

Effects of endurance training comprising cycling and electrical muscle stimulation of the lower limbs on vessel endothelial function

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Abstract

Purpose: This study aimed to determine the effects of cycling training with electrical muscle stimulation (EMS) applied to the lower limbs on brachial artery endothelial function.

Methods: Forty-six

healthy adult men were randomly assigned to moderate-intensity cycling at 50% maximal oxygen consumption (VO_{2max} ; C group; $n = 15$), low-intensity cycling (LC; $< 50\% VO_{2max}$) with EMS applied to the lower limbs, (equivalent to $50\% VO_{2max}$; LC+EMS group; $n = 14$), or LC (equivalent to cycling at $50\% VO_{2max}$ minus the oxygen uptake of EMS; LC group; $n = 17$). Participants performed 20 minutes of cycling under each condition twice per week for 8 weeks.

Results: Before and after the training session, flow-mediated vasodilation (FMD) at the brachial artery increased significantly in the C and LC+EMS groups. After training, FMD in the C and LC+EMS groups was significantly higher than that in the LC group.

Conclusion: Compared with LC without EMS, LC with EMS applied to the lower limbs can more markedly improve vascular endothelial function.

Introduction

Regular endurance exercise is a key strategy for preventing and treating cardiovascular diseases (CVD) (Pescatello et al. 2015). Moderate-intensity endurance training involving cycling or running is useful and recommended for improving arterial function (Fearheller et al. 2014; Tao et al. 2023). However, individuals with arthritis, osteoarthritis of the hip or knee, or physical frailty cannot perform such exercises for long periods. Usually, they perform such exercise at low intensity; however, this may be insufficient for improving arterial function.

Recently, electrical muscle stimulation (EMS) has been applied to voluntary exercise as a complementary intervention. EMS involves the application of an electric current by depolarizing motor endplates via the motor nerve, thereby inducing skeletal muscle contractions (Vivodtzev et al. 2008). In clinical practice, EMS of the lower limbs for 6 weeks resulted in vessel endothelial function improvement in patients with heart failure (Deftereos et al. 2010). Our team previously reported that training involving arm-cranking with EMS applied to the lower limbs could increase vessel endothelial function in healthy men (Miura et al. 2022). However, moderate-intensity arm-cranking is not a common exercise performed by individuals with arthritis, osteoarthritis or physical frailty and may increase inflammatory reactions. We hypothesized that EMS applied to the lower limbs during low-intensity exercise may increase both energy expenditure and muscle blood flow, which are related to improved vessel function.

Therefore, this study aimed to determine the effects of low-intensity-exercise training with EMS applied to the lower limb on vessel endothelial function and whether these effects results in greater

improvement in vessel endothelial function compared with low-intensity exercise training without EMS.

Methods

Participants

Fifty-one healthy men were enrolled in this study. However, five withdrew because personal reasons. Finally, 46 healthy men were randomly assigned to moderate-intensity cycling at 50% maximal oxygen consumption ($\text{VO}_{2\text{max}}$; C group; $n = 15$), low-intensity cycling (LC; $< 50\% \text{VO}_{2\text{max}}$; [approximately $34.5\% \text{VO}_{2\text{max}}$]) with EMS applied to the lower limbs, (equivalent to cycling at $50\% \text{VO}_{2\text{max}}$; LC + EMS group; $n = 14$), or LC (equivalent to cycling at $50\% \text{VO}_{2\text{max}}$ minus the oxygen uptake of EMS; LC group; $n = 17$). All participants performed 20 minutes of cycling under each condition twice per week for 8 weeks. The anthropometric variables in the training groups were homogeneous (C group; age, 22.9 ± 3.5 years; body mass, 62.2 ± 5.1 kg; height, 172.2 ± 4.8 cm; LC + EMS group; age, 21.4 ± 1.0 years; body mass, 62.0 ± 6.8 kg; height, 172.6 ± 4.8 cm; LC group; age, 22.6 ± 3.4 years; body mass, 62.7 ± 6.6 kg; height, 171.7 ± 3.1 cm).

