Chiba Medical J.　100E：39－48, 2024
doi:10.20776/S03035476-100E-4-P39

〔 Original Article 〕

Integrating low-frequency electrical stimulation with complementary and integrative health therapy

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（Received February 16, 2024, Accepted May 10, 2024, Published September 10, 2024.）

Abstract

【Background】Noncommunicable diseases（NCDs）substantially burden individuals and societies with enduring repercussions. We explored Low-Frequency Electrical Stimulation（LFES）as an accessible and cost-effective solution to mitigate the impact of NCDs. We specifically integrated LFES with Complementary and Integrative Health（CIH）therapy, creating LFES-CIH therapy to eliminate NCD-associated risk factors and optimize interventions for prevention and control.

【Methods】Seven healthy volunteers（median age 53.3 years）participated. LFES was administered to acupoints on the Bladder（BL）meridian. Various parameters, including blood flow volume, blood viscosity, heart rate, blood pressure, oxygen saturation, body surface temperature, balance of autonomic nerves, and pain assessment, were monitored. Statistical analysis was conducted employing the Wilcoxon matched-pairs signed-rank test with Holm correction.

【Results】We observed increased blood flow volume, reduced blood viscosity fluctuations, elevated body surface temperature, harmonized autonomic nervous system activity, and a gradual reduction in systolic blood pressure. However, no significant effects were observed in diastolic blood pressure and heart rate. These outcomes suggest that LFES-CIH therapy at these BL meridian acupoints replicates the therapeutic effect of acupuncture within CIH. Pain assessments post-treatment also demonstrated significant improvements, aligning with the holistic health principles of CIH.

【Conclusions】We revealed the potential of LFES-CIH therapy to replicate the therapeutic benefits of CIH practices and the promise of LFES-CIH therapy in personalized healthcare, particularly in addressing lifestyle-related diseases and mental health issues. LFES-CIH

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therapy has the potential to significantly contribute to NCD prevention and control and enhance overall quality of life.

***Key words*: Noncommunicable diseases, Low-Frequency Electrical Stimulation, Complementary and Integrative Health, Personalized Healthcare, Holistic Health**

Ⅰ. Introduction

Noncommunicable Diseases (NCDs)

Noncommunicable diseases (NCDs), commonly referred to as chronic diseases, are recognized outcomes of intricate interactions among genetic, physiological, environmental, and behavioral factors (WHO, Noncommunicable diseases. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases). The major NCD categories encompass cancer [1], cardiovascular disease [2], chronic respiratory ailments [3], and diabetes [4]. NCDs claim over 40 million lives annually, with most of these fatalities concentrated in low- and middle-income nations (WHO, Noncommunicable diseases. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases). As such, addressing the widespread and enduring impact of NCDs demands pragmatic, cost-effective solutions capable of eradicating the associated risk factors and facilitating strategies for prevention and control [5].

Personalized Healthcare and Traditional Alternative Medicine

Embracing a personalized healthcare approach is a pivotal intervention to tackle NCDs effectively through early identification and timely intervention (WHO, Operational Framework for Primary Health Care: Transforming Vision into Action. https://www.who.int/publications/i/item/9789240017832) [6]. Drawing inspiration from historical practices, such as the medical therapeutics akin to acupuncture used by the ancient Tyrolean Iceman, underscores the historical precedence of personalized healthcare [7,8].

Complementary and Integrative Health (CIH), such as Ayurvedic Medicine, Unai Medicine, and Traditional Chinese Medicine, renowned for its global popularity, offers a rich history of personalized health management, disease prevention, and treatment. Famous for its global popularity, it offers a rich history of personalized health management, disease prevention, and treatment [9,10] (NCI, Complementary and Alternative Medicine. https://www.cancer.gov/about-cancer/treatment/cam). Nonetheless, the intricate techniques, such as acupuncture and moxibustion, within CIH can be challenging for non-CIH practitioners to replicate accurately [11].

Thus, creating a device that ensures secure, convenient, and budget-friendly CIH procedures, on par with those conducted by trained CIH practitioners, presents a profound advancement in NCD treatment.

