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**[Title]** Effects of acute arm-cranking exercise with electrical muscle stimulation at different intensities on the vascular endothelial function

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**Running title:** Arm-cranking exercise plus EMS effect vascular function

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## **Abstract**

Arm-cranking exercises combined with electrical muscle stimulation (EMS) of the lower limbs at maximum intensity enhance vascular endothelial function. To bring this procedure into clinical application, we examined the effects of acute arm-cranking exercise combined with lower-extremity EMS at different intensities on vascular endothelial function. The study included eight healthy adult males. After resting in the supine position, arm-cranking exercises were performed at an intensity of 50%  $\dot{V}O_2$  max for 20 min, and the lower limb received EMS under three trials: maximum intensity trial (A+100%EMS trial), 50% intensity trial (A+50%EMS trial), and 25% intensity trial (A+25%EMS trial). Flow-mediated dilation (FMD), which reflects vascular endothelial function, was measured before and after the procedure, and the normalized FMD (nFMD) was calculated. The mean nFMD before and 30 min after the exercise was  $0.8 \pm 0.3$  and  $2.3 \pm 1.8$ , respectively, in the A+100%EMS trial and  $0.9 \pm 0.4$  and  $1.4 \pm 1.0$ , respectively, in the A+50%EMS trial, indicating a significant increase after exercise under both trials. No changes were observed in the A+25%EMS trial. The combination of arm-cranking

exercise and 50% intensity EMS appears to be a clinically applicable program for improving vascular endothelial function, even with reduced exercise intensity.

**[Keywords]** vasodilatation; electrical stimulation; aerobic exercise; upper extremity

### **Article title**

一過性の上肢の有酸素性運動と異なる強度の骨格筋電気刺激が血管内皮機能に及ぼす影響

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## Abstract

上肢の有酸素性運動と最大耐性強度の下肢への骨格筋電気刺激(EMS)の併用運動は血管内皮機能を向上させる。このプログラムを臨床応用させるためには、運動プログラムの低強度化が求められるが低強度化した運動プログラムが血管内皮機能に及ぼす影響については、十分に検討されていない。本研究では、一過性の上肢の有酸素性運動と異なる強度の下肢 EMS の併用が上腕動脈の血管内皮機能に及ぼす影響について検討した。被験者は、健康な成人男性 8 名であり仰臥位安静後、50%  $\dot{V}O_2\text{max}$  強度で 20 分間の上肢クラック運動と下肢への EMS を最大耐性強度 (A+100%EMS) 条件、50%強度 (A+50%EMS) 条件、25%強度 (A+25%EMS) 条件の 3 条件を実施させた。運動前後に血管内皮機能を反映する FMD を測定し、標準化 FMD (nFMD) を算出した。運動前および運動終了 30 分後の nFMD は、A+100%EMS 条件で  $0.8 \pm 0.3$ ,  $2.3 \pm 1.8$  であり、A+50%EMS 条件で  $0.9 \pm 0.4$ ,  $1.4 \pm 1.0$  であり、両条件ともに運動前と比較して運動終了 30 分後に有意な増加を示した。A+25%EMS 条件では、運動前後に変化は認められなかった。50%強度の EMS においても、他動的な筋収縮による血流量の増加、一酸化窒素などの血管拡張物質の産生促進などにより、nFMD が増加したことが考えられる。上肢の有酸素性運動と 50%強度の下肢 EMS の併用運動は、血管内皮機能の改善を目的とした臨床応用可能な運動プログラムとなる可能性が示唆された。

## 1 **Introduction**

2 Walking and bicycle pedaling are used as exercise therapies for cardiovascular  
3 diseases (CVDs) and metabolic diseases. The effects of such lower-limb aerobic exercises  
4 on arterial function include improved arterial compliance <sup>1)</sup>, improved flow-mediated  
5 dilation (FMD) <sup>2)</sup>, and decreased pulse wave velocity (PWV) <sup>3)</sup>. The mechanism for this  
6 is that increased blood flow due to exercise increases shear stress, a mechanical stress on  
7 the vessel wall that causes vasodilation due to the release of nitric oxide from vascular  
8 endothelial cells <sup>4)</sup>. Thus, aerobic exercise of the lower extremities has been shown to  
9 reduce the risk of developing CVDs.

10 However, patients with spinal cord injury (SCI) and paralysis of the lower extremities  
11 and orthopedic patients with joint pain and deformity have difficulty performing the  
12 recommended aerobic exercises, limiting daily physical activity and rehabilitation.  
13 Patients with SCI have higher resting femoral artery PWV <sup>5)</sup> and lower arterial  
14 compliance than healthy patients <sup>6)</sup>. Moreover, they are associated with increased  
15 mortality from CVD due to atherosclerosis and hypertension <sup>7)</sup>. Aerobic exercise of the  
16 upper extremities may be considered when aerobic exercise of the lower extremities is  
17 difficult. Miura et al. reported no significant change in the brachial-ankle PWV before  
18 and after 30 min of moderate-intensity arm crank exercise in healthy adult men <sup>8)</sup>. These

