Interval exercise, but not endurance exercise, prevents endothelial ischemia-reperfusion injury in healthy subjects

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Seeger JP, Lenting CJ, Schreuder TH, Landman TR, Cable NT, Hopman MT, Thijssen DH. Interval exercise, but not endurance exercise, prevents endothelial ischemia-reperfusion injury in healthy subjects. Am J Physiol Heart Circ Physiol 308: H351–H357, 2015. First published November 21, 2014; doi:10.1152/ajpheart.00647.2014.—Endothelial ischemia-reperfusion (I/R) injury contributes to the poor prognosis during ischemic (myocardial) events. Preconditioning, i.e., repeated exposure to short periods of ischemia, effectively reduces endothelial I/R injury. In the present study, we examined the hypothesis that exercise has preconditioning effects on endothelial I/R injury. Therefore, we studied whether an acute bout of endurance or interval exercise is able to protect against endothelial I/R injury. In 17 healthy young subjects, we examined changes in brachial artery endothelial function using flow-mediated dilation (FMD) before and after a bout of high-intensity interval exercise, moderate-intensity endurance exercise, or a control intervention. Subsequently, I/R injury was induced by inflation of a blood pressure cuff around the upper arm to 220 mmHg for 20 min and 20 min of reperfusion followed by another FMD measurement. Near-infrared spectrometry was used to examine local tissue oxygenation during exercise. No differences in brachial artery FMD were found at baseline for the three conditions. I/R induced a significant decline in FMD (7.1 ± 2.3 to 4.3 ± 2.3, P < 0.001). When preceded by the interval exercise bout, no change in FMD was present after I/R (7.7 ± 3.1 to 7.2 ± 3.1, P = 0.56), whereas the decrease in FMD after I/R could not be prevented by the endurance exercise bout (7.8 ± 3.1 to 3.8 ± 1.7, P < 0.001). In conclusion, a single bout of lower limb interval exercise, but not moderate-intensity endurance exercise, effectively prevents brachial artery endothelial I/R injury. This indicates the presence of a remote preconditioning effect of exercise, which is selectively present after short-term interval but not continuous exercise in healthy young subjects.

high intensity exercise; endothelial function; ischemic preconditioning; cardiovascular disease; prevention

DESPITE SIGNIFICANT IMPROVEMENTS in (pharmacological) treatment in recent decades, cardiovascular diseases remain the world’s leading cause of death. One effective strategy to reduce ischemia-reperfusion (I/R) injury of the myocardium was introduced by Murry and co-workers (23), who demonstrated in an animal model that cardiac infarction size was significantly smaller when prolonged lethal cardiac ischemia was preceded by short, repeated bouts of nonlethal ischemia. This intervention is commonly referred to as ischemic preconditioning (IPC). Since then, many others have confirmed the (clinical) effectiveness of IPC in preventing I/R injury using different models, species, and different organ sites, including the vascular endothelium (13, 25). It is hypothesised that I/R injury of the endothelium contributes to cardioprotection and, subsequently, contributes to the outcomes in patients with coronary heart disease (24).

Exercise may also have preconditioning effects that reduces endothelial I/R injury, especially since some types of exercise have similar characteristics as IPC (i.e., short, repeated bouts of exercise/ischemia). Preliminary data from animal studies revealed that (acute) exercise reduces cardiovascular injury associated with prolonged (potentially lethal) ischemia (4, 5, 19). Recently, Michelsen and co-workers (20) provided further support that exercise may possess preconditioning effects. They found that interval running exercise (4 × 2 min) and IPC (4 × 5 min) in humans, followed by blood withdrawal and perfusion through isolated rabbit hearts, were similarly effective in reducing infarct size in the rabbit hearts (20). These effects of exercise on cardiac I/R injury may also be present in humans adopting an in vivo model of endothelial I/R injury.

