity after stroke.

Discussion

Breathing-controlled electrical stimulation (BreEStim), as shown in the above two cases, has demonstrated clinical efficacy in spasticity management and subsequent hand function recovery in chronic stroke patients[16], as well as management of neuropathic pain of central origin in the above patient with a spinal cord injury or of peripheral origin in a patient with above-the-knee amputation[17]. This enhanced clinical outcome and broader clinical applications of BreEStim are attributed to its unique approach. Intervention with electrical stimulation targeted at the short window of voluntary breathing-associated cortical and subcortical activation [40-51] could augment its clinical efficacy via intrinsic physiological coupling, e.g., respiratory-motor coupling for spasticity management[16]. In this intervention, voluntary breathing becomes critical, particularly voluntary inspiration. Education for patients on proper breathing techniques and accurate measurement of breathing parameters (e.g., no air leakage) are measures to prevent failure of the BreEStim intervention.

The new intervention protocol – BreEStim, has a few advantages, in addition to better efficacy and broader applications.

BreEStim is patient-centered. BreEStim encourages active engagement of patients since voluntary breathing is required [17]. Patients feel they actively participate in managing their pain, rather than “a passive participant in their own care”. For example, the patient controls the intensity of electrical stimulation, starting from zero to the highest level that the patient could

tolerate[17]. This may enhance their treatment compliance. EMG-triggered EStim also involves active participation[36], but the patient can not control the intensity of electrical stimulation.

BreEStim takes an integrative, system-based approach. As demonstrated in an earlier study[17], different pain coping mechanisms are integrated into one protocol, including electrical stimulation, acupuncture, aversive stimulation, and the systemic effects of voluntary breathing. As such, patients are able to tolerate high levels of electrical stimulation, leading to enhanced analgesic effects. Such a positive feedback loop (activation of the reward system) results in greater clinical efficacy. Using this integrative, system-based approach, certain signals of voluntary breathing could also be used to identify the time window of interactions between systems. As such, BreEStim could be applied to patients with severe spasticity. These patients are usually not able to perform voluntary contraction, thus "clean" EMG signals from the target muscle are not available. In EMG-triggered electrical stimulation, EMG signals from the targeted muscles (e.g., finger extensors) are required to trigger electrical stimulation. Therefore, application of EMG-triggered EStim is limited to patients with mild to moderate spasticity.

BreEStim is a non-invasive, non-pharmacological treatment. This is critical because patients often require a long-term use of medications, and most medications for chronic pain and spasticity have side effects that can sometimes be very severe. The possible side effects include addiction, overdose, withdrawal symptoms, and constipation, etc. These potential side effects could be avoided in the BreEStim treatment.

BreEStim is an alternative choice. The alternative non-pharmacological treatment with better analgesic effects is important, particularly when neuropathic pain is difficult to manage. For example, only 7% of responders reported pharmacological treatment is effective for neuropathic pain following SCI in a postal survey [58].

In summary, this breathing-driven stimulation, BreEStim, is based on the newly discovered phenomenon of intrinsic physiological coupling activated during voluntary breathing. The BreEStim protocol has demonstrated clinical efficacy for neuropathic pain and post-stroke spasticity management. Further research is warranted to examine underlying mechanisms that mediate the intervention effect. Importantly, there may be other applications that have not yet discerned.

Figure Legends

Figure 1: Comparison of hand posture pre- and post-BreEStim. The stroke patient could open his hand after BreEStim.

Figure 2: Comparison of BreEStim and EStim effects on pain reduction.

Figure 3: Location of Neiguan. Note, Waiguan is the counterpart of Neiguan on the dorsal aspect of the forearm.

Figure 4: Placement of surface electrodes on finger extensors.

Figure 5: A patient during BreEStim. Surface electrodes are placed on Neiguan and Waiguan.

Figure 6: real-time measurement of airflow rate during voluntary inspiration and resting inspiration. Note that the airflow rate is much higher during voluntary inspiration than resting inspiration. It is noticeable that patient's breathing was interrupted by electrical stimulation.