19 results suggest that aerobic exercise of the upper extremities does not alter arterial  
20 function; however, electric muscle stimulation (EMS), which is effective in increasing  
21 muscle strength <sup>9)</sup>, energy metabolism <sup>10)</sup>, and blood flow <sup>11)</sup>, has attracted attention as a  
22 possible solution. Rappel et al. reported that a hybrid exercise involving arm-cranking  
23 (35.9±8.4 W, 50% of body mass) combined with EMS (4 Hz, 350 μs) at the maximum  
24 tolerated intensity increased oxygen uptake compared to arm-cranking exercise alone  
25 (hand cycle: approximately 13.5 ml/min/kg vs. hand cycle with EMS: approximately 19.0  
26 ml/min/kg) <sup>12)</sup>. In addition, arm-cranking exercise at 50%  $\dot{V}O_2$  max combined with EMS  
27 of the lower extremities at maximal tolerable intensity has been reported to improve  
28 brachial artery (BA) endothelial function <sup>13)</sup>, suggesting the possibility of improving  
29 endurance and cardiovascular performance in patients with SCI and those that are  
30 wheelchair-dependent. However, in both studies, the stimulation intensity of EMS was at  
31 the maximum tolerable intensity. In clinical physical therapy, it is difficult to actively  
32 perform high-intensity exercise because many patients have a combination of various  
33 diseases associated with poor physical function and various risks associated with exercise.  
34 In addition, discomfort and pain caused by high-intensity electrical stimulation (ES) may  
35 affect withdrawal from therapy <sup>14)</sup>. Therefore, identification of more clinically appropriate  
36 stimulus intensities for ES conditions is important to implement physical therapy. A new

37 program combining low-intensity aerobic exercise for the upper extremities and EMS for  
38 the lower extremities should be developed. If the beneficial effects of combined arm-  
39 cranking exercise and low-intensity EMS on vascular endothelial function are  
40 demonstrated, this could be a new exercise therapy that could be applicable to more  
41 patients; however, this point has not been adequately investigated and may be a factor  
42 preventing the widespread use of this hybrid exercise.

43 Therefore, this study aimed to investigate the effects of acute arm-cranking exercise  
44 combined with EMS of the lower extremities at different intensities on BA vascular  
45 endothelial function.

46

## 47 **Methods**

### 48 *Participants*

49 The study participants were eight healthy adult men (age:  $21.6 \pm 0.5$  years, height:  
50  $169.4 \pm 5.8$  cm, weight:  $67.1 \pm 9.1$  kg, body mass index:  $23.6 \pm 3.0$  kg/m<sup>2</sup>) who had never  
51 smoked, did not take regular medications or supplements, and exercised for 1–2  
52 times/week. This study was approved by the Research Ethics Committee of the  
53 Department of Physical Therapy, Faculty of Health Science, Osaka Yukioka College of  
54 Health Science (#33-0005), Japan. Additionally, the participants were provided with an

55 oral explanation of the content and purpose of the study, including refusal, withdrawal,  
56 and interruption of participation, and written informed consent was obtained.

57

## 58 ***Study Design***

59 The protocol used in this study and the picture of the experiment are shown in Figures  
60 1 and 2. All participants visited the laboratory four times for measurements. On the first  
61 day, a maximal exercise test with arm-cranking exercise was performed, and at least 1  
62 week after the test, the participants were randomly assigned to a trial combining EMS  
63 with maximum tolerable intensity for pain and moderate-intensity arm-cranking exercise  
64 (A+100% EMS trial), a trial combining moderate-intensity EMS (A+50%EMS trial), or  
65 a trial combining low-intensity EMS (A+25%EMS trial). For the maximal exercise  
66 tolerance test and arm-cranking exercise for each trial, the participants sat in a chair and  
67 grasped the pedals of a bicycle ergometer (AEROBIKE 75XL III; Combi Co., Tokyo,  
68 Japan) fixed on a platform with both hands. The bicycle ergometer was grounded such  
69 that the crankshaft and the participants' acromion were level, and the participants sat with  
70 their knee joints flexed at 90°. The rotation rate of the arm-cranking exercise in the  
71 maximal exercise tolerance test and each condition was defined as 60 rotations per minute.  
72 All the participants were instructed to limit their alcohol consumption, caffeine intake,



73 and strenuous exercise from the day before to the end of the experiment. Measurements  
74 were taken simultaneously in a room with controlled room temperature (23–25°C) and  
75 humidity (50–70%) at least 4 hours after eating.

76 **Figure 1**

77 **Figure 2**

78

### 79 ***Maximal Exercise Tolerance Test***

80 To determine the intensity of the arm-cranking exercise, a multistage exercise tolerance  
81 test was performed on a bicycle ergometer to measure the maximal oxygen uptake ( $\dot{V}O_2$   
82 max). After resting in a chair for 3 min, a maximal exercise tolerance test was performed,  
83 starting at 6W and increasing the load in 6 W/min steps.

