



## The influence of low-intensity resistance training combined with neuromuscular electrical stimulation on autonomic activity in healthy adults: A randomized controlled cross-over trial

Toshiki Kutsuna\*, Hitoshi Sugawara, Hideaki Kurita, Satomi Kusaka and Tetsuya Takahashi

*Department of Physical Therapy, School of Health Sciences  
Tokyo University of Technology, Tokyo, Japan*

\*[t.kutsuna.1981@gmail.com](mailto:t.kutsuna.1981@gmail.com)

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**Background:** Low-intensity resistance training (RT) combined with neuromuscular electrical stimulation (NMES) is one method of exercise to improve the deterioration of physical function. However, it is unclear whether low-intensity RT combined with NMES (RT + NMES) can be safely implemented.

**Objective:** This study aimed to examine the influence of low-intensity RT + NMES on autonomic activity and cardiovascular responses in healthy adults.

**Methods:** This study was an open-label, randomized controlled cross-over trial. The exercise intensity of isometric knee extension RT was set to 40% of the maximum voluntary contraction (peak torque). NMES was adjusted to a biphasic asymmetrical waveform with the frequency maintained at 50 Hz and a phase duration of 300  $\mu$ s. The difference in the change in autonomic activity and cardiovascular responses was compared by assessing heart rate variability, blood pressure, and heart rate during RT and RT + NMES.

**Results:** Twenty healthy male college students (mean age  $21.0 \pm 0.6$  years) participated in this study. The ratio of low- and high-frequency components of heart rate variability, systolic blood pressure, and heart rate increased during exercise in the RT and RT + NMES sessions ( $P < 0.05$ ). There were no significant differences in autonomic activity and cardiovascular responses throughout the sessions during RT and RT + NMES.

**Conclusion:** In conclusion, our results demonstrated that low-intensity RT + NMES was safe and did not induce excessive autonomic and cardiovascular responses in healthy adults.

\*Corresponding author.

**Keywords:** Autonomic nervous system; cardiovascular system; electrical stimulation; exercise; resistance training; safety.

## Introduction

Resistance training (RT) is widely used as one method of exercise to improve the deterioration of physical function and the occurrence of disability in older adults.<sup>1–5</sup> In recent years, RT has also been applied to patients with cardiovascular disease, who are recommended to adopt low-intensity RT in consideration of their physical risks and frailty.<sup>6–9</sup> There is a need for a safe and effective low-intensity RT method that can improve physical function such as increasing muscle strength in frail older patients with physical risks.

The effect of RT depends on the exercise intensity; low-intensity RT has been shown to be less effective than moderate- or high-intensity RT.<sup>10–12</sup> On the other hand, two studies have reported that RT combined with neuromuscular electrical stimulation (NMES) was more effective for the improvement of muscle strength than RT alone in healthy adults.<sup>13,14</sup> Moreover, a randomized controlled trial has shown that low-intensity RT combined with NMES (RT + NMES) can improve mobility, muscle cross-sectional area, and the capacity to perform daily tasks in older adults.<sup>15</sup> We believe that low-intensity RT + NMES could be an effective method of exercise in older patients who can exercise only at low intensities.

It is important to understand an effect of exercise training; however, how to exercise safely should be initially considered. In particular, older adults and patients with any disease for whom low-intensity exercise should be safely performed often have cardiovascular risk,<sup>16</sup> and it is important to reliably measure cardiovascular responses during or before and after exercise. Therefore, it is worthwhile to examine whether RT + NMES has a bad synergistic effect on cardiovascular response even during low-intensity exercise.

Excessive sympathetic activation precipitates arrhythmias, unexpected cardiovascular responses, and sudden cardiac death.<sup>17</sup> In a study that examined the cardiac autonomic activity during exercise, low-intensity RT did not alter cardiac autonomic modulation in patients with peripheral artery disease.<sup>18</sup> On the other hand, NMES was

reported to slightly but significantly increase the blood pressure and sympathetic activity in patients with acute myocardial infarction.<sup>19</sup> However, few studies have reported on autonomic activity and cardiovascular responses during RT + NMES, including reports on healthy subjects.