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Figure 1

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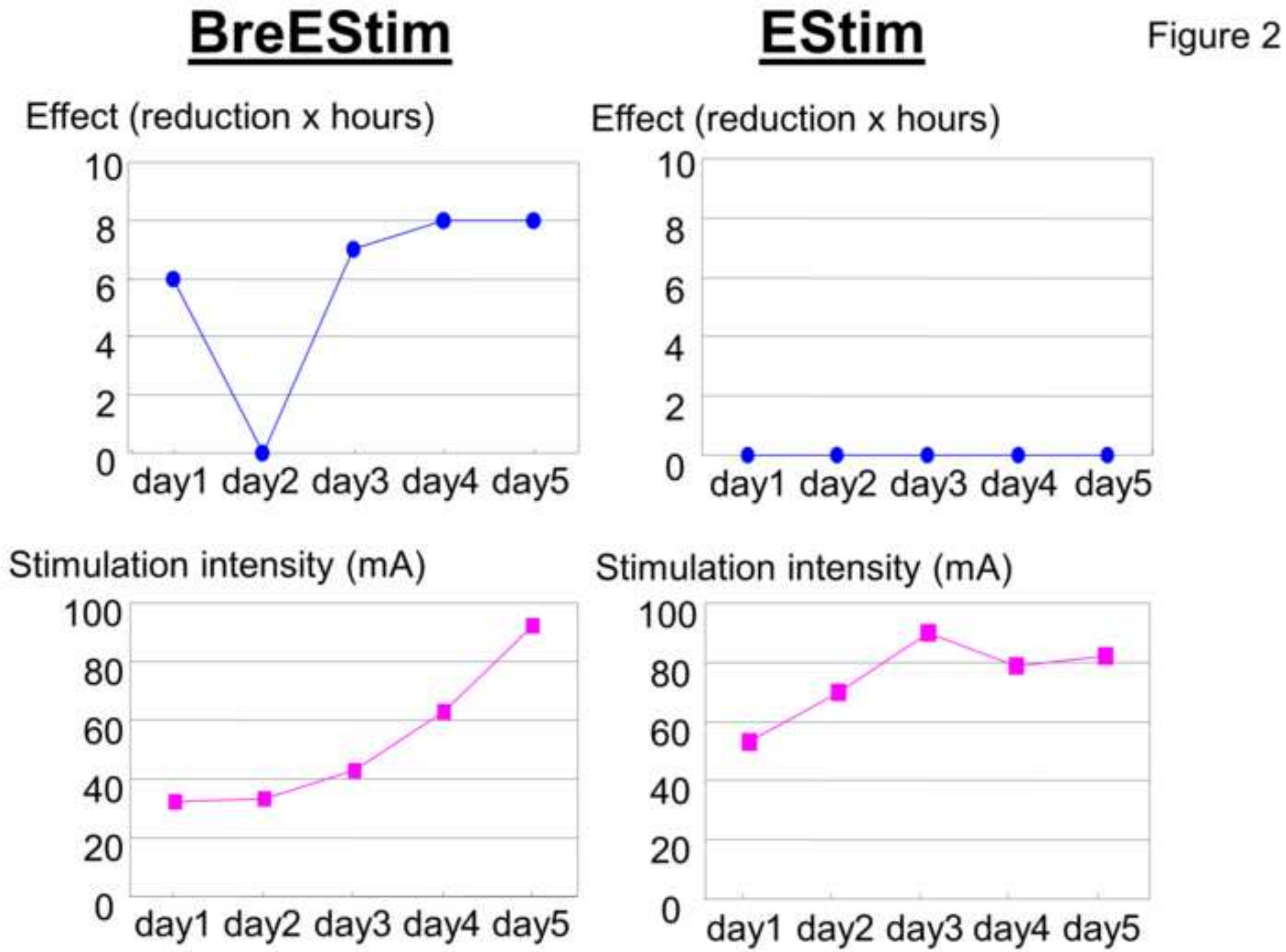