Electroceuticals and Low-frequency Electrical Stimulation (LFES)

Electroceuticals, an emergent realm within bioelectrical and bioelectronics medicine, capitalizes on electrical energy to stimulate specific pathways in the body, thereby modulating biological functions and pathological processes [12]. Notably, electroceuticals promise to deliver targeted, localized treatments with fewer side effects than conventional medications [13]. The customizability of these interventions to individual patient requirements further amplifies their potential [14].

Low-frequency electrical stimulation (LFES), a facet of electroceuticals, stands recognized for its safety and effectiveness in treating diverse musculoskeletal disorders, including pain management [15]. Consequently, LFES potentially mirrors the therapeutic effects of acupuncture, wherein practitioners employ fine needles or moxibustion at specific body points to stimulate energy or Qi flow in the body [16].

This Study

In this study, we delved into the potential of LFES treatment with CIH therapy, designated as LFES-CIH therapy, as an accessible remedy for NCDs, tracking alterations in vital signs correlated with LFES-CIH treatment. In addition, we assessed the viability of LFES-CIH as a secure and convenient alternative to traditional CIH procedures for NCD treatment. Through this study, we aim to shed light on the transformative possibilities of LFES-CIH therapy in redefining the landscape of NCD management.

Ⅱ. Methods

Ⅱ-1. Subjects

Seven healthy volunteers (median age of 53.3 years, a range of 29-66 years, and five females and two males) were recruited to participate in the study. The study received approval from the Ethics Committee of Chiba University School of Medicine (reference M10302), and the participants gave written informed consent to participate.

The specific inclusion and exclusion criteria are outlined below.

Selection criteria: Healthy adult volunteer.

Exclusion criteria:

(1) Unable to communicate during the interview. (2) Implantable electrical medical devices. (3) Acute (painful) illness of unknown cause. (4) Heat problems. (5) A high bleeding predisposition. (6) Malignant tumor. (7) Pregnancy or potential pregnancy in women. (8) Febrile illness. (9) Contagious diseases. (10) risk of vascular disorders such as thrombosis, venous thrombosis, varicose veins, etc. (11) Appendix: Subjects judged unsuitable by the investigator.

Ⅱ-2. Study Design

For coverage with two gel-pad electrodes (113 cm^2: 15.0 cm x 7.5 cm) positioned on either side of the waist, we selected acupoints of the Bladder (BL) meridian, BL23, 24, and 52 (Products, A. Acupuncture Point Locations. https://www.acupunctureproducts.com/downloads/AcupuncturePointLocations.pdf), (WHO international standard terminologies on traditional Chinese medicine. https://iris.who.int/bitstream/handle/10665/352306/9789240042322-eng.pdf?sequence=1). Then, LFES-CIH treatment was performed for 20 minutes in the treatment chair (LIMONIS: TAKARA BELMONT Co., Osaka, Japan), providing relaxing patient support (Supplementary Fig. 1A).

BL23 (Kidney Transport) is positioned 1.5 cun lateral to both sides of the second lumbar vertebra's spinous process (L2). BL24 (Sea-of-Qi Transport) is positioned 1.5 cun lateral to both sides of the third lumbar vertebra's spinous process (L3). BL52 (Zhishi Will Chamber) is located 3 cun lateral to both sides of the second lumbar vertebra's spinous process of (L2). *Note: cun represents a traditional Chinese unit of length, where 30 cun equals 1 meter.*

Ⅱ-3. Low-frequency Electrical Stimulation (LFES)

As an Arbitrary Waveform Generator, the low-frequency electrical stimulation was administered using AC5100 (Japanese Medical Device Approval Number: 230ADBZX00035000, ASIAS Co., Hamamatsu, Japan, Supplementary Fig. 1B). The device's specifications are as follows: a maximum output current of 50 mA, with a fundamental frequency range of approximately 15–10000 Hz, a rated output voltage of a maximum of 70 V, and a maximum pulse width of less than 1000 Hz.

The LFES-CIH therapy was administered using an AC5100 device, which is classified as a medical device for arbitrary waveform generation attached to two gel-pad electrodes.

In this study, we utilized the vasodilation mode, with a total treatment time of 21 minutes (3 minutes allocated to each of 7 different frequencies) and an intensity level adjusted to be optimized for each subject.