All participants had normal blood pressure, were not obese, and were free from overt chronic diseases, as determined by assessing by their medical histories, physical examination results, complete blood chemistry results, and hematological evaluation results. All participants provided written informed consent to participate. All procedures were approved by the ethics committee of the Faculty of Integrated Arts and Sciences of the Tokushima University (no. 151). The participants arrived at the laboratory at 9:00 AM and remained there until 11:00 AM. Testing was performed in a quiet temperature-controlled room (23°C – 26°C).

Experimental design

Protocol

Before the training session, participants presented to the laboratory three times. To determine the exercise intensity and training effect on the first day, they underwent continuous incremental tests until volitional exhaustion during cycling. The initial resistance of 50 W was increased by 10 to 20W every minute until exhaustion. At least 3 days after the maximal test, all participants underwent EMS applied to the lower limbs for 15 to 20 minutes to allow acclimation. Energy expenditure during 20 minutes of EMS was measured while participants were in the sitting position at least 3 days after the initial EMS experience.

Each training session consisted of cycling for 20 minutes with or without EMS, 2 days per week for 8 weeks. The C group performed moderate-intensity cycling at $50\% \text{VO}_{2\text{max}}$. The LC + EMS group performed cycling at $< 50\% \text{VO}_{2\text{max}}$ (28.4 – 37.5% of $\text{VO}_{2\text{max}}$) with EMS applied to the lower limbs (equivalent to

cycling at 50% $\text{VO}_{2\text{max}}$). The LC group performed cycling at 27.9% to 38.6% $\text{VO}_{2\text{max}}$, (equivalent to cycling at 50% $\text{VO}_{2\text{max}}$ minus the oxygen uptake of EMS). All groups performed cycling on an electromagnetic cycle ergometer (Fujin-Raijin, OCL Co. Ltd., Tokyo, Japan). Cadence of 60 rpm was used for all exercise session.

Electrical muscle stimulation

In the LC + EMS group, EMS was applied to the calf and thigh muscle groups, including the quadriceps femoris, hamstrings, gastrocnemius, and hip adductor muscles, using a stimulator (G-TES; Homer Iron Co. Ltd., Tokyo, Japan) (Fig. 1). The stimulation current waveform had designed at a frequency of 4 Hz and pulse width of 250 μs . Detailed information regarding this pulse was published previously (Hasegawa et al. 2011). Simultaneous stimulation was performed to synchronize the stimulation cycle applied to the bilateral thighs and calves. One silicon rubber electrode band ($5.3 \times 93.3 \text{ cm}$) was wrapped around the lumbar region, two bands ($5.3 \times 69.6 \text{ cm}$) were wrapped around the distal parts of both thighs, and two bands ($5.3 \times 54.6 \text{ cm}$) were applied to both ankles with the help of a specially designed strap. The contact areas between the skin and electrodes were covered with a specially designed wet cloth. Stimulation was set to the highest bearable intensity that did not cause discomfort (58–77 mA for the thighs and 28–49 mA for the ankles).

Measurements

Vessel endothelial function

To measure flow-mediated vasodilation (FMD), a novel vascular ultrasound system comprising an edge-tracking system for two-dimensional imaging and pulsed Doppler flow velocimeter for automatic measurements (UNEX EF; UNEX Co. Ltd., Aichi, Japan) was used. Participants were asked to rest in the supine position for at least 5 minutes to obtain the upper arm systolic blood pressure (SBP) and diastolic blood pressure (DBP) using a standard sphygmomanometer on the left arm. An occlusion cuff was placed around the right forearm and two electrocardiogram leads were attached to the wrists to measure the heart rate (HR). Subsequently, a linear-array transducer operating at 10 MHz was used to acquire longitudinal images of the right brachial artery (BA). After baseline images were obtained, the cuff on the right forearm was inflated to 50 mmHg above the SBP for 5 minutes. The diastolic pre-beat diameter of the BA was determined semi automatically using an instrument equipped with software (PC analysis software for UNEX EF38G; UNEX Co. Ltd., Aichi, Japan) to monitor the BA diameter. Digital images of the right BA were captured continuously for 30 seconds before cuff inflation and 2 minutes beginning immediately before cuff deflation to document the vasodilator response. Next, FMD was calculated as the percentage change in the diameter based on a comparison of the baseline value (Di_{base}) before cuff release and peak value (Di_{peak}) after cuff release.

