

ORIGINAL ARTICLE

Short-term cycling restores endothelial dysfunction after resistance exercise

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Resistance exercise impairs endothelial function. Therefore, it is of paramount importance to devise an effective strategy for restoring endothelial function after resistance exercise. Herein, we tested the hypothesis that resistance exercise-induced endothelial dysfunction would be restored by low-to-moderate intensity cycling. Seventeen young healthy subjects completed two randomized experimental trials: (a) resistance exercise only trial; and (b) cycling after the resistance exercise trial. Following baseline brachial artery flow-mediated dilation (FMD), subjects performed the resistance exercise. Following the resistance exercise, they were asked to rest in the supine position for the assessments of FMD. Subjects in the resistance exercise only trial maintained this supine position for 60 minutes, whereas those in the other trial cycled for 10 minutes after the resistance exercise trial. Subjects were again asked to rest in the supine position after cycling. Then FMD were repeated at 30 and 60 minutes after the resistance exercise in both trials. In the resistance exercise only trial, the increased blood flow and shear rate were disappeared after 1 hour of resting in the supine position, but were maintained in those in the cycling after the resistance trial due to subsequent cycling. Both trials caused a significant impairment in FMD at 10 minutes after the resistance exercise ($P < 0.05$). This decline was sustained for 60 minutes in the resistance exercise only trial. However, the impaired FMD was restored in the cycling after the resistance exercise trial. In conclusion, impaired endothelial function after the resistance exercise can be restored with 10 minutes of low-to-moderate intensity cycling.

KEYWORDS

aerobic exercise, endothelial dysfunction, resistance exercise

1 | INTRODUCTION

The vascular endothelium is critical for the regulation of vascular health probably through the release of endothelial-derived factors such as nitric oxide (NO), which has antiproliferative, anti-inflammatory, and antithrombotic properties as well as causes vasodilation.¹ Endothelial dysfunction, as evaluated by endothelium-dependent flow-mediated dilation

(FMD), is an early hallmark of cardiovascular disease.²⁻⁷ Although the prevalence of resistance exercise as an exercise prescription has augmented in the last few decades, resistance exercise using moderate-intensity and moderate repetitions induces acute endothelial dysfunction.⁸ Indeed, chronic resistance training increased arterial stiffness.⁹⁻¹² Endothelial dysfunction caused by a single bout of resistance exercise would be one of the underlying mechanisms by which the chronic

arterial adaptation following resistance training. Therefore, a novel resistance exercise program without induction of endothelial dysfunction could be beneficial.

We recently reported that high-intensity resistance exercise with low repetitions prevents endothelial dysfunction.¹³ However, an important limitation of this previous study is its clinical application. Because the high-intensity resistance exercise with low repetitions is not appropriate protocol for muscle hypertrophy. Given that muscle hypertrophy is one of the first goals of resistance exercise, it is necessary to propose a novel resistance exercise program that improves both muscle mass and vascular function. However, since resistance exercise-induced production of vasoconstrictors, such as endothelin-1,¹⁴ reduces NO synthesis, restoring this reduced NO synthesis is important for counteracting resistance exercise-induced endothelial dysfunction. Conventionally, low-to-moderate intensity aerobic exercise has been shown to improve endothelial function via shear stress-induced augmentation of NO synthesis.¹⁵⁻¹⁸ Meanwhile, exercise including resistance and aerobic exercise is known to increase adenosine monophosphate-activated protein kinase (AMPK) levels, a key down-regulator of muscle hypertrophy-related protein signaling.^{19,20} Interestingly, AMPK is activated in the human skeletal muscle during aerobic exercise in an exercise time- and exercise intensity-dependent manner.²¹⁻²³ If short-term, low-to-moderate intensity aerobic exercise minimizes the activation of AMPK, resulting in the restorations of impaired endothelial function after resistance exercise, the resistance exercise could improve both muscle mass and vascular function. However, the effect of short-term, low-to-moderate aerobic exercise as a recovery strategy after resistance exercise, which leads to muscle hypertrophy, on endothelial function remains unclear.