As shown in Figure 1, this therapy employed a gel-pad electrode (113 cm^2: 15.0 cm x 7.5 cm) positioned on either side of the waist to cover acupoints BL23, 24, and 52, belonging to the B.L. meridian[17], guided by the locations of the tattoo groups on the Tyrolean Iceman and their corresponding acupuncture points, which is concerning NCD (Products, A. Acupuncture Point Locations. https://www.acupunctureproducts.com/downloads/AcupuncturePointLocations.pdf), (WHO

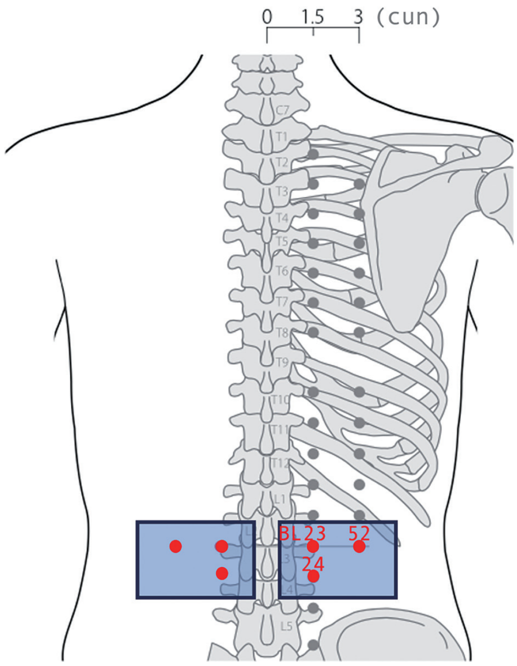

Fig. 1 Illustrated Acupuncture Points of Bladder Meridian. LFES-CIH therapy was administered using gel-pad electrodes (113 cm^2: 15.0 cm x 7.5 cm, Black Circle) on each side of acupoints BL23, 24, and 52. These acupoints were targeted for treatment with the AC5100 device, which generated arbitrary waveforms. *Note: cun represents a traditional Chinese unit of length, where 30 cun equals 1 meter.*

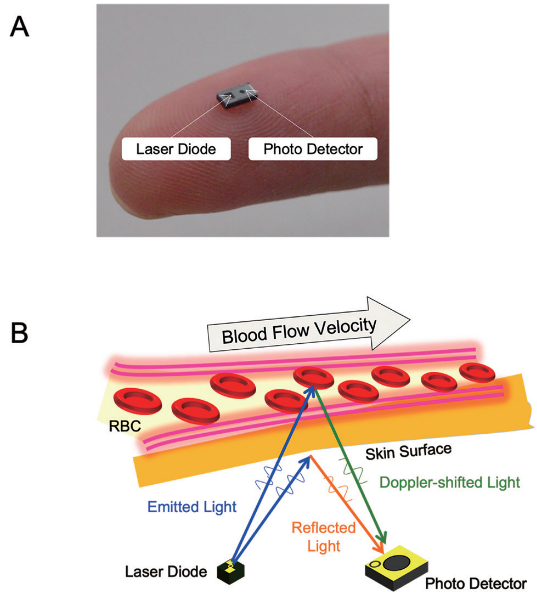

Fig. 2 Blood-flow Sensor Device. A. Picture of the Blood-flow Sensor. This sensor measures 1 mm in height, 1.6 mm in length, and 3.2 mm in width. **B**. Principle of the Blood-flow Measurement. The device detects optical beat signals by analyzing the interference between reflected skin light (orange) and doppler-shifted light from red blood cells (green). RBC: Red Blood Cell

international standard terminologies on traditional Chinese medicine. https://iris.who.int/bitstream/handle/10665/352306/9789240042322-eng.pdf?sequence=1).

Ⅱ-4. Blood Flow Volume, Blood Viscosity, and Heart Rate

Blood flow volume (mL/sec), blood viscosity (Pa・s), and heart rate (bpm) were continuously monitored during LFES treatment by a laser Doppler-type blood flow measurement device (KYOCERA Co., Kyoto, Japan) and optimized specifically for this study. The device's specifications are as follows: laser output of 0.5 mW, a wavelength of 850 nm, and a measurement range of approximately 100 mL/min.