To date, little is known about the possible preconditioning effects of (acute) exercise in humans. Therefore, the aim of the present study was to investigate the ability of an acute bout of exercise to prevent endothelial I/R injury in healthy, young humans. To study endothelial I/R injury, we adopted a frequently used and validated human in vivo model (14, 17, 32). Second, we hypothesized that a single bout of interval exercise represents a more potent preconditioning stimulus than endurance exercise. We speculated that interval exercise would lead to short periods of local deoxygenation of the working muscle mass, thereby mimicking “mechanical” IPC application. Therefore, our second aim was to compare the ability of a single bout of interval exercise versus endurance exercise to prevent endothelial I/R injury in healthy, young humans.

METHODS

Subjects

A total of 17 healthy volunteers were included to participate in this study (Table 1). All subjects performed regular physical activity, with an average sport participation of 6.7 ± 5.0 h (range: 1.5–17.5 h). Subjects were nonsmokers and were free of any cardiovascular disease, diabetes mellitus, hypertension (diastolic blood pressure > 90 mmHg and/or systolic blood pressure > 140 mmHg), and hypercholesterolemia (total cholesterol > 6.5 mmol/l). In addition, obese subjects (body mass index ≥30 kg/m²), and those on medication potentially influencing the cardiovascular system were excluded. All subjects signed an informed consent. The study was conducted according to the Declaration of Helsinki (2000) and approved by the...
TABLE 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>10/7</td>
</tr>
<tr>
<td>Age, yr</td>
<td>23 ± 4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21.8 ± 1.5</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>121 ± 9</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>73 ± 8</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>57 ± 9</td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>4.3 ± 0.5</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>3.6 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 17 subjects. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Ethics Committee of the Radboud University Nijmegen Medical Centre.

Experimental Design

First, subjects performed an incremental cycling test to determine maximal O₂ consumption (V\textsubscript{O₂}) and maximum workload (in W). Subsequently, participants visited our laboratory on three different occasions (separated by at least 7 days, with a maximum of 1 mo; Fig. 1). During these visits, brachial artery endothelial function [using flow-mediated dilation (FMD)] was examined under resting conditions, after the intervention (interval exercise, endurance exercise, and or control), and after I/R (20 min of arm ischemia and 20 min of reperfusion).

Assessment of prolonged ischemia (40–60 min), as applied in animal studies to the myocardium, is for obvious reasons not possible in humans. Given the correlation between brachial and coronary artery responses to assess endothelial function (28), this technique is hypothesized to provide in vivo insight into (endothelial) I/R injury. This method has been frequently used by others to examine endothelial changes to I/R (14, 16, 32).

Interventions

**Interval exercise.** After a 10-min warmup period at 30% of maximum workload, subjects performed ten 1-min cycle exercise bouts at 100% of maximum workload. These 100% bouts were separated by 2-min recovery periods at cycle exercise at 25% of maximum workload. The interval exercise session was finished with a 5-min cool down period at 30% of maximum workload.

**Endurance exercise.** Cycle endurance exercise consisted of a 10-min warmup period at 30% of maximum workload followed by a
28-min exercise at 50% of maximum workload. The cycle endurance exercise session concluded with a 5-min cooldown period at 30% of maximum workload. We ensured that subjects performed the same amount of total workload during both exercise bouts.

Control. Subjects rested in the supine position for 43 min.

Measurements

FMD. Brachial artery diameter and blood flow velocity were determined using noninvasive echo-Doppler equipment. Subjects rested in a supine position with the right arm extended. For the assessment of FMD, a rapid inflation/deflation pneumatic cuff (E10 rapid cuff inflator, Hokanson) was placed around the right arm distal to the olecranon process to provide an ischemic stimulus distal from the brachial artery to provoke vasodilation and subsequent shear stress. The right arm was extended to the side and positioned at the heart level and was supported with towels to provide a stable position for recordings. A 10-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine was used to perform imaging (T3000, Terason, Aloka, UK). The brachial artery was imaged in the distal third of the upper arm. Ultrasound parameters were set to optimize longitudinal B-mode images of the luminal-arterial wall interface. A continuous Doppler velocity assessment was obtained simultaneously, and data were collected using the lowest possible insonation angle (always <60°), which did not vary during each study. After a resting period of at least 15 min, 1 min of baseline recording of the arterial diameter and blood flow velocity was performed. Subsequently, the occlusion cuff was inflated to 220 mmHg for 5 min. Arterial diameter and blood flow velocity recordings were restarted at least 30 s before cuff deflation and continued for at least 3 min after deflation.