84

### 85 ***Flow-Mediated Vasodilation***

86 In this study, the endothelial function of the BA was assessed. The endothelial function  
87 of the BA is an indicator of systemic endothelial function. Moreover, the FMD of the BA  
88 is highly significant because it is a predictor of CVDs <sup>15, 16</sup>. The participants were asked  
89 to rest in the supine position for at least 15 min to obtain the resting arm systolic blood  
90 pressure (SBP) and diastolic blood pressure (DBP) using a standard sphygmomanometer

91 on their left arm. An occlusion cuff was placed around the right forearm, and two  
92 electrocardiogram leads were attached to the wrists to measure the heart rate (HR). The  
93 FMD was quantified using high-resolution ultrasonography (UNEXEF 38G; UNEX Co.,  
94 Nagoya, Japan) to measure endothelial function. The BA was scanned longitudinally 5–  
95 10 cm proximal to the elbow joint. To occlude the blood flow, the cuff was inflated to 50  
96 mmHg above the SBP for 5 min. Upon cuff deflation, the blood flow velocity and arterial  
97 diameter were measured for an additional 3 min, and the change in the BA diameter was  
98 immediately expressed as a percentage change relative to the vessel diameter before cuff  
99 inflation. The FMD was calculated as the baseline value ( $D_i$  base) before the cuff was  
100 released to the peak value after cuff release ( $D_i$  peak). The FMD was calculated using the  
101 following equation:  $FMD (\%) = \{(D_i \text{ peak} - D_i \text{ base}) / D_i \text{ base}\} \times 100$ . A detailed  
102 description of the measurements was provided in a previous study <sup>17)</sup>.

103 In this study, peak shear rate (PSR) was calculated from the vessel diameter and blood  
104 flow velocity to compare the FMD in different trials. The blood flow velocity was  
105 calculated from the color Doppler data and displayed as a waveform in real-time. The  
106 PSR was calculated using the formula:  $PSR = [\text{difference in flow velocity between the}$   
107  $\text{hyperemic response (peak after cuff deflation; FV peak) - baseline (FV base)}] / \text{baseline}$   
108  $\text{BA diameter}$ . Subsequently, the normalized FMD (nFMD) was calculated as follows <sup>18)</sup>:

109 nFMD (a. u.) =FMD/PSR

110 All measurements were performed after 15 min of supine rest and 30 min after each  
111 trial. FMD was measured by all participants with the right hand. The HR was measured  
112 every 5 min during each trial using thoracic bipolar induction (POLAR H-10; Polar Co.,  
113 Ltd., Tokyo, Japan).

114

### 115 ***Electrical Muscle Stimulation***

116 In the EMS trial, belt electrode-skeletal muscle electrical stimulation (G-TES; Homer  
117 Ion Co., Ltd., Tokyo, Japan) was performed at a frequency of 4 Hz, pulse width of 250  $\mu$ s  
118 <sup>19)</sup>, and exponentially increasing waves. EMS was applied to the calf and thigh muscles,  
119 including the quadriceps femoris, hamstrings, gastrocnemius, and hip adductor muscles,  
120 using a stimulator. A value of 4 Hz was selected because this study aimed to promote  
121 peripheral circulation through aerobic exercises <sup>20)</sup>. One silicon-rubber electrode band  
122 (5.3×93.3 cm) was wrapped around the lumbar region, two bands (5.3×69.6 cm) were  
123 wrapped around both distal parts of the thighs, and two bands (5.3×54.6 cm) were  
124 wrapped around both ankles. As the stimulation cycles of the bilateral thighs and lower  
125 legs were synchronized, the bilateral lower-extremity muscle groups were simultaneously  
126 stimulated. The average stimulus intensity was approximately 3.0±0.6 mA in the thighs

127 and  $0.8\pm 0.2$  mA in the ankle in the A+100%EMS trial,  $1.6\pm 0.3$  mA in the thighs and  
128  $0.4\pm 0.1$  mA in the ankle in A+50%EMS trial, and  $0.8\pm 0.1$  mA in the thighs and  $0.3\pm 0.1$   
129 mA in the ankle in the A+25%EMS trial.

130

### 131 ***Statistical Analysis***

132 The results of this study were analyzed for normality using the Shapiro–Wilk test to  
133 confirm distribution of the data. The measurements for each trial were compared using a  
134 two-way repeated-measures analysis of variance to test for the presence or absence of an  
135 interaction. Moreover, the Bonferroni test was performed for posterior analysis. All  
136 measurements are expressed as means and standard deviations and were considered  
137 statistically significant at a significance level of  $<5\%$ .

138

### 139 **Results**

#### 140 ***HR and $\dot{V}O_2$ during each trial***

141 The changes in HR and  $\dot{V}O_2$  during the three trials are shown in Figures 3 and 4. There  
142 was a significant difference in the HR at 5 and 20 min during exercise in the A+100%EMS  
143 trial. Moreover, the HR in the A+100%EMS trial was significantly higher than that in the  
144 A+25%EMS trial at 5 and 10 min during exercise. From the 5 to 20 min timepoints, the

145  $\dot{V}O_2$  during exercise was significantly higher in the A+100%EMS trial than in the  
146 A+25%EMS trial.  $\dot{V}O_2$  during exercise was also higher in the A+100%EMS trial than in  
147 the A+50%EMS trial at 5 and 20 min. Moreover, in the A+100%EMS trial, there was a  
148 significant increase in  $\dot{V}O_2$  at 20 min of exercise compared with that at 5 min. The average  
149  $\dot{V}O_2$  from 5 to 15 min of exercise was as follows:  $19.1 \pm 1.02$  ml/kg/min (85%  $\dot{V}O_2$  max)  
150 in the A+100%EMS trial,  $15.75 \pm 0.65$  ml/kg/min (70%  $\dot{V}O_2$  max) in the A+50%EMS trial,  
151 and  $13.7 \pm 0.20$  ml/kg/min (60%  $\dot{V}O_2$  max) in the A+25%EMS trial.