Older adults often have some disease (e.g., hypertension, dyslipidemia), and the disease or drug may affect autonomic activity and cardiovascular response. Therefore, the participants of this study were healthy adults. The purpose of this study is to examine whether low-intensity RT + NMES could be performed without inducing autonomic imbalance and cardiovascular instability in healthy adults.

## Methods

### *Participants*

Study participants were students at the Tokyo University of Technology. To be included in this study, participants needed to be age 20 years and older and male. All subjects participated in the study as volunteers, and none of them received monetary compensation. Participants were excluded if they engaged in regular exercise or had a history of smoking, cardiopulmonary disease, or motor dysfunction due to neurological or orthopaedic disease. The participants were instructed to refrain from vigorous activities, maintain their usual sleep patterns, and abstain from caffeine and other autonomic stimulants for one day before starting the study.

### *Study design*

This study was an open-label, randomized controlled cross-over trial. All procedures of this study were performed by the authors who were registered physiotherapists in Japan. Participants were allocated randomly to the RT or RT + NMES session using block randomization. The two sessions were performed at the same time in two consecutive days.<sup>20</sup>

The study protocol was approved by the Ethics Committee of Tokyo University of Technology

(approval number: E17HS - 035). All subjects were informed about the purpose and contents of the study, and personal information management. Written informed consent was obtained. This study was registered at the University Hospital Medical Information Clinical Trials Registry (registration number: UMIN000031069).

### **Outcome measures**

The peak torque of isometric knee extensor strength was assessed using a dynamometer (Biodex Multi-Joint System 3, Biodex Medical, Shirley, NY, USA). The knee extensor strength is widely used as a representative of lower limb muscle strength and is strongly related to various physical functions from young to older adults.<sup>21,22</sup> We chose this dynamometer because this dynamometer shows acceptable mechanical reliability and validity,<sup>23,24</sup> and is capable of quantifying exercise intensity using measured muscle strength. The non-dominant lower extremity was chosen for the assessment. Participants were seated in an upright posture with the knee flexed to 60°.<sup>13,23</sup> Before testing, all participants received instructions from the examiner regarding the appropriate evaluation of muscle strength. Participants were asked to push against the dynamometer pad by attempting to straighten their knee for a period of 5 s and to increase the force gradually to maximum voluntary effort. The isometric knee extensor strength was measured three times with a 2 min break between each measurement. The highest value of the maximum voluntary contraction was used to decide the exercise intensity.

The systolic blood pressure, diastolic blood pressure, and heart rate were measured as parameters of the cardiovascular response. The systolic blood pressure and diastolic blood pressure were measured using an automatic sphygmomanometer (TM-2572, A & D, Saitama, Japan). The heart rate was measured using a chest-worn monitoring device (Actiheart, CamNtech, Cambridge, United Kingdom).

The heart rate variability was assessed as autonomic activity using RR intervals obtained at a temporal resolution of 1 ms from the digitized Actiheart recorder.<sup>25</sup> It is reported that this recorder is technically reliable and valid to sense the heart rate.<sup>26,27</sup> The power spectra of the low-frequency component (LF; 0.04–0.15 Hz) and high-frequency component (HF; 0.15–0.40 Hz) were

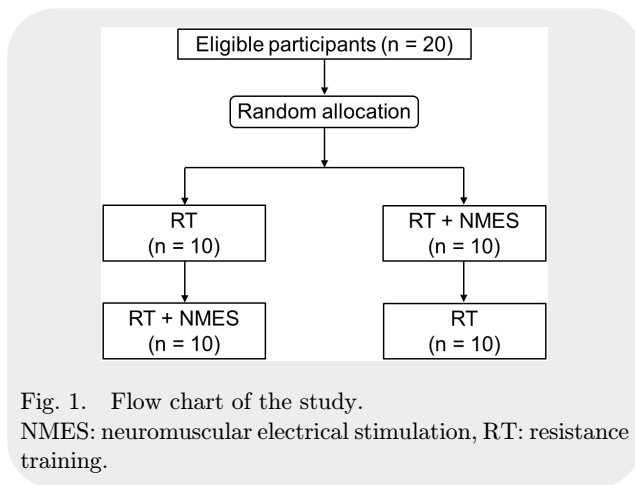
analyzed by power spectrum analysis of heart rate fluctuations using the exclusive software (Actiheart Software version 4.0.116, CamNtech, Cambridge, United Kingdom). The LF/HF ratio was calculated by dividing the LF component by the HF component. The power spectra of the HF component and LF/HF ratio were used as parameters reflecting cardiac parasympathetic and sympathetic activities, respectively.<sup>28,29</sup>