Brachial artery diameter and blood flow analysis. Analysis of the brachial artery diameter was performed using custom-designed edge-detection and wall-tracking software, which is independent of investigator bias (34). Baseline data were calculated across the 1 min preceding cuff inflation. After cuff deflation, peak diameter was automatically detected according to an algorithm previously described in detail elsewhere (3). Within-subject reproducibility of FMD using this semiautomated software has a coefficient of variation of 6.7–10.5% (30). Postdeflation shear rate data, derived from velocity and diameter measures, were used to calculate the shear rate area under the curve (SR\textsubscript{AUC}).

NIRS. NIRS was used to measure local oxygenation in the lower limb tissue during exercise by assessing regional concentration changes in oxyhemoglobin (O\textsub{s}Hb) and deoxyhemoglobin (HHb) using a continuous-wave near-infrared spectrophotometer (OXY-MON, Artinis Medical Systems). NIRS optodes were positioned on the right thigh, 12 cm proximal to the fibular head, on the vastus lateralis muscle parallel to the long axis of the muscle. NIRS measurements were performed continuously. An interoptode distance of 35 mm was used, resulting in a penetration depth of ~15–20 mm (6). Briefly, this technique is based on the relative transparency of tissue for light in the near-infrared region and on changes in O\textsub{s}Hb concentration of hemoglobin and myoglobin. As one cannot distinguish between myoglobin and hemoglobin, the combined effect of these two substances is studied. Changes in absorption measured by NIRS are converted into estimates of concentration changes of O\text{s}Hb and HHb. The sum of O\text{s}Hb and HHb reflects changes in blood volume, represented by the total hemoglobin signal (Fig. 2).

NIRS analysis. The baseline O\text{s}Hb level was determined by averaging the 7-min baseline period during warmup. This typically represented a stable recording of O\text{s}Hb (Fig. 2). Subsequently, for each intervention, total O\text{s}Hb area under the curve (HbO\text{s} total area) was calculated. Second, local oxygenation status was determined by calculating the positive area under the curve above baseline ("positive area") and local deoxygenation/hypoxia as the negative area under the curve below baseline ("negative area").

Statistical Analysis

All statistical analyses were performed using SPSS (version 20, SPSS, Chicago, IL) software. Data are reported as means ± SD unless stated otherwise. Statistical significance was set at $P < 0.05$. Baseline characteristics were compared with paired Student’s $t$-tests. To evaluate the effect of (different types of) exercise on endothelial I/R injury, we used a linear mixed model with a random factor of “subject” and fixed factors of “intervention” (interval exercise, endurance exercise, or control), “time” (preintervention, postintervention, and post-I/R), and the interaction of “intervention $\times$ time.” In an additional analysis, SR\textsubscript{AUC} and baseline diameter were added as covariates. A recent study (2) has described that inadequate scaling for FMD would be present if the upper confidence limit of the regression slope of the relationship between logarithmically transformed base diameter and peak diameter is <1. In such an event, FMD (in %) may not be an appropriate measure to estimate endothelial function. Therefore, we repeated the analysis for FMD using allometric modeling (2).