As shown in Figure 2A, we utilized a blood-flow sensor device designed for portability and robustness through miniaturization and enhanced durability to objectively evaluate vital signs during LFES-CIH therapy[18]. This innovative device is capable of measuring several critical parameters, including blood flow volume (mL/sec), blood viscosity (Pa・s), and heart rate (bpm) in subcutaneous tissue. It achieves this by leveraging the optical Doppler effect, which stems from a shift in optical frequency due to the movement speed of red blood cells within capillaries and arterioles (Fig. 2B)[19]. Moreover, for the specific requirements of our research, the device has been meticulously optimized to reduce its size and power consumption without compromising functionality[20,21].

Ⅱ-5. Blood Pressure, Oxygen Saturation, and Heart Rate

Blood pressure, oxygen saturation, and heart rate were measured using WB-100 (Japanese Medical Device Approval Number: 224AGBZX00023000, JAPAN PRECISION INSTRUMENTS, Inc., Gunma, Japan).

Pre- and post-LFES-CIH therapy assessments were conducted for all subjects' blood pressure, oxygen saturation, and heart rate using a sphygmomanometer/pulse meter/pulse oximeter meter attached to the wrist and fingertips (Supplementary Fig. 5B).

Ⅱ-6. Body Surface Temperature

Thermographic measurements were conducted using a testo 885 device (Testo SE & Co. KGaA, Titisee-Neustadt, Germany).

Ⅱ-7. Balance of Autonomic Nerves

The excitation balance of the sympathetic and parasympathetic nerves within the autonomic nervous system was assessed using the Body Checker NEO (Japanese Medical Device Approval Number: 13B1 X10074000014, Tokyo Iken Co., LTD, Tokyo, Japan).

We assessed the balance of excitation between the sympathetic and parasympathetic nerves within the autonomic nervous system before and after LFES-CIH therapy for all subjects by monitoring heart rate variability at fingertip capillaries (Supplementary Fig. 5A)[22].

Ⅱ-8. Pain Assessment

The participants' pain assessment was conducted by asking them to indicate the location and intensity of pain across segmented body areas on a four-point scale questionnaire, as shown in Supplementary Figure 2.

Ⅱ-9. Statistical Analysis

Statistical analyses were performed using GraphPad Prism software (GraphPad Software, La Jolla, CA, USA), which included the Wilcoxon matched-pairs signed-rank test with Holm correction. The Wilcoxon matched-pairs signed-rank test, a nonparametric alternative to paired Student's t-tests, was used for comparing two related samples or conducting paired difference tests on repeated measurements from a single sample to assess differences in population mean ranks[23].

A p-value < 0.05 was applied to determine statistical significance.

Ⅲ. Results

Ⅲ-1. Study Population

Between 21 November and 21 December 2022, a total of seven healthy subjects (five female and two male) were randomly assigned to receive low-frequency electrical stimulation (LFES) treatment in conjunction with Complementary and Integrative Health (CIH) therapy, which we will refer to as LFES-CIH therapy.

This treatment was administered once a week for a total of four sessions.

As a treatment comparison group without LFES-CIH therapy, two patients (one female and one male) were selected.

Ⅲ-2. Blood Flow Volume, Blood Viscosity, and Heart Rate

Throughout the LFES-CIH therapy sessions, we continuously monitored blood flow volume, blood viscosity, and heart rate in the peripheral blood vessels of the finger. As the treatment progressed, we observed a gradual increase in blood flow volume (Fig. 3A) alongside a corresponding decrease in blood viscosity fluctuations (Fig. 3B).

Subsequently, we conducted a comparative analysis of blood flow volume and viscosity immediately following treatment initiation (0-3 minutes) and during the treatment session (18-21 minutes). Figure 4A shows that blood flow volume increases with significant