The psychological stress throughout the session was assessed because the psychological stress has been shown to affect the blood pressure and heart rate variability.<sup>30,31</sup> The rating of perceived exertion of the lower extremity was measured using the original Borg scale (6–20).<sup>32</sup> The perceived pain level of the lower extremity was assessed using the numerical rating scale.<sup>33</sup>

### **Study protocol**

The study was performed between 10:00 and 16:00 in an air-conditioned room kept at 23–25°, 2 or more h after lunch. Participants rested for 10 min (pre-exercise phase), exercised for 6 min (3 min in the first half of the exercise phase and 3 min in the second half of the exercise phase), and then rested again for 10 min (post-exercise phase). The systolic blood pressure, diastolic blood pressure, Borg scale, and numerical rating scale were measured at four points: 9 min into the pre-exercise phase, 2 min into the first half of the exercise phase, 2 min into the second half of the exercise phase, and 1 min into the post-exercise phase. The heart rate, LF, HF, and LF/HF were measured throughout the session; the mean values were calculated in each phase because at least a 2-min sample is required to calculate the outcomes of heart rate variability.<sup>29</sup>

For the RT session, the participants performed the isometric knee extension exercise using the dynamometer. They flexed the non-dominant knee to 60° and the process was repeated as 6 s of muscle isometric contraction and 6 s of rest, for a total of 30 repetitions (6 min). The exercise intensity (as low-intensity) was set to 40% of the maximum voluntary contraction (peak torque), as referred to in a previous report.<sup>11</sup> For the RT + NMES session, NMES was applied simultaneously with muscle exercise (contraction) described above. During the RT, the participants were given the feedback of 40% of the maximum voluntary contraction, looking at a monitor that showed the exerted torque in real-time.



### Neuromuscular electrical stimulation

NMES was applied to the *rectus femoris* and *vastus medialis* of the non-dominant lower extremity.<sup>34</sup> Self-adhering surface electrodes  $50 \times 90$  mm (PALS, Axelgaard, Fallbrook, CA, USA) were placed on four areas of the skin: the motor points of the *rectus femoris/vastus medialis* and the point approximately 5 cm distal to the other electrodes. NMES was performed with a duty cycle of 6 s stimulation and 6 s rest simultaneously with muscle voluntary contraction using a portable electrical stimulation device (NM-F1, Ito, Tokyo, Japan). A biphasic asymmetrical waveform with a frequency maintained at 50 Hz and a phase duration of  $300 \mu\text{s}$  was used. Stimulus intensity was set to the intensity beyond the motor threshold to evoke visible muscle contractions.

### Statistical analyses

Sample size calculation was performed using the pilot data of the LF/HF ratio in our pre-study. We calculated a target sample size of 20 participants to provide 80% power to detect a 2.0 difference between the RT and RT + NMES sessions, with a two-sided alpha level of 0.05 using a standard deviation of 3.0.

Data were expressed as means  $\pm$  standard deviations or medians (25th, 75th percentiles). The changes in cardiovascular responses and autonomic activity were analyzed using two-way analysis of variance (ANOVA) for repeated measures (group vs. time course) and post-hoc analysis with the Bonferroni test. The changes in the Borg scale and numerical rating scale were analyzed using Friedman's test and Wilcoxon signed-ranks test with Bonferroni

correction. The Statistical Package for the Social Sciences (SPSS version 21.0, SPSS, Chicago, IL, USA) was used for analyses, and a  $P$  value less than 0.05 was considered statistically significant.