All measurements were performed after fasting at least 2 hours with abstinence from caffeine. The participants were studied at the same time of day before and after the training session. Post-training measurements were performed 2 to 3 days after the last exercise session.

All tests were performed simultaneously by the same examiner. To determine the intersession reliability of the Di_{base} values, measurements were performed three times for nine healthy young men, resulting intraclass correlation coefficient of 0.93.

Cardiorespiratory function

Oxygen consumption (VO_2), carbon dioxide production, and ventilation were measured every 30 seconds using a gas analyzer system (AR-1 Type-3; Arco System Co. Ltd., Tokyo, Japan). The HR of all participants was monitored (Polar H10 N; Polar Co. Ltd., Northern Ostrobothnia, Finland).

Statistical analysis

The results are expressed as the mean $\pm$ standard deviation. Homogeneity of variances was analyzed using the Shapiro-Wilk normality test. Data acquired under each condition were analyzed using a two-way analysis of variance (ANOVA) and Bonferroni post hoc condition comparisons (condition: C vs. LC + EMS vs. LC group; time: before and after each training session). Statistical analyses were performed using SPSS software (SPSS, Chicago, IL, USA). Statistical significance was defined as $p < 0.05$.

Results

$\%VO_{2max}$ and $\%HR_{max}$ on the first training day

The mean $\%VO_{2max}$ and $\%HR_{max}$, respectively, during the last 5 min were $52.9 \pm 4.2\%$ and $70.5 \pm 3.3\%$ in the C group, $51.8 \pm 4.7\%$ and $70.2 \pm 2.7\%$ in the LC + EMS group and $36.8 \pm 6.8\%$ and $59.1 \pm 4.4\%$ in the LC group. Significant differences in these values were observed between the C and LC groups and between the LC + EMS and LC groups throughout the first training session ($p < 0.001$).

VO_{2max} and vessel function before and after each training session

Forty-six participants completed the training program. In the LC group, no significant difference in VO_{2max} was observed (from 38.1 ± 5.6 to 39.1 ± 6.5 $ml \cdot kg^{-1} \cdot min^{-1}$; $p =$ not significant). However, the VO_{2max} increased significantly in the C group (from 39.0 ± 5.2 to 43.6 ± 5.0 $ml \cdot kg^{-1} \cdot min^{-1}$; $p < 0.001$) and LC + EMS group (from 40.8 ± 6.9 to 45.0 ± 6.4 $ml \cdot kg^{-1} \cdot min^{-1}$; $p < 0.001$).

Table 1 shows changes in vessel function before and after each training session. Significant interactions were not observed with SBP, DBP, HR, and Di_{base} ; however, a significant interaction was observed with Di

peak. FMD increased significantly in the C group (from $8.4 \pm 0.6\%$ to $12.3 \pm 1.0\%$; $p < 0.001$) and LC + EMS group (from 7.9 ± 1.7 to $11.2 \pm 0.9\%$; $p < 0.001$) before and after each training session [time: $F_{(1, 13)} = 147.833$; $p < 0.001$] (Fig. 2). However, no significant difference was observed in the LC group (from $8.1 \pm 0.6\%$ to $8.6 \pm 0.6\%$; p – not significant). After 8 weeks of training, FMD in the C ($p < 0.001$) and LC + EMS ($p < 0.01$) groups was significantly higher than that in the LC group [group: $F_{(2, 26)} = 21.128$, $p < 0.001$].