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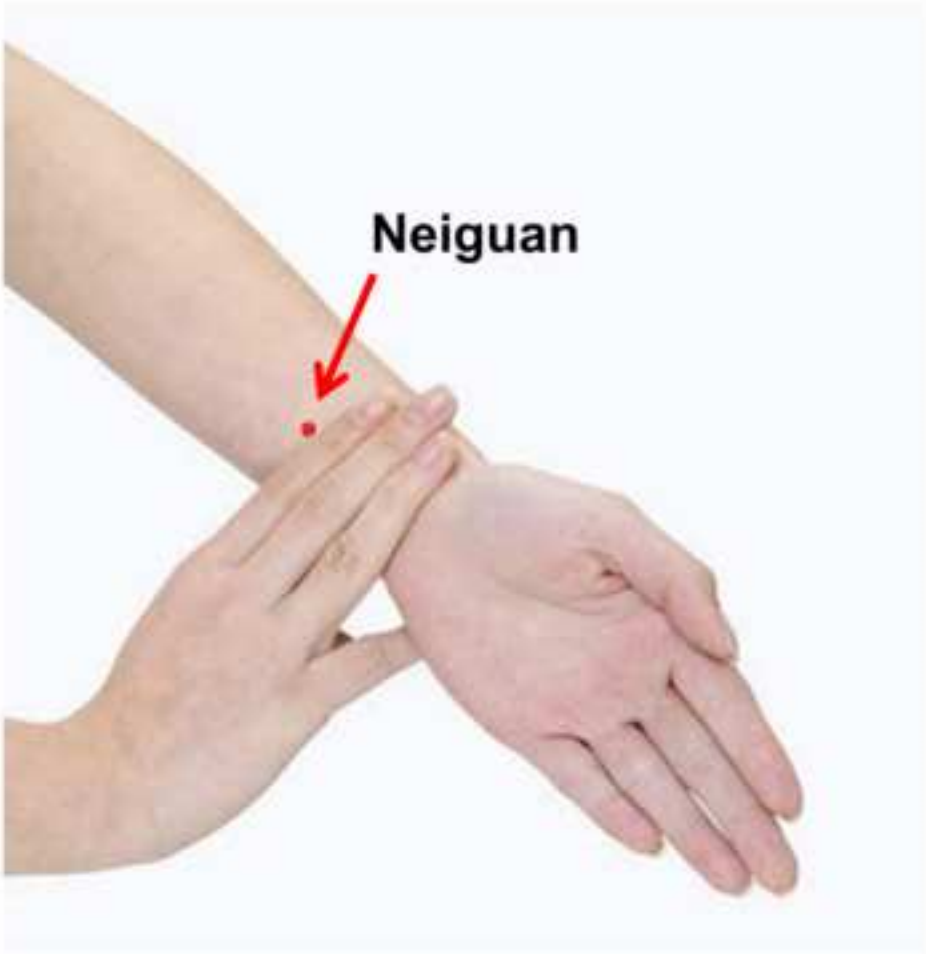

Figure 3

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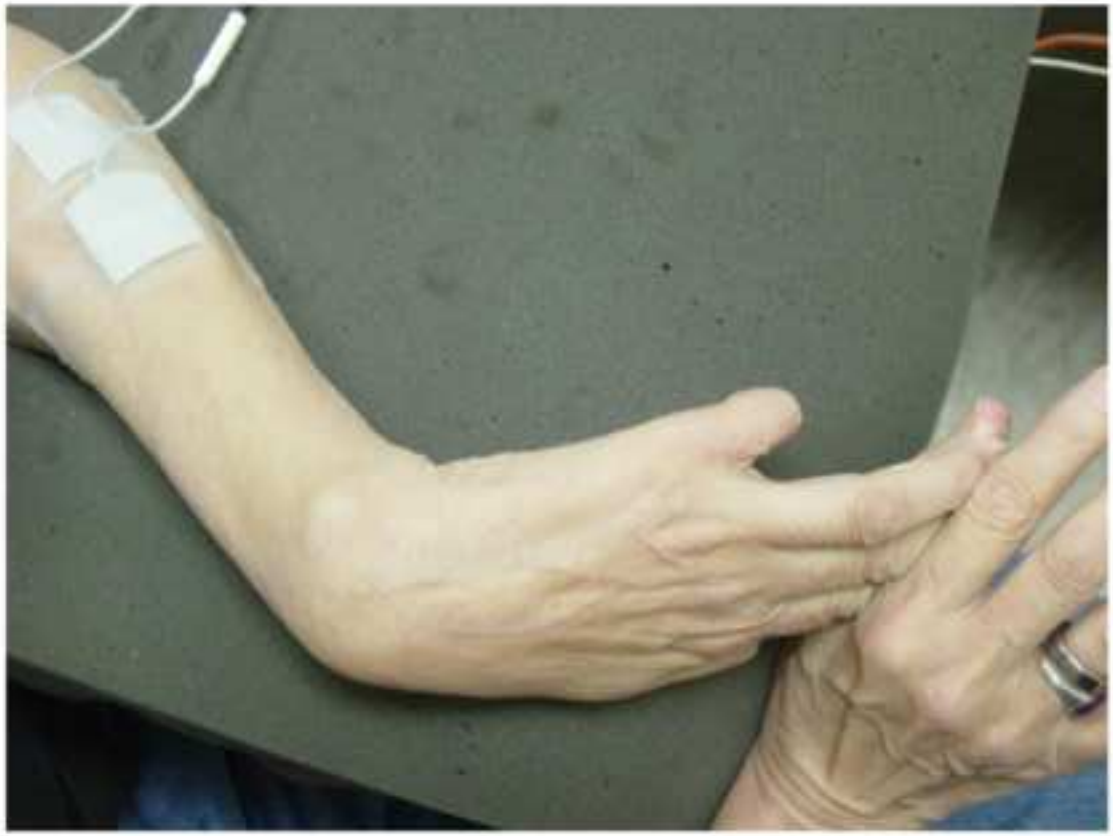