## Results

A flow chart of the study is shown in Fig. 1. Twenty subjects (mean age  $21.0 \pm 0.6$  years, mean height  $172.8 \pm 6.0$  cm, mean body weight  $63.5 \pm 7.5$  kg, mean body mass index  $21.2 \pm 1.8 \text{ kg/m}^2$ ) were enrolled in this study. Their maximum isometric knee extensor strength (peak torque) was  $208.8 \pm 43.5$  Nm. All participants completed both experimental sessions without any injuries, and no participants dropped out.

Changes in the cardiovascular responses are shown in Fig. 2. The results of the two-way ANOVA showed no significant group or time interaction effect for systolic blood pressure, diastolic blood pressure, and heart rate. There were no significant differences in systolic blood pressure, diastolic blood pressure, and heart rate throughout the session between the RT and RT + NMES sessions. The systolic blood pressure was significantly increased during the first half and second half of exercise as compared with the pre-exercise levels in both sessions ( $P < 0.05$ , respectively). The heart rate was significantly increased during the first half and second half of the exercise, and post-exercise as compared with pre-exercise readings in both sessions ( $P < 0.05$ , respectively).

Changes in autonomic activity are shown in Fig. 3. The results of the two-way ANOVA showed no significant group or time interaction effects for LF, HF, and LF/HF. There were no significant differences in LF, HF, and LF/HF between the RT and RT + NMES sessions throughout a single session. The LF and LF/HF were significantly increased during the first half of and second half of the exercise when compared to the pre-exercise levels in both sessions ( $P < 0.05$ , respectively).

Changes in the Borg scale and the numerical rating scale are shown in Table 1. There were no significant differences in the Borg scale or the numerical rating scale between the RT and RT + NMES sessions throughout a single session. The Borg scale was significantly increased during the first and second halves of the exercise, and during post-exercise when compared to the pre-exercise readings in both sessions ( $P < 0.05$ , respectively).