152

### 153 ***Brachial artery function before and after each trial***

154 The changes in SBP, DBP, HR, Di base, Di peak, FV base, FV peak, PSR, and FMD  
155 before and after each trial are shown in Table 1. No interactions were observed for all  
156 measurements. In the A+50%EMS and A+25%EMS trials, a significant decrease was  
157 observed in the DBP 30 min after exercise compared to before ( $p < 0.05$ ). In addition, a  
158 significant increase was observed in the HR 30 min after exercise compared to before in  
159 the A+100%EMS trial ( $p < 0.05$ ). In all trials, there was a significant increase in the Di  
160 base and Di peak 30 min after exercise compared to before exercise ( $p < 0.05$  and  $p < 0.001$ ,  
161 respectively). There was no significant main effect or interaction among the SBP, FV base,  
162 FV peak, FMD, and PSR before and 30 min after exercise completion in each trial. The

163 changes in nFMD before and 30 min after exercise completion are shown in Figure 5  
164 ( $0.8\pm0.3$  and  $2.3\pm1.8$  in the A+100%EMS trial,  $0.9\pm0.4$  and  $1.4\pm1.0$  in the A+50%EMS  
165 trial, and  $0.8\pm0.2$  and  $1.1\pm0.5$  in the A+25%EMS trial, respectively). In the A+100%EMS  
166 and A+50%EMS trials, a significant increase in the nFMD was observed 30 min after  
167 exercise completion compared with that before ( $p<0.05$ ).

168 **Table 1**

169 **Figures 3, 4, and 5**

170

## 171 **Discussion**

172 In this study, we investigated the effects of moderate-intensity arm-cranking exercises  
173 with different EMS intensities on vascular endothelial function in healthy adult men. The  
174 results showed that the BA nFMD increased 30 min after exercise completion compared  
175 to that before in the maximum tolerable intensity EMS trial (A+100%EMS trial) and  
176 moderate-intensity EMS trial (A+50%EMS trial). It even showed a higher trend in the  
177 A+100%EMS trial than in the A+50%EMS trial. These results suggest that moderate-  
178 intensity arm-cranking exercise with 100%EMS enhances vascular endothelial function,  
179 similar to the results of previous studies<sup>13</sup>. However, a lower intensity of 50%EMS also  
180 enhances vascular function.

181 Acute responses after EMS include increases in oxygen uptake and HR <sup>21)</sup>, which have  
182 been reported to rise with increasing intensity of ES <sup>22)</sup> and combined upper- and lower-  
183 extremity exercise rather than with upper- and lower-extremity exercise alone. Rappel et  
184 al. found that exercise with EMS to the lower-extremity (4 Hz, 250  $\mu$ s, maximal tolerance)  
185 combined with a hand cycling resulted in higher  $\dot{V}O_2$  and vasodilatory blood lactate levels  
186 than using the hand cycling alone or EMS to the lower-extremity alone <sup>12)</sup>. Moreover,  
187 increases in stimulus intensity and pulse width have also been reported to increase blood  
188 flow <sup>23)</sup>. This finding indicates that the combination of active exercise and ES has  
189 beneficial effects on cardiac dynamics and metabolism. In the A+50%EMS and  
190 A+25%EMS trials, DBP decreased significantly 30 min after exercise compared to before.  
191 This may be due to an increase in circulating blood flow caused by the muscle pumping  
192 action of EMS to the lower limbs at low to moderate intensities. However, no change in  
193 blood pressure was observed before and after exercise in the A+100%EMS trial, possibly  
194 due to the effects of high-intensity ES and high-intensity aerobic exercise on the  
195 autonomic nervous system. Painful ES, such as in the A+100%EMS trial, may be  
196 perceived as a nociceptive stimulus, which increases sympathetic nerve activity, resulting  
197 in the inhibition of peripheral vasodilation, and high-intensity aerobic exercise may  
198 increase the level of protein carbonyl, an oxidative stress marker, and contribute to

199 inactivation of nitric oxide <sup>24</sup>). Thus, A+100%EMS trial had no effect on blood pressure  
200 before or after exercise, suggesting that the A+50%EMS and A+25%EMS trials are not  
201 overloading exercises for blood pressure.