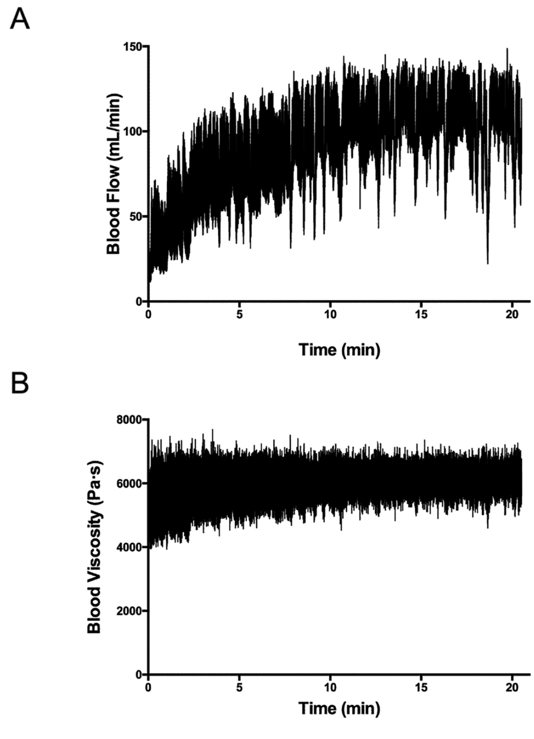

Fig. 3 Typical Sensor Gram of the Blood-flow Measurement. The graph displays (**A**) blood flow volume (mL/sec) and (**B**) blood viscosity (Pa·s).

differences across all subjects during LFES-CIH therapy. Figure 4B shows that blood viscosity increases with significant differences across all subjects during LFES-CIH therapy, but the rate of blood viscosity fluctuations consistently decreases. However, no significant changes were observed in heart rate (Supplementary Fig. 3).

Ⅲ-3. Body Surface Temperature

Thermographic measurements were taken before and immediately after LFES-CIH therapy for all subjects (Supplementary Fig. 4). Significantly elevated temperatures were explicitly noted on the palm and back of the hand, regions rich in peripheral blood vessels (Fig. 5A and B).

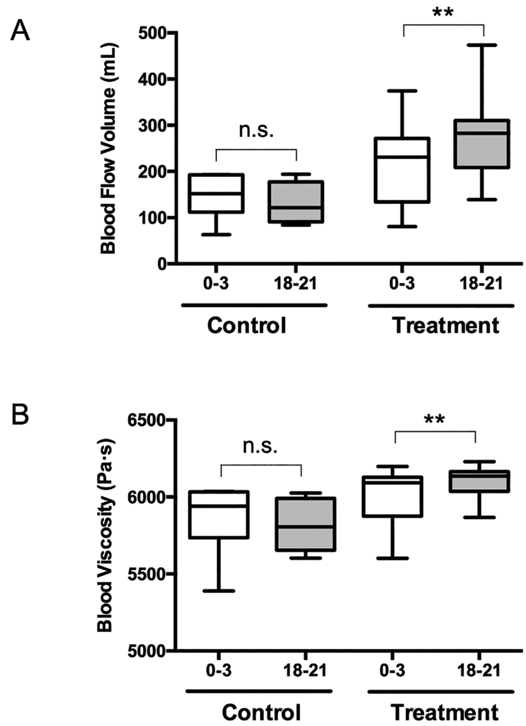

Fig. 4 Comparative Analysis of Blood Flow Volume and Blood Viscosity. Comparative analyses were conducted for blood flow volume (**A**) and blood viscosity (**B**) during LFES-CIH therapy, both at the initiation of treatment (0-3 minutes) and during the treatment session (18-21 minutes). **: p=0.002, N.S.: not significant

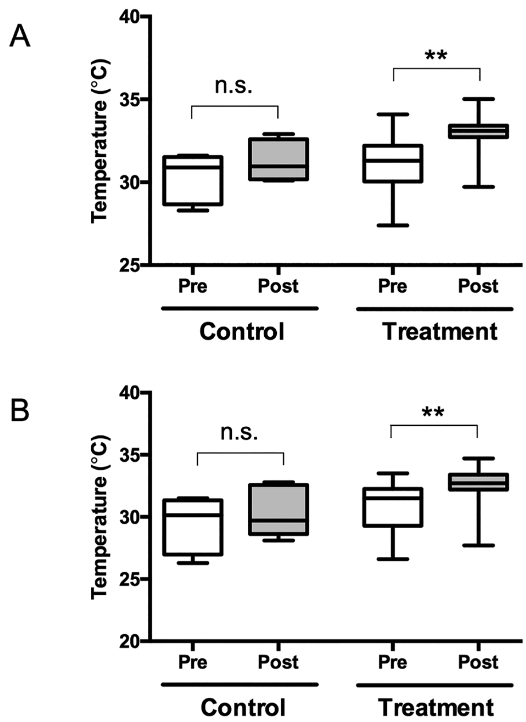

Fig. 5 Comparative Analysis of Body Surface Temperature. Thermographic measurements were taken before and immediately after LFES-CIH therapy for the palm (**A**) and back (**B**) regions. **: p=0.002, N.S.: not significant