Fig. 2. Near-infrared spectroscopy data for one subject. A: interval exercise. B: endurance exercise. The green line indicates total hemoglobin, the blue line indicates deoxyhemoglobin, and the red line indicates oxyhemoglobin. The x-axis shows time (in s), and the y-axis shows hemoglobin concentration (in $\mu$M). Vertical lines represent markers given every 3 min for additional data analysis afterward.
While post hoc analysis revealed no change in brachial artery FMD (in %) after I/R (P 0.05; Table 3). The eliciting shear rate stimulus $\text{SR}_{\text{AUC}}$ was significantly higher after interval exercise (Table 3) but returned to baseline levels during the post-I/R measurement. The control and endurance exercise interventions showed no changes in $\text{SR}_{\text{AUC}}$. To statistically control for the potential influence of these parameters, we repeated our linear mixed model analysis with baseline diameter and $\text{SR}_{\text{AUC}}$ as covariates. Our analysis confirmed our earlier findings and revealed

### Table 2. Exercise characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>$P$ value</th>
<th>Before</th>
<th>After</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>114 ± 10</td>
<td>109 ± 11</td>
<td>0.020</td>
<td>113 ± 9</td>
<td>108 ± 8</td>
<td>0.008</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>70 ± 11</td>
<td>70 ± 10</td>
<td>0.887</td>
<td>68 ± 7</td>
<td>69 ± 7</td>
<td>0.771</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>2.4 ± 0.8</td>
<td>3.3 ± 2.2</td>
<td>0.141</td>
<td>2.7 ± 1.2</td>
<td>14.0 ± 2.7*</td>
<td>0.000</td>
</tr>
<tr>
<td>Borg score</td>
<td>15 ± 2</td>
<td>18 ± 2*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak heart rate</td>
<td>160 ± 18</td>
<td>188 ± 11*</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. $P$ values represent Student’s paired t-tests between before and after exercise. *Significantly different between endurance and interval exercise at $P < 0.05$ (by Student’s paired t-test).

### RESULTS

Interval exercise resulted in a higher postexercise blood lactate, average heart rate, and postexercise Borg score compared with endurance exercise (Table 2). There were no significant differences in (pre- and postexercise) blood pressure between both exercise bouts (Table 2). During the endurance exercise bout, heart rate and estimated $V_O_2$ uptake were 152 ± 19 beats/min and 33.9 ± 10.6 ml $O_2$·kg$^{-1}$·min$^{-1}$ (i.e., 64 ± 14% of peak $V_O_2$). During high-intensity exercise, heart rate and estimated $V_O_2$ uptake of the first bout of high-intensity exercise was 167 ± 11 beats/min and 38.8 ± 9.7 ml $O_2$·kg$^{-1}$·min$^{-1}$ (i.e., 73 ± 11% of peak $V_O_2$). The last bout of high-intensity exercise was performed at 188 ± 11 beats/min and 49.4 ± 9.7 ml $O_2$·kg$^{-1}$·min$^{-1}$ (i.e., 95 ± 6% of peak $V_O_2$). Heart rate and estimated $V_O_2$ uptake during the rest intervals were 147 ± 14 beats/min and 30.0 ± 8.7 ml $O_2$·kg$^{-1}$·min$^{-1}$ (i.e., 58 ± 13% of peak $V_O_2$).

**Impact of Exercise on Endothelial I/R**

We found a significant interaction effect for the change in brachial artery FMD (in %) after I/R ($P < 0.001$; Table 3). While post hoc analysis revealed no change in brachial artery FMD immediately after the intervention for all three conditions, a significant decrease was observed in FMD after I/R during the endurance and control conditions (linear mixed model for time, $P < 0.001$). In marked contrast, the decline in FMD after I/R was prevented by interval exercise (post hoc $P = 0.56$; Fig. 3). Repeating this analysis using allometric scaling to control for the potential impact of (inter- and intrindividual differences in) baseline diameter confirmed the presence of a significant intervention ($P = 0.034$), time ($P < 0.001$), and intervention × time effect ($P < 0.001$).