202 Most importantly, the nFMD increased significantly in the A+100%EMS and  
203 A+50%EMS trials after exercise completion compared to that before exercise, with the  
204 degree of increase being greater in the A+100%EMS trial but not significantly different  
205 between trials. Regarding the stimulation intensity of EMS, Karavidas et al. found that  
206 after 6 weeks of functional ES training (25 Hz; stimulus intensity was a visible, painless  
207 muscle contraction) in 16 patients with chronic heart failure, the BA FMD improved  
208 compared to before the training ( $5.77\pm 2.58\%$ , before;  $7.56\pm 2.63\%$ , after) <sup>25</sup>). It has also  
209 been reported that acute low-intensity EMS ( $10.7\pm 4.7\%$  of HR reserve, approximately 2  
210 metabolic equivalent during EMS exercise) improves brachial-ankle PWV and cardio-  
211 ankle vascular index, which reflect arterial function <sup>26</sup>). This was attributed to increased  
212 local blood flow due to EMS-induced muscle pumping in the lower-extremity muscles.  
213 However, no effect on arterial function in the upper extremity was observed. In the present  
214 study, it was suggested that blood flow in the lower extremities, the site of stimulation,  
215 may have increased; however, the increase in nFMD in the BA may have been due to a  
216 greater effect of EMS-induced metabolites. Muscle contraction induced by ES partially



217 reverses the order of motor units to be mobilized <sup>27)</sup>. Moreover, when more type II fibers  
218 are mobilized (type II fiber preferential recruitment) during ES, the release of vasodilators,  
219 such as hydrogen ions and phosphate, increases, which may affect vasodilation <sup>28)</sup>. Since  
220 these vasodilators increase depending on the ES intensity, a similar vasodilatory response  
221 to stimulation intensity may have been observed in the present study <sup>29)</sup>. In addition, EMS  
222 stimulation releases vasodilator P and calcitonin gene-related peptides from nociceptive  
223 C fibers, which causes dilation of the skin vessels. The dilation of cutaneous vessels  
224 requires an increase in cardiac output, which may be involved in the increase in blood  
225 flow in the conduit arteries. These factors suggest that EMS can promote peripheral  
226 circulation and vasodilation even without the maximum intensity that can be tolerated,  
227 and the nFMD may have been improved by medium-intensity EMS in this study.

228       It has been reported that individuals with SCI (especially those with high lesions)  
229 have lower aerobic capacity than normal and healthy individuals due to reduced physical  
230 activity (due to wheelchair-dependent living) and that aerobic capacity decreases linearly  
231 with increasing injury levels <sup>30)</sup>. To address this issue, previous studies have examined the  
232 effects of hybrid exercise combining active exercise and ES on cardiorespiratory function.  
233 These studies have reported that combined exercise of the upper extremities and ES of  
234 the lower extremities improves aerobic capacity in wheelchair-dependent individuals with

235 SCI<sup>12</sup>). In the present study, the oxygen uptake during the hybrid exercise was  
236 approximately 85% $\dot{V}O_2$  max in the A+100%EMS trial and 70% $\dot{V}O_2$  max in the  
237 A+50%EMS trial, suggesting the possibility of improving endurance capacity with  
238 habitual continuation. These results suggest that EMS at 50% of the maximum tolerable  
239 intensity may be a new exercise program that can improve vascular function and  
240 endurance at a lower intensity than that used in the A+100%EMS trial.

241 The clinical implications of the present study are that the combined use of arm-  
242 cranking exercises with EMS at a lower intensity may be indicated for more patients with  
243 the goal of improving vascular endothelial function. Previous studies have reported that  
244 the stronger the intensity of ES, the greater the effect on circulatory dynamics; however,  
245 in clinical practice, the appropriate exercise intensity should be set while assessing the  
246 respiratory-circulatory response to exercise due to the reduced physical activity and  
247 exercise tolerance caused by paralysis of the lower extremities, such as in patients with  
248 SCI. Furthermore, ES therapy often requires a gradual increase in exercise intensity  
249 because patients may discontinue treatment due to discomfort caused by stimulation.  
250 Therefore, combining arm-cranking exercise with moderate-intensity lower-extremity  
251 EMS may be a more clinically suitable exercise program compared to combining it with  
252 ES of maximum tolerable intensity.

253 This study had several limitations. In clinical applications, it is necessary to consider  
254 paralysis accompanied by sensory disturbances, such as SCI. In this study, low-strength  
255 conditions were set from the maximum tolerable strength; however, it is necessary that  
256 the examiner objectively evaluates muscle contraction because it may be difficult to  
257 report the maximum tolerance due to sensory impairment. In addition, it has been shown  
258 that the percentage of type II fibers is higher in paralyzed muscles than in non-paralyzed  
259 muscles <sup>31)</sup>; therefore, whether the results of that study will be similar to those of the  
260 present study remains unclear. Furthermore, since the present study was conducted in the  
261 acute phase, changes in vascular function and aerobic capacity due to the intervention  
262 were unknown. The vasoactive substances produced by exercise, such as nitric oxide,  
263 were also unknown, as no biochemical tests were performed. The FMD is usually  
264 normalized using the area under the curve of the shear rate. However, in the present study,  
265 it was normalized using PSR only. Furthermore, since the stimulation intensity of EMS  
266 was determined subjectively, the possibility of individual differences in muscle  
267 contraction and body composition (lean body mass, subcutaneous fat thickness, and  
268 circumference) cannot be ignored. Muscle contraction and body composition should be  
269 measured in future studies.