Table 1
Vessel function before and after each training session

Variable	Group	Before	After	ANOVA		
				Time	Group	Interaction
SBP (mmHg)	C	126.9 ± 9.3	121.8 ± 9.6	$F_{(1, 13)} = 10.319$	$F_{(2, 26)} = 2.647$	$F_{(2, 26)} = 0.692$
	LC + EMS	120.4 ± 9.8	117.1 ± 9.0	$p = 0.007$	$p = 0.090$	$p = 0.510$
	LC	121.8 ± 9.6	121.7 ± 8.6			
DBP (mmHg)	C	67.7 ± 6.6	65.5 ± 5.5	$F_{(1, 13)} = 1.204$	$F_{(2, 26)} = 0.120$	$F_{(2, 26)} = 0.247$
	LC + EMS	66.9 ± 5.4	66.0 ± 10.1	$p = 0.292$	$p = 0.887$	$p = 0.783$
	LC	66.2 ± 7.7	66.9 ± 5.4			
HR (b·min ⁻¹)	C	71.2 ± 8.9	68.8 ± 7.9	$F_{(1, 13)} = 2.214$	$F_{(2, 26)} = 0.551$	$F_{(2, 26)} = 0.245$
	LC + EMS	68.6 ± 7.8	66.0 ± 9.9	$p = 0.161$	$p = 0.515$	$p = 0.785$
	LC	67.7 ± 9.8	66.1 ± 10.8			
Di _{base} (mm)	C	3.67 ± 0.19	3.65 ± 0.21	$F_{(1, 13)} = 0.565$	$F_{(2, 26)} = 0.277$	$F_{(2, 26)} = 3.886$
	LC + EMS	3.64 ± 0.33	3.63 ± 0.35	$p = 0.761$	$p = 0.761$	$p = 0.033$
	LC	3.60 ± 0.35	3.63 ± 0.36			
Di _{peak} (mm)	C	3.98 ± 0.20	4.10 ± 0.23*	$F_{(1, 13)} = 19.874$	$F_{(2, 26)} = 0.277$	$F_{(2, 26)} = 5.345$
	LC + EMS	3.92 ± 0.35	4.03 ± 0.38*	$p < 0.001$	$p = 0.398$	$p = 0.011$
	LC	3.89 ± 0.37	3.94 ± 0.39			

Values are presented as the mean ± standard deviation.

ANOVA, analysis of variance; C, moderate-intensity cycling; DBP, diastolic blood pressure; Di_{base}, baseline diameter before cuff inflation; Di_{peak}, peak diameter after cuff release; HR, heart rate; LC, low-intensity cycling; LC + EMS, low-intensity cycling with EMS; SBP, systolic blood pressure.

* $p < 0.05$ vs. values before training.

Discussion

This study investigated the effects of low-intensity endurance training with EMS applied to the lower limbs on vessel endothelial function in healthy adult men. The results indicated a significant increase in FMD before and after training in the C and LC + EMS groups. Significant differences in FMD after training were also observed between the LC and C groups and between the LC and LC + EMS groups; however, no significant differences were observed between the C and LC + EMS groups.

FMD is an independent predictor of future cardiovascular events (Green et al. 2011). In healthy asymptomatic adults, a 1% increase in FMD was associated with a 4% reduction in the CVD risk (Ras et al. 2013). Although the mechanism by which endurance training improves vessel function has not been fully elucidated, the beneficial effects of endurance training on vessel function may be mediated several possible mechanisms. Shear stress, the frictional force exerted by blood on the vessel wall, is a regulator of the vascular endothelium (Girard et al. 1995). Previous studies have shown that endurance exercise increase blood flow and shear stress (Goto et al. 2003), which can directly increase nitric oxide (NO) synthesis and release from the vascular endothelium (Green et al. 2004), increase NO bioavailability (Taddei et al. 2000), and enhance endothelial NO synthesis expression (Hambrecht et al. 2003). Inflammation may also play a significant role in endothelial dysfunction. Endurance exercise can reduce serum amyloid A, interleukin-6, and tumor necrosis factor- α (Vandercappellen et al. 2022). Oxidative stress is a risk factor for vascular endothelial disorders (Yilmaz et al. 2020). Endurance exercise can modulate oxidative stress, increase antioxidant enzyme expression, and regulate reactive oxygen species (ROS) in mitochondria (St-Pierre et al. 2006). Furthermore, endurance training can normalize basal overactivity of the sympathetic nervous system (Antunes-Correa et al. 2012). Muscle sympathetic nerve activity (MSNA), which is a measure of sympathetic nerve passage, is reduced by endurance exercise (Notarius et al. 2015).