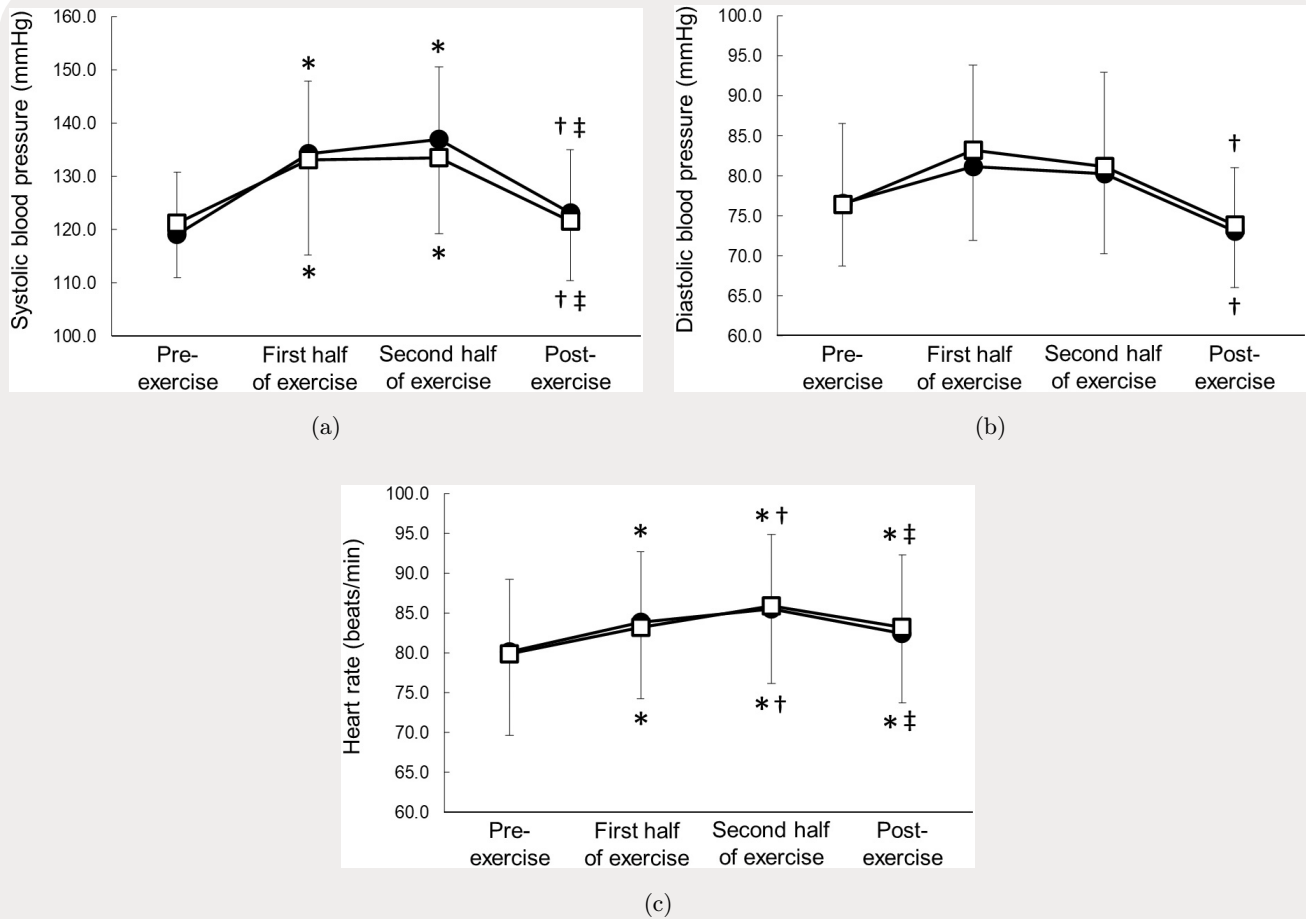


Fig. 2. Changes in the cardiovascular responses throughout the session (a) Systolic blood pressure, (b) diastolic blood pressure, (c) heart rate. Data are expressed as means  $\pm$  standard deviations. Closed circles and open squares stand for RT and RT + NMES sessions, respectively. \*  $P < 0.05$  vs. pre-exercise, †  $P < 0.05$  vs. first half of the exercise, ‡  $P < 0.05$  vs. second half of the exercise. NMES: neuromuscular electrical stimulation, RT: resistance training.