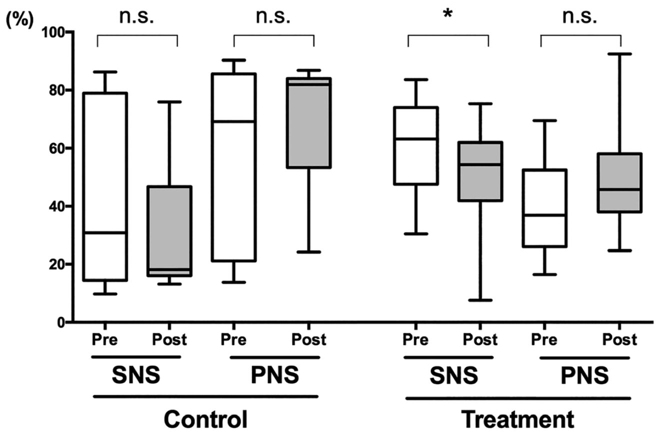

Fig. 6 Comparative Analysis of Balance of Autonomic Nerves. The balance of excitation between the sympathetic and parasympathetic nerves within the autonomic nervous system was assessed before and after LFES-CIH therapy. *: p=0.043, N.S.: not significant

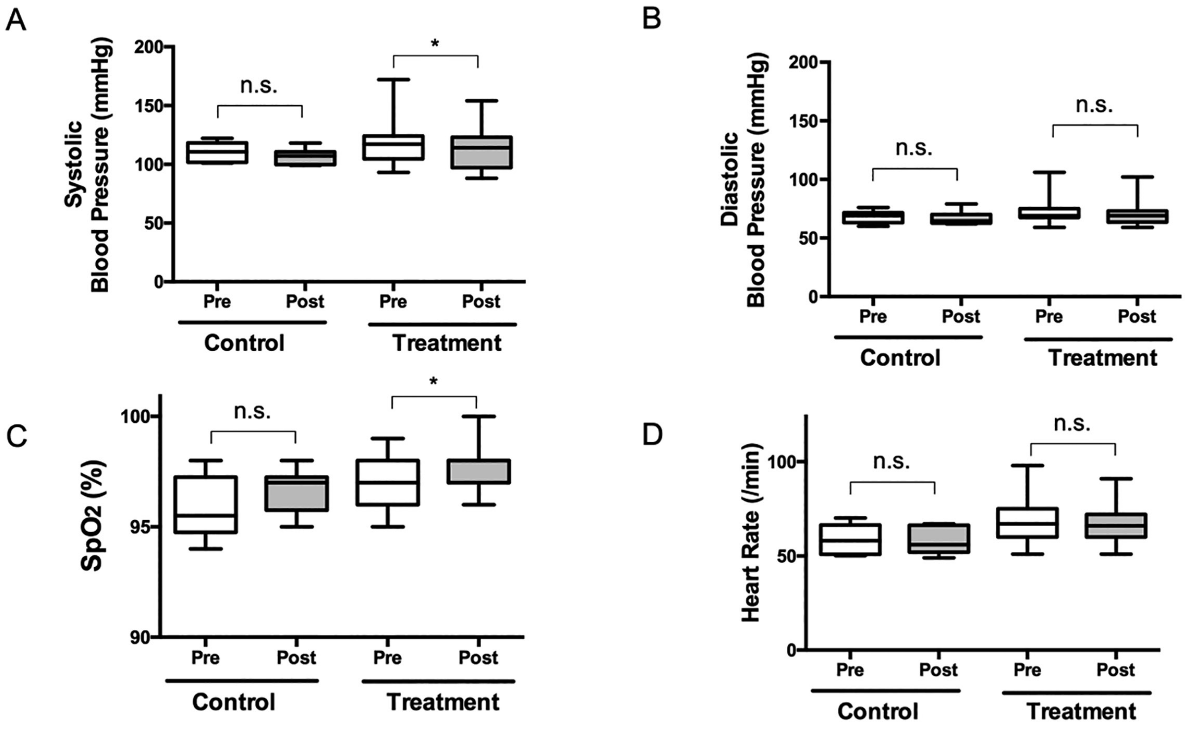

Fig. 7 Comparative Analysis of Blood Pressure, Oxygen Saturation, and Heart Rate. Pre- and post-LFES-CIH therapy assessments were conducted for diastolic blood pressure (**A**, *: p=0.045, N.S.: not significant), systolic blood pressure (**B**, N.S.: not significant), oxygen saturation (**C**, *: p=0.045, N.S.: not significant), and heart rate (**D**, N.S.: not significant).