270

271 **Conclusion**

272 The beneficial effects of ES on the body have been shown in various studies, making it  
273 an important therapeutic option in rehabilitation. However, patients' disability profiles  
274 vary widely, and rehabilitation needs to be tailored to their unique severity and symptoms.

275 In the present study, the combination of moderate-intensity arm rotation exercise and 50%  
276 intensity EMS suggests that vascular endothelial function can be improved even at  
277 reduced exercise intensity. Therefore, this may be a new exercise program option for  
278 patients who are harmed by the intensity and stimulation of ES and high exercise intensity.

279

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284

285 **Conflict of Interests**

286 There is no conflict of interests for this study.

287

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289 **Contributions**

290 All authors contributed to the study conception and design. MN collected the data and  
291 drafted the manuscript. HM, AM, and YT revised the manuscript. All authors approved  
292 the final version of the manuscript.

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Table 1. Changes in brachial artery function before and after each trial

	A+100%EMS trial			A+50%EMS trial			A+25%EMS trial			group × time interaction p-value
	before	after 30 minutes	time effect within-group p-value	before	after 30 minutes	time effect within-group p-value	before	after 30 minutes	time effect within-group p-value	
SBP (mmHg)	118.9 ± 11.6	118.0 ± 6.6	0.80	119.8 ± 10.5	120.3 ± 10.1	0.81	119.4 ± 15.4	121.0 ± 16.8	0.35	0.50
DBP (mmHg)	66.3 ± 6.9	62.0 ± 5.1	0.18	67.0 ± 6.4	61.1 ± 6.5	0.04*	67.4 ± 5.5	62.3 ± 6.0	0.01*	0.72
HR (bpm)	63.8 ± 10.0	74.4 ± 8.4	0.03*	63.5 ± 10.0	70.5 ± 6.8	0.06	64.3 ± 10.0	72.3 ± 7.7	0.12	0.60
Di <sub>base</sub> (mm)	3.8 ± 0.2	4.3 ± 0.3	0.002*	3.7 ± 0.2	4.15 ± 0.4	0.003*	3.8 ± 0.2	4.1 ± 0.5	0.03*	0.47
Di <sub>peak</sub> (mm)	4.1 ± 0.3	4.6 ± 0.3	0.001**	4.0 ± 0.2	4.5 ± 0.4	0.002*	4.0 ± 0.2	4.4 ± 0.5	0.03*	0.14
FV <sub>base</sub> (cm/sec)	10.4 ± 5.2	11.4 ± 6.6	0.33	11.8 ± 8.7	10.3 ± 3.1	0.53	11.0 ± 5.5	12.6 ± 8.8	0.48	0.65
FV <sub>peak</sub> (cm/sec)	48.1 ± 12.8	40.8 ± 6.6	0.33	47.4 ± 17.8	43.8 ± 19.0	0.51	46.1 ± 5.5	44.2 ± 21.0	0.83	0.83
FMD (%)	7.3 ± 1.0	8.3 ± 2.3	0.31	7.4 ± 0.8	8.3 ± 0.9	0.13	7.3 ± 1.0	6.7 ± 0.8	0.29	0.15
PSR (s <sup>-1</sup> )	10.0 ± 3.6	7.1 ± 5.7	0.08	9.7 ± 4.4	8.2 ± 4.4	0.26	9.4 ± 3.2	7.7 ± 3.6	0.42	0.14

SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, Di base: diameter baseline, Di peak: diameter peak line, FV base: flow volume base, FV peak: flow volume peak, FMD: flow-mediated dilation, PSR: peak shear rate. \*p<0.05, \*\*p<0.01 vs. before.