This study is the first to our knowledge to evaluate the effects of cycling training with EMS on vessel function. An important finding of this study was that the LC + EMS group, which performed LC with EMS applied to the lower limbs, experienced a significant increase in FMD compared with that observed in the LC group.

Although upper extremity crank exercise with lower extremity EMS training can improve arterial function (Miura et al. 2022), the effects of lower extremity exercise with EMS applied to the lower limbs on arterial function have not been reported. Previous studies have reported that long-term functional EMS applied to the lower limbs can improve endothelial function in patients with chronic heart failure (Karavidas et al. 2006), and that EMS applied to the lower limbs can increase blood flow at the common femoral artery (Janssen and Hopman 2003). Furthermore, rhythmic increases and decreases in intramuscular pressure caused by skeletal muscle contraction can increase blood flow and induce a vasodilatory response by increasing shear stress, which is a type of mechanical stress, on vascular endothelial cells (Hambrecht et al. 1998). In the present study, exercise intensities were approximately 50% VO_{2max} in the C group, approximately 50% VO_{2max} in the LC + EMS group, and approximately 35.4% VO_{2max} in the LC group.

Exercise intensity is usually influenced by muscle blood flow (Saltin et al. 1998); therefore, muscle blood flow in the lower limbs during LC without EMS may be less than that during LC with EMS, which may have been the same as that in the C group. Low-intensity endurance exercise may provide slight shear stress stimulation with the potential to improve endothelial function, whereas moderate-intensity endurance exercise and low-intensity endurance exercise with EMS can enhance endothelial-dependent vasodilation by increasing NO production, blood flow, flow velocity, and shear stress and reducing ROS production.

Furthermore, vascular endothelial function improvement requires an increase in muscle blood flow by contracting more skeletal muscle (Schardong et al. 2017). Other studies have shown that active muscle blood flow is strongly influenced by metabolism associated with muscle activity and that muscle blood flow increases despite the increased sympathetic activity associated with exercise (Remensnyder et al. 1962). Based on these findings, although the cycling-exercise-intensity in the LC + EMS group was relatively low, LC combined with EMS applied to the lower limbs caused muscle contraction in more skeletal muscles and increased active muscle mass, which increased blood flow by producing intramuscular pressure fluctuations. Additionally, the enhanced production of NO, which is a metabolite of EMS-induced muscle contraction, may have increased FMD by inducing vasodilation. Therefore, the LC + EMS group, which included voluntary LC and EMS applied to the lower limbs, experienced a significant increase in FMD before and after training.

Clinical Implications

Individuals with arthritis, osteoarthritis of the hip or knee, or physical frailty are at a high risk for CVD (Miyatani et al. 2009; Wecht et al. 2004; Yoshimura et al. 2009). Usually, they cannot perform moderate-intensity lower-limb exercise, such as walking, running, or cycling, for long periods. An important clinical implication of this study is that LC training with EMS results in greater change in FMD compared with that associated with LC training without EMS. Previous studies have shown that increasing FMD is positively related to a reduced risk of CVD, and that every 1% increase in FMD decreases the CVD risk by 13% (Inaba et al. 2010; Ras et al. 2013). Although the present study did not measure vessel function in such patients or those with frailty, our findings suggest that LC with EMS is useful for reducing the risk of CVD.