Ⅲ-4. Balance of Autonomic Nerves

LFES-CIH therapy consistently reduced sympathetic excitability and increased parasympathetic excitability in all subjects (Fig. 6). A notable reversal phenomenon was observed in two subjects, where the dominance of the sympathetic nervous system shifted towards parasympathetic dominance. Conversely, in the control group, there was no observed improvement in the balance between sympathetic and parasympathetic nerves (Fig. 6).

Ⅲ-5. Blood Pressure, Oxygen Saturation, and Heart Rate

We observed a gradual decrease in systolic blood pressure (Fig. 7A) and an increase in oxygen saturation (Fig. 7C). No significant effects were observed in diastolic blood pressure (Fig. 7B) and heart rate (Fig. 7D).

Ⅲ-6. Pain Assessment

As a subjective study, we asked participants to rate their pain using a questionnaire that indicated the location and intensity of pain across segmented body regions on a four-point scale (Supplementary Fig. 2). Significant differences were observed before and after LFES-CIH therapy, indicating that the efficacy of the administered treatment contributed to pain alleviation (Fig. 8).

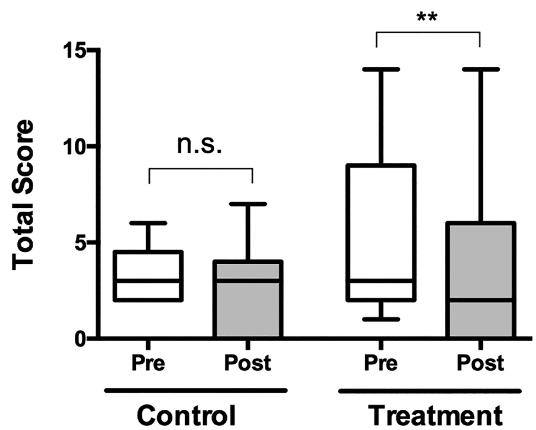

Fig. 8 Comparative Analysis of Pain Assessment. Participants' pain levels were analyzed using a questionnaire that indicated the location and intensity of pain across segmented body regions on a four-point scale before and after LFES-CIH therapy. **: p=0.002, N.S.: not significant

Ⅳ. Discussion

Aiming to mitigate Noncommunicable diseases (NCDs) impact on individuals and society and recognize their long-term repercussions, we explored Low-Frequency Electrical Stimulation (LFES) as an accessible and cost-effective solution. We specifically integrated LFES with Complementary and Integrative Health (CIH) therapy, designated as LFES-CIH therapy, seeking to eliminate NCD-associated risk factors and optimize interventions for prevention and control.

In this study, we assessed the feasibility of LFES treatment in safe and convenient CIH procedures for personalized healthcare and disease prevention for NCD, closely monitoring vital signs.

Our focus on the Bladder (BL) meridian of Traditional Chinese Medicine (TCM) runs alongside the spine and down the back of the legs, one on each side of the body. The BL meridian has also been linked to lifestyle-related diseases, mental health concerns, interpersonal stress, and coldness in the lower body in CIH. Remarkably, the treatment of BL23 (an indication of Nephritis, neurogenic bladder, lumbosacral neuralgia, menstrual disorders, and urinary illness), BL24 (a sign of Lumbar and back pain, hemorrhoids, dysmenorrhea, and functional uterine bleeding), and BL52 (an indication of Stiffness and pain in the lumbar spine, gripping pain in the kidneys, seminal emissions, impotence, edema, and all diseases of the genitals) in the B.L. meridian demonstrated influence over the autonomic nerve (pituitary gland), urinary excretion, reproductive function, and urinary tract-related organs.

Our observations, as illustrated in Figures 3, 4, 5, and 6, revealed increased blood flow volume, reduced blood viscosity fluctuations, significant temperature increases in the palm and back of the hand, a harmonized autonomic nervous system, a gradual reduction in systolic blood pressure, and increased oxygen saturation. However, no significant effects were observed in diastolic blood pressure and heart rate. These outcomes suggest that LFES-CIH treatment at these BL meridian points mirrors the therapeutic effects of acupuncture and moxibustion within TCM[24].