Figure 4

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Figure 5

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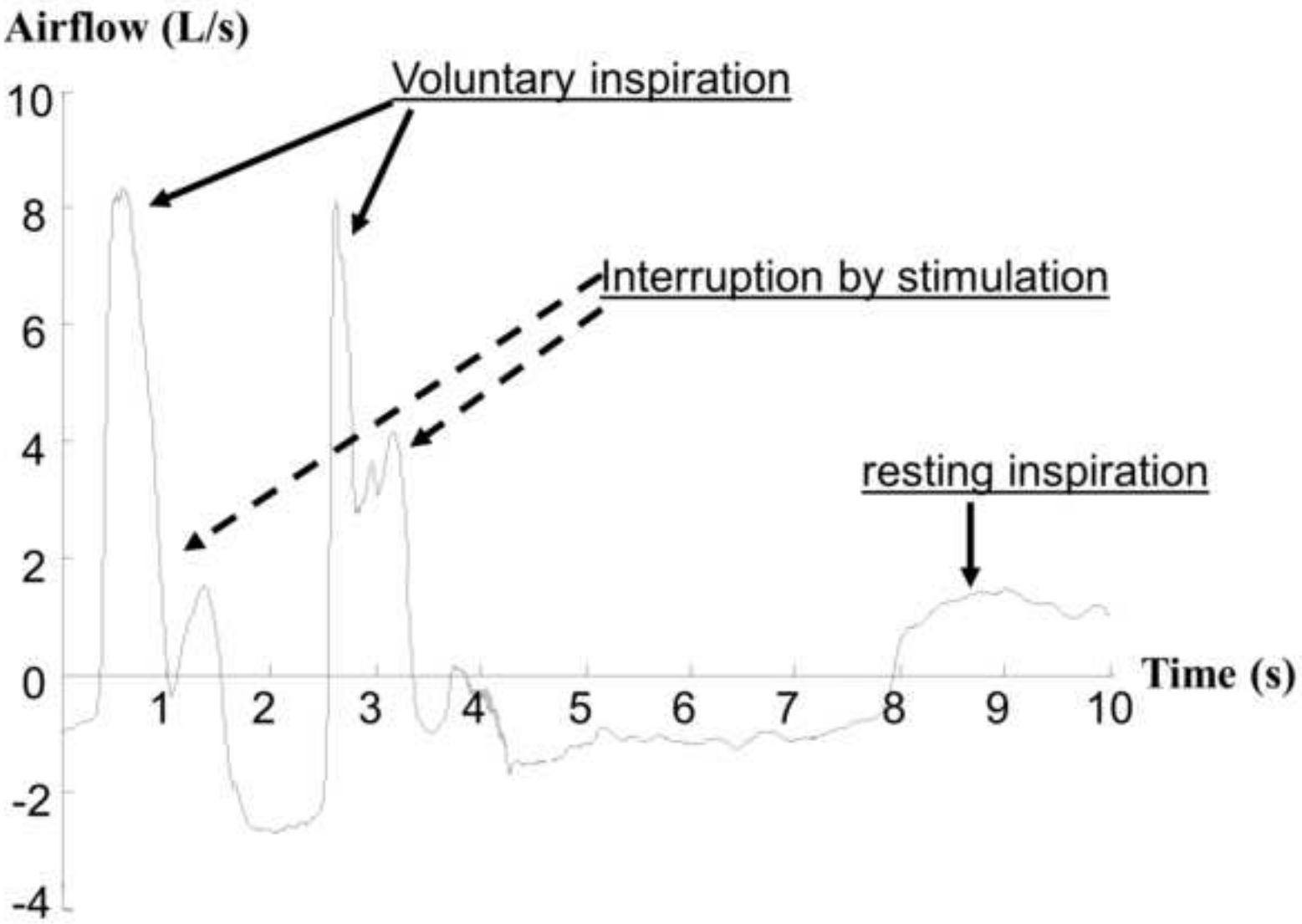

Figure 6

*Table of Reagents/ Materials Used

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Name of Reagent/Material	Company	Catalogue Number	Comments
Electrical stimulator	Digitimer	DS7A	http://www.digitimer.com
Pneumotach system	Hans Rodolph Inc	Series 1110A	http://www.rudolphkc.com

*Rebuttal Comments
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Reviewer #1:

Summary:

This is a very well written manuscript with significant contribution to both clinical and research communities. The author proposed a novel breathing driven stimulation strategy based on the new findings of intrinsic physiological coupling activated during voluntary breathing (from the research group led by the author). The clinical efficacy of this novel strategy was clearly demonstrated in this study for management of neuropathic pain and post-stroke spasticity. There are many other potential clinical applications of this novel electrical stimulation strategy for patients with neuromusuclar disorders or impairments.