Accordingly, we examined if moderate-intensity resistance exercise-induced endothelial dysfunction could be restored by low-to-moderate aerobic exercise. Specifically, brachial artery endothelial functions were assessed via FMD before and after resistance exercise under two conditions: where a 10 minutes of cycling was performed after resistance exercise and where a supine resting position was maintained after resistance exercise. This study used a minimum aerobic

exercise because a 10 minutes of aerobic exercise had previously restored an impaired endothelial function caused by sitting.²⁴ We hypothesize that resistance exercise-induced endothelial dysfunction would be restored by a 10 minutes of low-to-moderate cycling.

2 | METHODS

2.1 | Subjects

Seventeen young, untrained, male subjects (age: 20.0 ± 0.6 years, height: 173.8 ± 1.3 cm, weight: 63.4 ± 1.2 kg, body mass index: 20.9 ± 0.2 kg/m²) participated in the present study. The subjects were not participating in any training programs at the start of this study. Subjects were recreationally active (performing moderate exercise two to three days per week), non-smokers, with no history or symptoms of cardiovascular, pulmonary, metabolic, or neurological disease. No subjects reported taking medications. All subjects were informed about the purpose of the present study and experimental procedure, and provided written informed consent. The study was approved by the Ethics Committee for Human Experiments at Sports Research Center, Hosei University, Japan (ID: 2017-003).

2.2 | Experimental procedures

Subjects visited the laboratory three times throughout the experimental period. During the first visit, the subject's one repetition maximum (1RM) for leg extension was assessed using weight stack machines. Before measuring 1RM, the subjects performed warm-up sets with 10 repetitions at 50% and 70% of the predicted 1RM and stretching of the major muscle groups that were subjected to the exercises. The intensity was increased until the subjects were unable to perform a lift. A schematic of the study design is presented in Figure 1. The order of experimental visits was randomized, and each visit was separated by at least 7 days. The two experimental visits consisted of the following conditions (a) resistance exercise only trial and (b) cycling after the resistance exercise trial. Subjects were instructed to eat a light meal 2 or more

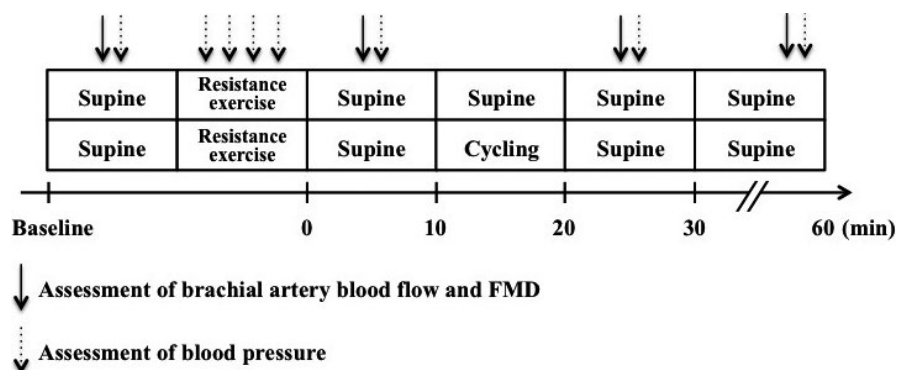


FIGURE 1 Experimental design. The intensity of resistance exercise was 10 repetitions for five sets at 70% of one repetition maximum. The workload of cycling was individualized for each subject to target a rate of perceived exertion of 11-13