Limitations

The present study had several limitations. First, for safety reasons, the study participants were healthy adult men; therefore, the results of this study should not be extrapolated to patients with osteoarthritis or physical frailty. The effects of this intervention on such participants should be evaluated in the future, however. Second, to identify the mechanism underlying improved vessel function associated with LC with EMS, measurements of the cardiac output/muscle blood flow and analyzes of atrial natriuretic peptide, NO, and endothelin-1 levels are needed. Finally, in the present study, EMS was applied for 20 minutes at the highest bearable intensity that did not cause discomfort. Despite these limitations, our

results may have scientific and clinical importance because changes in vessel function that result from exercise with EMS have not been well-established.

Conclusion

In conclusion, the results of this study indicate that both moderate-intensity cycling and LC with EMS applied to the lower limbs can result in more marked improvement in vessel endothelial function compared with that associated with LC without EMS. A combination of endurance exercise and EMS may be a useful rehabilitation strategy for patients with osteoarthritis or physical frailty. Further studies are needed to establish an exercise program involving endurance exercise with EMS for rehabilitation.

Declarations

Competing Interests

The authors declare no conflicts of interest with the present research.

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Author Contribution

HM conceptualized and designed the research. HM and MN performed the experiments. HW, MN, AM, and YT analyzed the data, HM and JD interpreted the results of the experiments, HM prepared the figures and table. HM and MN drafted the manuscript. All authors edited and revised the manuscript. All authors approved the final version of the manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article.

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Figures

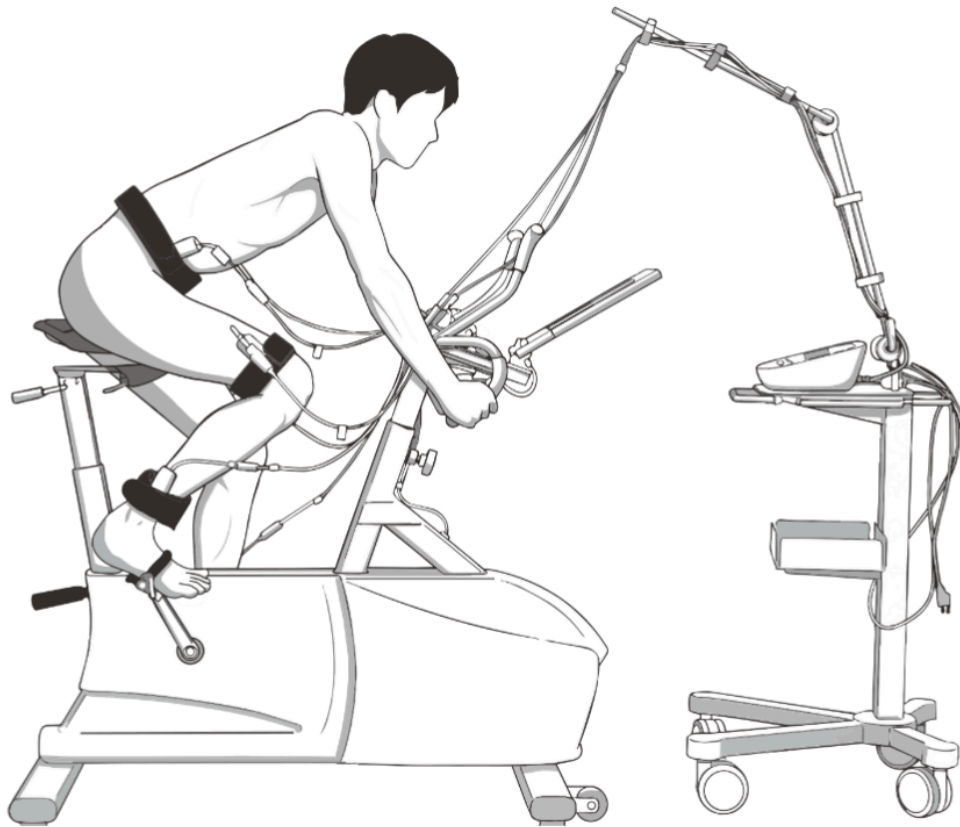


Figure 1

The experimental setting for low-intensity cycling with electrical muscle stimulation applied to the lower limbs.