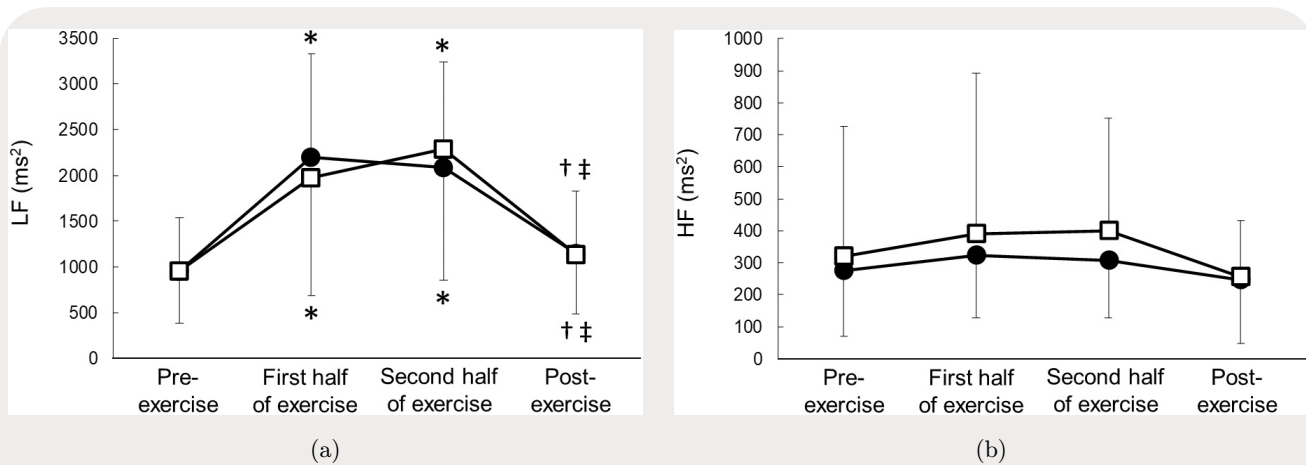


Fig. 3. Changes in autonomic activity throughout the session (a) LF, (b) HF and (c) LF/HF. Data are expressed as means  $\pm$  standard deviations. Closed circles and open squares stand for RT and RT + NMES sessions, respectively. \*  $P < 0.05$  vs. pre-exercise, †  $P < 0.05$  vs. first half of the exercise, ‡  $P < 0.05$  vs. second half of the exercise. HF: high-frequency component, LF: low-frequency component, NMES: neuromuscular electrical stimulation, RT: resistance training.



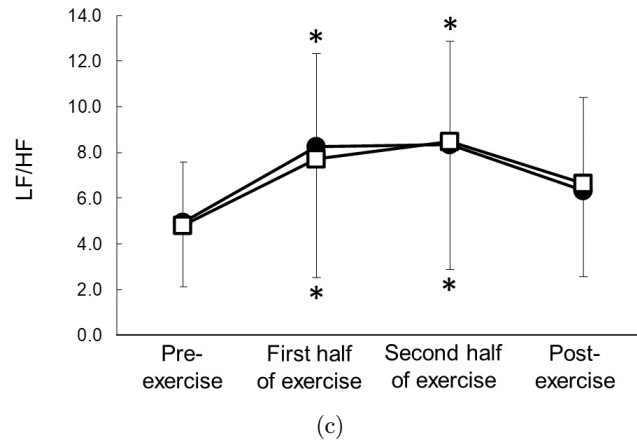


Fig. 3. (Continued)

Table 1. Changes in the Borg scale and the numerical rating scale.

		Pre-exercise	First half of exercise	Second half of exercise	Post-exercise
Borg scale	RT	7 (6, 9)	9 (7, 11)*	10 (8, 13)* †	10 (7, 13)*
	RT + NMES	7 (6, 9)	9 (7, 11)*	11 (7, 12)* †	10 (8, 11)*
Numerical rating scale	RT	0 (0, 1)	0 (0, 2)	0 (0, 2)	0 (0, 1)
	RT + NMES	0 (0, 0)	0 (0, 2)	1 (0, 2)	0 (0, 1)

Notes: Data are expressed as medians (25th, 75th percentiles). The numerical rating scale represents the perceived pain level of the lower extremity. \*  $P < 0.05$  vs. pre-exercise, †  $P < 0.05$  vs. first half of exercise. NMES: neuromuscular electrical stimulation, RT: resistance training.

## Discussion

This study investigated autonomic activity and cardiovascular responses during low-intensity RT + NMES in healthy adults. The results showed that changes in autonomic activity and cardiovascular responses showed no differences between RT and RT + NMES sessions; however, a significant increase in LF/HF (sympathetic activity), systolic blood pressure, and heart rate were observed during exercise. Therefore, the results illustrated that the addition of NMES to RT did not compromise the safety of low-intensity RT.

Previous reports showed that RT + NMES improves physical function without causing adverse events; however, few studies have reported on autonomic activity and cardiovascular responses during the pre-exercise, in-exercise, and post-exercise periods.<sup>35,36</sup> In contrast, several studies have suggested changes in autonomic activity and cardiovascular response when subjects performed RT or NMES alone.<sup>18,19,37</sup> This study did not show that adding NMES to RT elicited a worse response

to autonomic activity or cardiovascular response compared to RT alone. The results from this study support the safety of RT + NMES, as shown in the results of previous studies investigating RT or NMES alone from the aspect of evaluating autonomic activity and cardiovascular response.

Observing the intensity of RT was very important in this study. After measuring the peak torque of knee extensor, 40% of the maximum voluntary contraction was calculated. A monitor was set up in front of the participants, and the monitor displayed a bar graph that moved up and down when power was applied and a line indicating 40% of maximum voluntary contraction. The participant looked at the monitor and adjusted the output of muscle strength, and if the intensity was too high or too low, the instructor explained the appropriate intensity. The monitor feedback provided the participant with immediate exercise intensity, and most subjects did not require explanation by the instructor. Therefore, it was considered that the exercise intensity complied during either RT or RT + NMES sessions.