hour prior to arriving to the laboratory. In addition, subjects were asked to refrain from caffeine and alcohol for at least 10 hour as well as from exercise for 24 hour prior to the study visit. All experimental timing was kept constant among visits. All studies were performed in a temperature-controlled room kept at 23°C. Upon arrival to the laboratory, subjects were placed in a supine position and instrumented with an automated sphygmomanometer (Omron Cooperation, Kyoto, Japan) for periodic measurements of systolic and diastolic blood pressure after resting quietly for 10 minutes. All vascular measurements in the brachial artery were performed in the right arm. Brachial artery diameter and blood velocity were measured using duplex Doppler ultrasound (Aixplorer, Supersonic Imagine, France). A 10-MHz linear array transducer was placed over the brachial artery just distal to the brachial fossa. Simultaneous diameter and velocity signals were obtained in duplex mode at a pulsed frequency of 30-MHz and corrected with an insonation angle of 60°. Brachial artery FMD was assessed as previously described.^{25,26} Briefly, a cuff was placed on the lower arm. Two minutes of baseline hemodynamics were recorded, and then, the cuff was inflated to a pressure of 220 mm Hg for 5 minutes. Continuous diameter and blood velocity measures were recorded for 3 minutes following cuff deflation. Recordings of all vascular variables were analyzed offline using specialized edge-detection software (S-13037 ver. 2.0.1, Takei Kiki Kogyo, Japan).

Following baseline FMD and blood pressure measurements, subjects performed resistance exercise (leg extension). The exercise intensity consisted of 10 repetitions for five sets at 70% of 1RM. The resting period among all sets was 60 s. The intensity during the resistance exercise was adjusted to allow the subjects to complete 10 repetitions in each set (approximately 70% of 1RM for the first set). During resting period between sets, systolic and diastolic blood pressures were measured. Following the resistance exercise, subjects were again asked to rest in the supine position. In the present study, the point that subjects finished the resistance exercise was defined as the starting point (0 minutes) of post-exercise measurement. FMD and blood pressure assessments were then conducted. Both measurements have completed at 10 minutes after resistance exercise (Figure 1). Subjects in the resistance exercise only trial maintained the supine position for 60 minutes, whereas those in other trial cycled for 10 minutes on a stationary bike (Aerobike 75XLIII, Combi wellness Co, Tokyo, Japan) after the resistance exercise. During the cycling exercise, subjects maintained a cycling cadence of 60 rpm. The workload was individualized for each subject to target a rate of perceived exertion (RPE) of 11-13 (Borg scale, 6-20). Heart rate (HR) and RPE were monitored throughout the exercise bout. Percentages of HRmax consisted of the age-predicted HRmax ([The average HR during cycling/[220–age] × 100]). Subjects were

again asked to rest in the supine position after cycling. FMD and blood pressure measurements were repeated at 30 and 60 minutes after resistance exercise in both trials. Therefore, the timing of post-exercise measurements was same in both trials.

2.3 | Data analysis

Blood flow was calculated from the continuous diameter and mean blood velocity recordings at each of the experimental time points using the following equation: $3.14 \times (\text{diameter}/2)^2 \times \text{mean blood velocity} \times 60$. Shear rate, an estimate of shear stress without blood viscosity, was calculated as $4 \times \text{mean blood velocity}/\text{diameter}$. Basal diameter, blood flow, and shear rate were represented as average values of 2-minutes baseline during FMD assessment (before inflation cuff). Brachial artery FMD percent change was calculated using the following equation: $\%FMD = (\text{peak diameter} - \text{base diameter})/(\text{base diameter}) \times 100$. Hyperemic shear rate area under the curve (AUC) up to peak diameter was calculated as stimulus for FMD, as described previously.^{25,27}

2.4 | Statistical analysis

A two-way (time × trial) repeated measures analysis of variance (ANOVA) with Tukey's post-hoc testing was performed on all dependent variables. FMD was also adjusted for basal diameter and hyperemic shear rate AUC via analysis of covariance (ANCOVA) in order to statistically control for the influence of basal diameter and shear stimulus on FMD response. ANCOVA and ANOVA tests were performed using SPSS software (version 23). Significance was accepted at $P \leq 0.05$. Data are expressed as means ± SE.