While blood flow volume increased during LFES-CIH therapy, a concomitant reduction in blood viscosity fluctuations aimed at maintaining homeostasis may have contributed to the decrease in systolic blood pressure.

Our findings showcase LFES-CIH's potential to replicate the therapeutic benefits of CIH practices, which employ fine needles or moxibustion at specific body points to stimulate energy or Qi flow in the body. Additionally, pain assessments highlighted significant improvements post-treatment, as depicted in Figure 7, aligning with CIH principles of holistic health approaches.

Our study ensured the safety and tolerability of LFES-CIH treatment among healthy participants, facilitating a comprehensive analysis of LFES-CIH therapy's multifaceted impact. The encouraging outcomes underscore LFES-CIH's promise in personalized healthcare, notably in tackling lifestyle-related diseases and mental health issues.

While our study was conducted in a well-equipped research environment, its implications extend beyond addressing conventional healthcare limitations, particularly in low- and middle-income countries. Our research introduced the Arbitrary Waveform Generator (AWG) as a crucial component, despite its classification as a medical device, which incurs significant costs, approximately $50,000 (Supplementary Fig. 1B). Pursuing cost-effective LFES equipment becomes a pivotal aspect of LFES-CIH therapy for NCDs.

A low-cost, easy-to-operate portable device for personal care, costing approximately $10,000, has already been developed (Supplementary Fig. 6A). However, an alternative avenue emerges by applying electrical muscle stimulation body massagers (EMS-BMs), categorized as health devices, offering cost-effectiveness at approximately $50 (Supplementary Fig. 6B). Comparing the efficacy of LFES-CIH therapy using AWG and EMS-BM may help optimize the balance between therapeutic efficacy and economic burden when implementing NCD treatment in low- and middle-income countries.

In this study, the limited cohort size of only seven participants may not fully represent the range of responses that a more extensive and diverse group could provide[25]. However, the results of statistical analyses employing the Wilcoxon matched-pairs signed-rank test with Holm correction demonstrate the significance of this study[23]. Further investigations with larger cohorts, longer follow-up periods, and varied treatment methodologies could offer deeper insights into the mechanisms underlying the observed effects of LFES-CIH therapy.

V. Conclusions

We hold firm that LFES-CIH therapy represents a critical stride toward eradicating NCD risk factors and advancing interventions for prevention and control. Furthermore, the potential of LFES-CIH therapy extends to constrained environments, such as disaster shelters and space stations, where sustaining physical and mental well-being is paramount. LFES-CIH therapy holds promise in mitigating the negative consequences of isolation and confinement, improving the overall quality of life by addressing physical discomfort and psychological challenges.

Our study illuminates LFES-CIH therapy's potential in addressing NCDs, but its transformative impact hinges on equitable LFES equipment distribution, particularly to low- and middle-income nations. Collaborations with stakeholders to ensure LFES-CIH therapy's accessibility is at the forefront of our future endeavors, aiming to extend a healthier life to countless individuals, irrespective of their economic circumstances.

Contributors

A.S., M.G., and Y.T. designed the experiments. A.S. and Y.T. optimized the Blood Flow Measurement Device. A.S. and Y.T. performed the clinical study. A.S. and Y.T. performed the data analysis. A.S., M.G., and Y.T. discussed the results. A.S. wrote the original draft manuscript. Y.T. reviewed and edited the manuscript. All authors read and approved the final manuscript.

Financial support

This work was funded by ASIAS Co., Hamamatsu, Japan.

Confict of interest

Y.T. had received funding support from ASIAS Co., Hamamatsu, Japan. Other authors declare no COI. The company had no control over the design of the study, in the interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

Ethical approval

The present study has received approval from the Ethics Committee of Chiba University School of Medicine (reference M10302). University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), ID: 000051291, Registered 8 June 2023.

Data availability

Data supplementary to findings of this work are available within the paper and its Supplementary Information files and University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), ID: 000051291, Registered 8 June 2023.

Acknowledgements

We express our gratitude to ASIAS Co., KYOCERA Co., and JAPAN PRECISION INSTRUMENTS, Inc., for their help in facilitating this study.

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