There were significant increases in perceived exertion in the RT and RT + NMES sessions and a slight increase in pain perception in the RT + NMES session. The previous study has shown that fatigue increased according to the increase of resistance exercise duration.<sup>38</sup> The result of this study supported the previous study. On the other hand, pain perception increased slightly only at RT + NMES sessions, but not significantly. Therefore, it was considered that the addition of NMES did not cause a meaningful increase in pain.

There were no differences in autonomic activity and cardiovascular responses in between the RT and RT + NMES sessions when exercise intensity was the same. The exercise intensity in both sessions was low (40% of the maximum voluntary contraction), and almost all participants felt light fatigue, as rated less than “somewhat hard” using the Borg scale, and very slight pain using the numerical rating scale. In these results, it was considered that perceived exertion and pain did not increase by combining NMES and RT. The blood pressure and heart rate increase during isometric exercise were nearly proportional to the exercise intensity.<sup>39,40</sup> As mentioned above, no difference in autonomic activity and/or cardiovascular responses occurred between the RT and RT + NMES sessions because the mental influence of NMES was small and the exercise intensity was equivalent.

In this study, the LF/HF, systolic blood pressure, and heart rate were slightly but significantly increased during each session. Excessive sympathetic activity has been reported to cause arrhythmias, excessive increase of blood pressure, and even sudden death.<sup>17</sup> Accordingly, it is important to suppress excessive sympathetic activity during exercise, especially for patients with several diseases to exercise safely. It is well known that activation of sympathetic activity occurs during exercise and that autonomic activity alters the heart rate and haemodynamic.<sup>41</sup> Moreover, the blood pressure and heart rate increase during isometric exercise because of the vasoconstriction and increased cardiac output.<sup>39,40</sup> Therefore, autonomic activity and cardiac responses obtained from this study are physiologically explainable. In addition, the 10–15 mmHg increase in the systolic blood pressure during exercise was statistically significant but may be unimportant from a clinical standpoint.

There are some limitations to this study. First, the participants of this study were healthy male college students. It is considered that the biological

response to exercise changes depending on disease or physical condition. Therefore, further research is needed to prove the safety of RT + NMES for patients with different diseases by observing the biological reactions. Secondly, autonomic activity was evaluated only by the heart rate variability in this study, which is an indirect indicator of autonomic activity. This heart rate variability may limit the reliability and validity of the research results. Therefore, the use of other indicators of autonomic activity such as plasma epinephrine and norepinephrine concentrations and the arterial baroreflex sensitivity<sup>42</sup> are worth exploring as evaluation markers in future research in order to improve the reliability and validity of autonomic activity results. Although this study had some limitations, the results are thought to be useful as basic data for the application of low-intensity RT + NMES to older patients in the future.

In conclusion, our results demonstrated that low-intensity RT + NMES was safe and did not induce excessive cardiovascular and autonomic responses in healthy adults.

## **Conflict of Interest**

The authors have no conflict of interest relevant to this paper.

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## **Author Contributions**

Conception and design of the study was made by T. Kutsuna, H. Sugawara, H. Kurita, and T. Takahashi; acquisition of data were made by T. Kutsuna, H. Sugawara, and S. Kusaka; analysis and/or interpretation of data were made by T. Kutsuna, H. Sugawara, H. Kurita, and T. Takahashi; drafting the manuscript was made by T. Kutsuna; revising the manuscript critically for important intellectual content was made by H. Sugawara and H. Kurita. All authors were involved in the approval of the manuscript to be published.

Randomization and statistical analysis was made by T. Kutsuna; measuring the outcome measures were made by T. Kutsuna and S. Kusaka;

instruction of RT was made by T. Kutsuna and H. Sugawara; location of the electrodes of NMES was made by H. Sugawara. The authors' specialties were physiotherapy for respiratory, circulatory, and metabolic disorders (T. Kutsuna, H. Kurita, S. Kusaka, and T. Takahashi) and electrophysical agents (H. Sugawara), and they had enough experience in the specialized areas.

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