3 | RESULTS

The average load during resistance exercise was 64.2 ± 4.9 kg. The average workload during cycling was 89.7 ± 4.1 watts, and the absolute and relative exercise intensity was 134 ± 3 bpm and $67.0 \pm 1.7\%$ HR max. The average RPE during cycling was 12.1 ± 0.2 .

Following resistance exercise, while in the supine position, brachial artery blood flow and shear rate were significantly increased relative to baseline in both trials ($P < 0.05$, Table S1). In the resistance exercise only trial, this initial increase in blood flow and shear rate caused by resistance exercise was disappeared after 1 hour of rest in the supine position (Figure 2A and Table S1); however, this increase was maintained in those in cycling after the resistance exercise trial due to subsequent cycling. Statistical differences were detected in shear rate at 30 minutes after resistance exercise between trials ($P < 0.05$, Figure 2A).

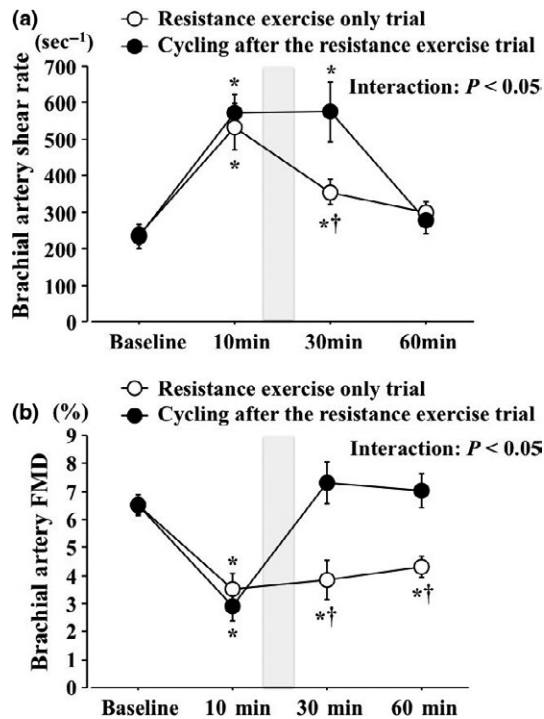


FIGURE 2 Brachial artery shear rate (A) and FMD (B) in the resistance exercise only trial and cycling after the resistance exercise trial. The shaded box indicates the duration of cycling. Data are expressed as means \pm SE $n = 17$. * $P < 0.05$ vs Baseline. † $P < 0.05$ vs cycling after the resistance exercise trial

Importantly, both trials caused a significant impairment in brachial artery FMD at 10 minutes after the resistance exercise ($P < 0.05$ Figure 2B), and this decline was sustained for 60 minutes in those in the resistance exercise only trial. However, the impaired brachial artery FMD was restored in the cycling after the resistance exercise trial (Figure 2B). FMD corrected for basal diameter and hyperemic shear rate AUC by ANCOVA did not affect the interpretation of the main findings as impaired FMDs were sustained in the resistance exercise only trial and restored in the cycling after the resistance exercise trial (Table S1). In the resistance exercise only trial, the brachial artery diameter was significantly increased at 30 minutes after the resistance exercise. However, no differences in the brachial artery diameter between trials were detected across time points (Table S1).

In the resistance exercise only trial, the resistance exercise significantly raised mean arterial pressure ($P < 0.05$, Table S1), this elevation returned toward resting baseline values after the exercise. Although mean arterial pressure was significantly higher in the resistance exercise only trial than in those in the cycling after the resistance trial at 30 minutes after the resistance exercise ($P < 0.05$), this difference disappeared at 60 minutes after the resistance exercise (Table S1).

4 | DISCUSSION

The main finding of the present study is that endothelial dysfunction caused by resistance exercise can be restored by a 10 minutes of low-to-moderate intensity cycling. Indeed, we found that the impaired brachial artery FMD was recovered in the cycling after the resistance exercise trial but sustained in those in the resistance exercise only trial. In support of this result, a previous work has demonstrated that running after resistance exercise for eight weeks prevented resistance exercise-induced increase in arterial stiffness.²⁸ The finding of the present study supports the notion that 10 minutes of low-to-moderate intensity cycling after resistance exercise is sufficient for restoring impaired endothelial function in young healthy individuals.