Minor Concerns:

Page 3: second paragraph, line 10, typo, "inexpensice"

REPLY: I appreciate the Reviewer's encouraging comments. The sentence has been deleted.

Reviewer #2:

Summary:

The paper presents a unique premise but organization, multiple grammatical errors, insufficient documentation of results and claims that exceed data distract from the overall message. As an example of organizational difficulties, the author, in the Introduction, introduces recovery of hand function in one paragraph and breathing in another without any transitional sentences or ideas. The paper will need editing.

Reply: a transitional sentence has now been added.

Minor Concerns:

Abstract:

grammar- 3rd and 5th sentences; also coupling between what?

Reply: the word "coupling" has been changed to "interactions".

Page 3:

last sentence, 1st para - grammar correction needed here and throughout

Reply: I have carefully checked grammar throughout and have corrected what I could.

2nd para - reference needed for claim that acupuncture is widely accepted

Reply: a reference has been added

2nd para - integration of which coping mechanisms?

Reply: The mechanisms (acupuncture, electrical stimulation, aversiveness) have been specified.

last para - reference needed for statement that "this intervention protocol superior to NMES?"

Reply: references have been added.

Page 4:

1st para - brief description of MRI results would be helpful

Reply: brief description of MRI results has been provided.

2nd para - More detail is needed regarding comparison and contrast between Brestim and NMES. Author states that Brestim is superior but why would the addition of a breathing trigger result in totally differing results from estim alone? If, as author suggests, breathing augment the effects of stimulation, then wouldn't results be similar?
Reply: Comparisons between BreEStim and NMES are found in the Discussion section, not in the Introduction section.

Case presentation - For case studies it is typical to have much more patient information than is provided here. (e.g. MRIs, structures involved in stroke, rehabilitation hx more detailed clinical exam, etc.)
Reply: the stroke patient was discharged from outpatient PT/OT programs because he was stable and plateaued in therapy. MRI results were not available at the time of experiments. These have been clarified in the text. See page 4, last para for details.

Page 5:
Author reports MAS of 1+ pre-test but only says minimal for post test. What was the actual score. Also does the change exceed the published minimum clinical significance change? Doubtful. Author talks about finger movements but provides no data. Was something like a Fugl-Meyer test used?
Reply: The post-test assessment of finger flexor tone does not qualify for MAS=1, but not completely normal. This could be due to the MAS measurement itself that is not sensitive enough to detect minor difference, and/or assessment was masked by tone from other muscles, such as wrist flexors or intrinsic muscles. On the other hand, it was a surprise to the author as well that a single session of treatment could lead to such long-lasting reduction in muscle tone and significant improvement in hand function. No Fugl-Meyer tests were used pre- and post-treatment.

Results 1st para - How can author make the claim that Breestim success depends on severity of pretreatment conditions when only one subject was tested?
Reply: This is a method-based paper. Case presentation showcases how the method could be applied for. It does not mean that only one subject was tested. As stated in Results, finger flexor spasticity was reduced from MAS=3 to MAS=1 in another patient.

Discussion, 1st para - "unique approach" This Reviewer agrees but wonders whether it really differs from any other technique that requires voluntary effort to initiate estim. For instance, EMG or electrogoniometry. Perhaps results are due solely to attentional demands of task. Brief discussion comparing and discussing these possibilities would be helpful.
Reply: a sentence has been added:" EMG-triggered EStim also involves active participation[33]. But BreEStim integrates other additional mechanisms."

Page 8:
4th para - "extensive cortical?" Describe or list and reference. What is meant by "short window"
Reply: references for extensive cortical/subcortical activation during voluntary breathing has been

provided. Short window refers to “short window of breathing-associated cortical and subcortical activation”

Page 9:

1st para - earlier author states that it is not effective with severe spasticity

Reply: In the Results section, the author mentioned that “It is important to note that other patients may not have the amount of spasticity reduction”. Spasticity reduction from MAS=3 to MAS=1 in a patient with severe spasticity does not mean it is not effective. The author does not want to overestimate the effect of treatment. This sentence has been revised further to “It is important to note that other patients may not have the same degree of spasticity reduction and functional improvement”.

4th para - study does not permit the author to conclude "excellent clinical efficacy?"

Reply: It is been changed to “clinical efficacy”.