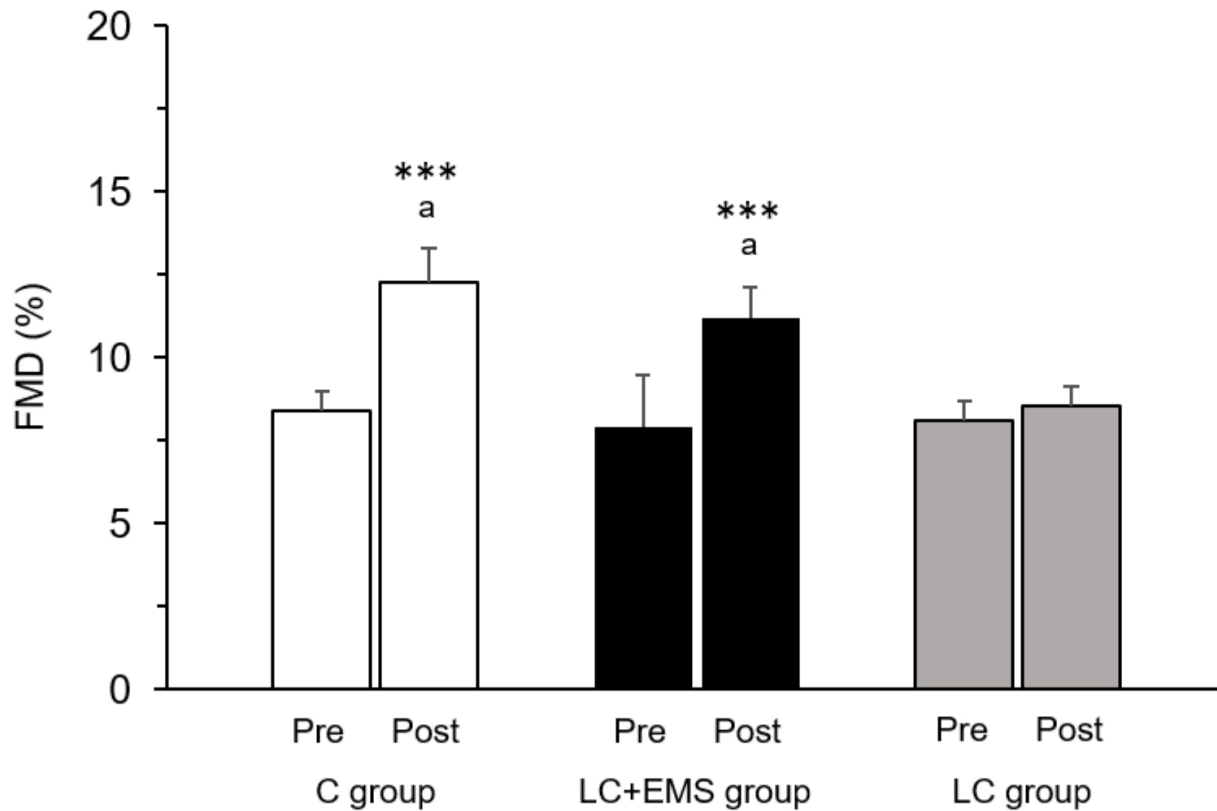


Figure 2

FMD changes pre (before) and post (after) each training session.

Values are presented as the mean $\pm$ standard deviation. C, moderate-intensity cycling; DBP, diastolic blood pressure; Di_{base} , baseline diameter before cuff inflation; Di_{peak} , peak diameter after cuff release; FMD, flow-mediated vasodilation, blood pressure; HR, heart rate; LC, low-intensity cycling; LC+EMS, low-intensity cycling with electrical muscle stimulation. *** $p < 0.001$ vs. values before training; $a p < 0.05$ vs. values after training in the LC group