Although one of the first priorities of resistance exercise is muscle hypertrophy, moderate-intensity resistance exercise with moderate repetitions, which leads to muscle hypertrophy, induces acute endothelial dysfunction.⁸ In contrast, low-to-moderate intensity aerobic exercise improves endothelial function,¹⁵⁻¹⁸ whereas muscle hypertrophy-related protein signaling is attenuated by aerobic exercise-induced activation of AMPK in the skeletal muscle. The present study used low-to-moderate intensity and short-term cycling in order to minimize the activation of AMPK after aerobic exercise. As a result, a 10 minutes of low-to-moderate intensity (average value: 67%HRmax) cycling restored impaired endothelial function after moderate-intensity resistance exercise with moderate repetitions. Indeed, a previous study has shown that AMPK activity in the skeletal muscle is not induced by low-to-moderate intensity exercise (50% of maximal oxygen uptake) for 10 minutes.²³ In the future study, we need to investigate the muscle AMPK response to low-to-moderate intensity aerobic exercise after resistance exercise.

Factors responsible for this cycling-induced vascular rescue after resistance exercise are unknown. One possibility is that shear stress-induced augmentation of NO synthesis is sufficient to offset the prior negative effects of resistance exercise. Indeed, the factor has been shown to mediate post-exercise FMD responses.^{16,18,29,30} In this study, shear stress was significantly higher in the cycling after the resistance exercise trial than in those in the resistance exercise only trial (Figure 2A). In addition, FMD corrected for hyperemic shear rate AUC by ANCOVA did not affect the interpretation of FMD response to cycling after resistance exercise, suggesting improved NO synthesis after cycling has offset the negative effects of the resistance exercise in the vasculature. Previous study reported that a single bout of cycling at 50% of maximal oxygen uptake increased NO synthesis and the effect can be induced in the first 10 minutes of exercise.³¹ Therefore, it may be possible to enhance NO production even from short-term exercise. Based on these findings, it is reasonable to

speculate that increased shear stress-induced augmentation of NO synthesis after 10-minutes cycling after resistance exercise promotes vascular rescue. However, other protective shear stress-independent mechanisms are also likely involved.

Discussions of experimental considerations are warranted. First, present study included only healthy subjects and thus future studies need to examine if these findings can be extrapolated to patients with cardiovascular diseases. Second, the present study investigated the acute endothelial response following a single bout of aerobic exercise after resistance exercise. It is difficult to conclude the arterial adaptation after chronic resistance training from these results in this study since we focused on the acute FMD response due to a single bout of resistance exercise. Therefore, future study is needed to test whether chronic exercise training using the present protocol can achieve both muscle hypertrophy and vascular health. Third, subjects ate non-standardized meal 2 hour prior to experimental visits, and they changed posture (ie, supine and sitting positions) during experimental period. These two methodological factors may affect the results of the present study.

In conclusion, the present study revealed that a 10 minutes of low-to-moderate intensity cycling is effective for counteracting the detrimental effects of resistance exercise on endothelial function.

5 | PERSPECTIVE

This study provides the first evidence that the detrimental vascular effects of resistance exercise are restorable in untrained subjects. This study will be helpful in formulating exercise strategy to prevent resistance exercise-induced endothelial dysfunction. Light aerobic exercise after resistance exercise would be effective as an exercise prescription for people of a wide range of ages.

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CONFLICT OF INTEREST

No conflicts of interest, financial or otherwise, are declared by the authors(s).

AUTHOR CONTRIBUTION

TM, MI, and EO conceptualized and designed the study; TM and EO performed experiments; TM analyzed data; TM, MI, and EO interpreted the results of experiments; TM prepared figures and table. TM and EO drafted the manuscript; TM,

MI, and EO edited and revised manuscript; TM, MI, and EO approved the final version of manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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