Figure 1

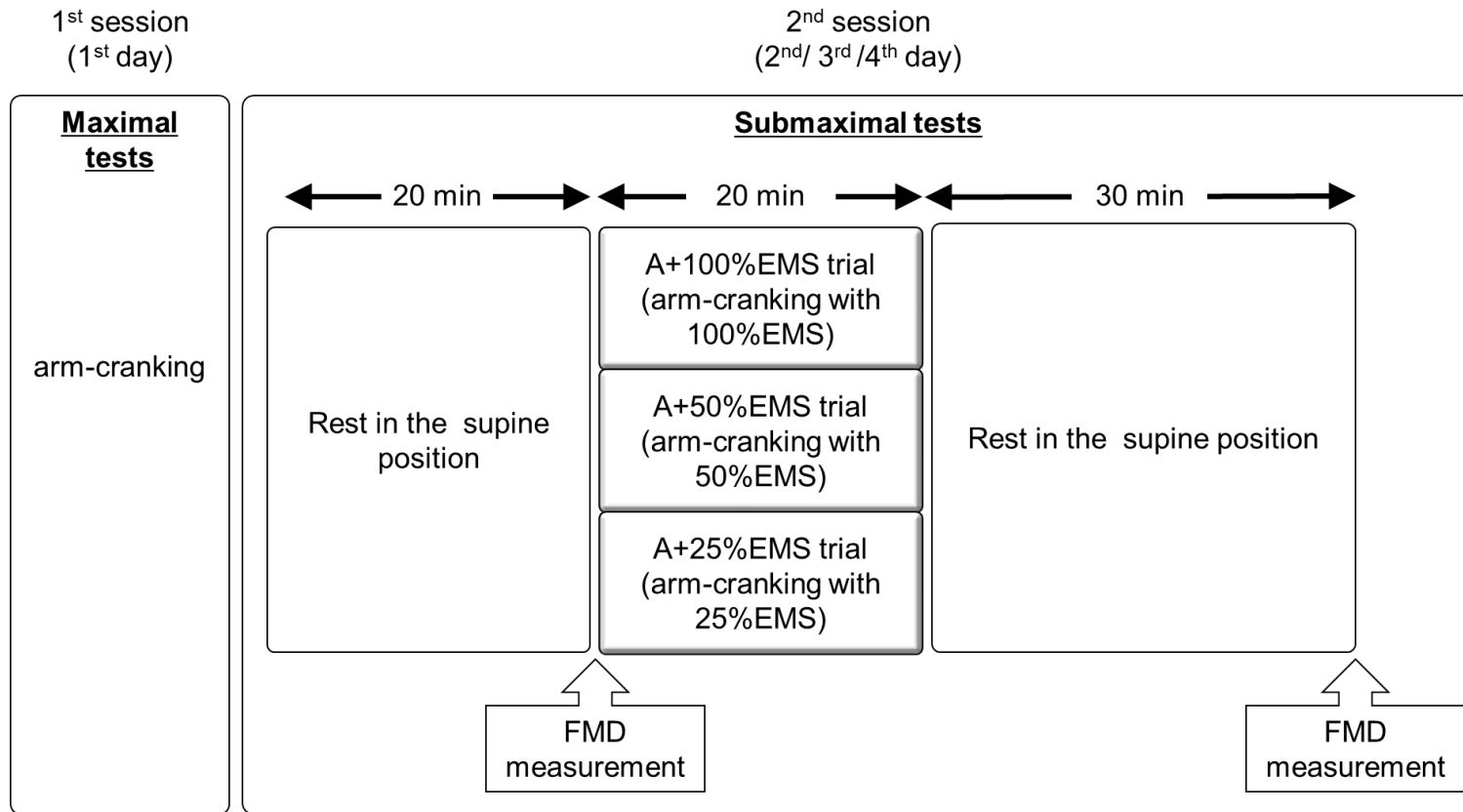


Figure 2



Figure 3

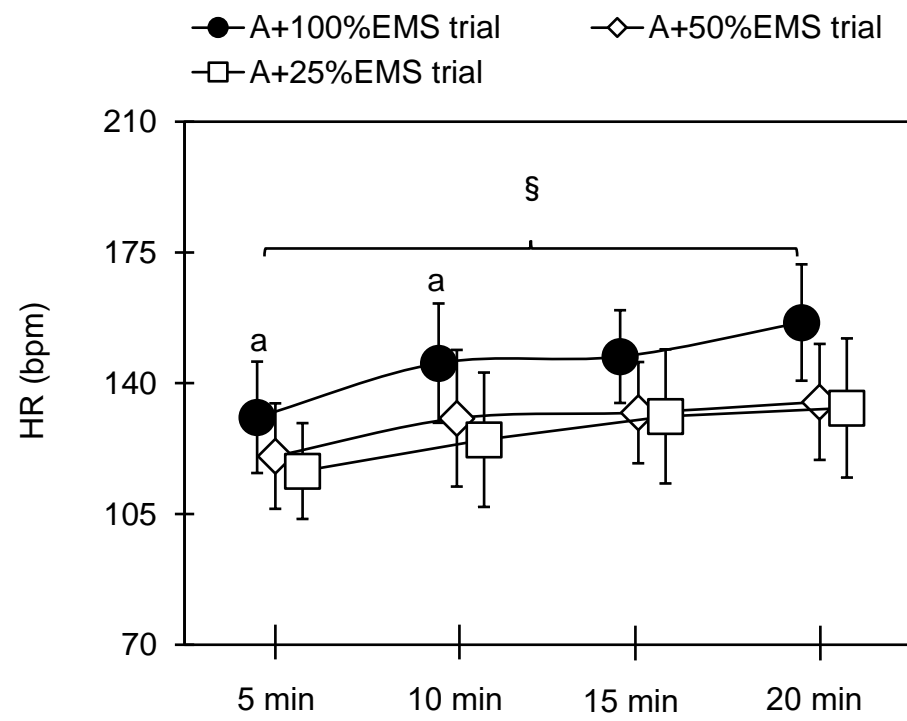


Figure.4

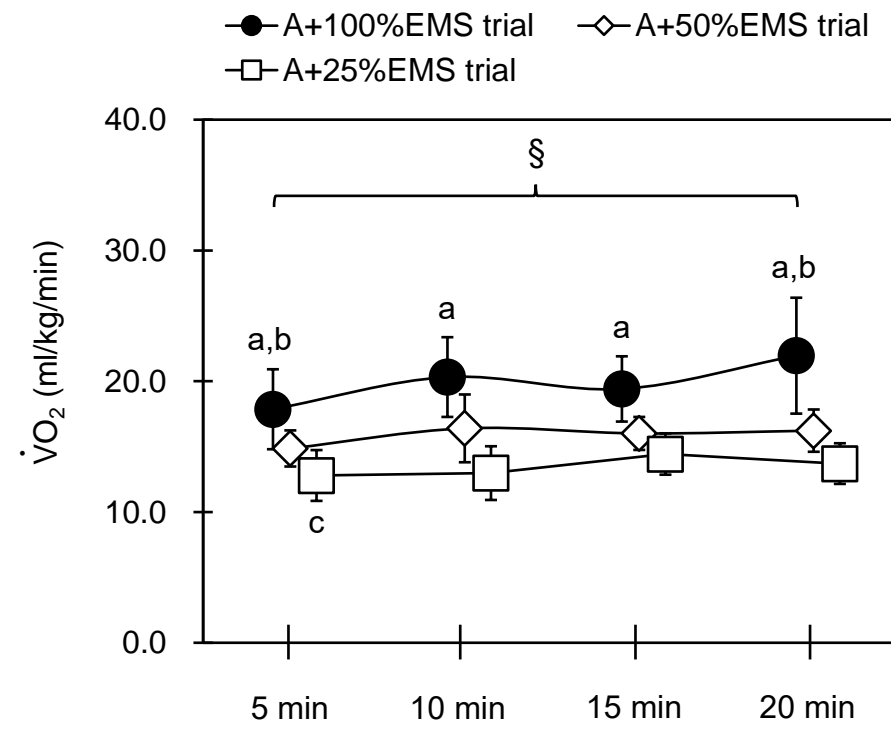
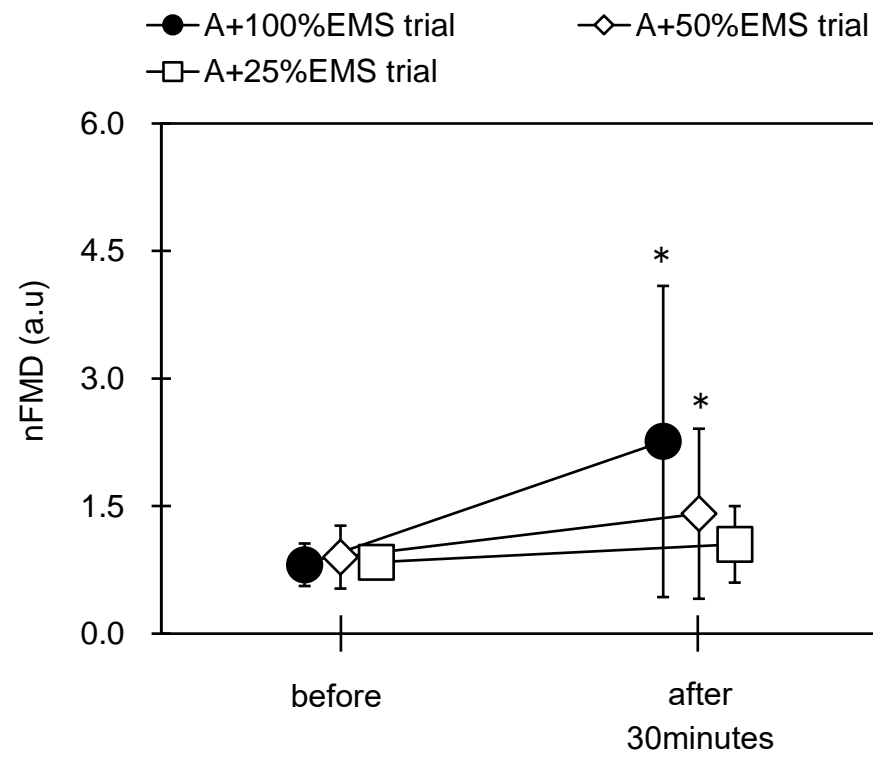




Figure 5



## Figure Legends

Figure 1. Experimental protocol of test sessions. All subjects performed each test in random order. EMS: electrical muscle stimulation, FMD: flow-mediated dilation

Figure 2. A picture of the experiment.

Figure 3. Changes in heart rate (HR) during each trial.

Values are presented as mean  $\pm$  standard deviation (SD).

<sup>a</sup>p<0.05 vs. A+25%EMS trial, <sup>§</sup>p<0.05 vs. 5min.

A: arm-cranking exercise

EMS: electrical muscle stimulation

Figure 4. Changes in oxygen uptake ( $\dot{V}O_2$ ) during each trial.

Values are presented as mean  $\pm$  standard deviation (SD).

<sup>a</sup>p<0.05 vs. A+25%EMS trial, <sup>b</sup>p<0.05 vs. A+50%EMS trial, <sup>c</sup>p<0.05 vs. A+50%EMS trial, <sup>§</sup>p<0.05 vs. 5min.

Figure 5. Changes in normalized flow-mediated dilation (nFMD) before and after each trial.

\*p<0.05 vs. before.