The I/R procedure did not change brachial artery diameter (Table 3). No change in diameter was found after the control and endurance exercise session, whereas a significant increase in diameter was observed immediately after interval exercise ($P < 0.05$; Table 3). The eliciting shear rate stimulus $\text{SR}_{\text{AUC}}$ was significantly higher after interval exercise (Table 3) but returned to baseline levels during the post-I/R measurement. The control and endurance exercise interventions showed no changes in $\text{SR}_{\text{AUC}}$. To statistically control for the potential influence of these parameters, we repeated our linear mixed model analysis with baseline diameter and $\text{SR}_{\text{AUC}}$ as covariates. Our analysis confirmed our earlier findings and revealed

### Table 3. Brachial artery characteristics preintervention, postintervention, and post-I/R in control, endurance, and interval interventions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preintervention</th>
<th>Postintervention</th>
<th>Post-I/R</th>
<th>Time</th>
<th>Intervention</th>
<th>Time × intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline diameter, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3.65 ± 0.55</td>
<td>3.62 ± 0.54</td>
<td>3.75 ± 0.64</td>
<td>0.20</td>
<td>0.29</td>
<td>0.11</td>
</tr>
<tr>
<td>Endurance</td>
<td>3.59 ± 0.64</td>
<td>3.61 ± 0.66</td>
<td>3.69 ± 0.65</td>
<td>&lt;0.001</td>
<td>0.021</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interval</td>
<td>3.62 ± 0.68</td>
<td>3.81 ± 0.69</td>
<td>3.67 ± 0.62</td>
<td>&lt;0.001</td>
<td>0.036</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FMD, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.26 ± 0.08</td>
<td>0.25 ± 0.11</td>
<td>0.16 ± 0.09*</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>0.001</td>
</tr>
<tr>
<td>Endurance</td>
<td>0.27 ± 0.10</td>
<td>0.30 ± 0.09</td>
<td>0.14 ± 0.06*</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.32</td>
</tr>
<tr>
<td>Interval</td>
<td>0.27 ± 0.11</td>
<td>0.25 ± 0.11</td>
<td>0.25 ± 0.09</td>
<td>&lt;0.001</td>
<td>0.025</td>
<td>0.37</td>
</tr>
<tr>
<td>FMD, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>7.1 ± 2.3</td>
<td>6.9 ± 3.0</td>
<td>4.3 ± 2.3*</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Endurance</td>
<td>7.8 ± 3.1</td>
<td>8.5 ± 2.8</td>
<td>3.8 ± 1.7*</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Interval</td>
<td>7.7 ± 3.1</td>
<td>7.0 ± 3.4</td>
<td>7.2 ± 3.1</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Area under the shear rate curve, s (10$^3$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>29.9 ± 6.9</td>
<td>28.1 ± 10.3</td>
<td>26.5 ± 11.7</td>
<td>0.004</td>
<td>0.001</td>
<td>0.32</td>
</tr>
<tr>
<td>Endurance</td>
<td>31.8 ± 7.1</td>
<td>33.8 ± 6.9</td>
<td>28.0 ± 8.1</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Interval</td>
<td>32.5 ± 9.8</td>
<td>38.0 ± 7.1*</td>
<td>30.6 ± 8.5</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Time to peak diameter, s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>49 ± 15</td>
<td>53 ± 21</td>
<td>46 ± 25</td>
<td>0.001</td>
<td>0.025</td>
<td>0.37</td>
</tr>
<tr>
<td>Endurance</td>
<td>48 ± 19</td>
<td>60 ± 20*</td>
<td>43 ± 15</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Interval</td>
<td>47 ± 20</td>
<td>65 ± 23*</td>
<td>53 ± 25</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 17 subjects. I/R, ischemia-reperfusion; FMD, flow-mediated dilation. *Post hoc significantly different from preintervention at $P < 0.05$. 

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a significant interaction effect between time and intervention ($P < 0.001$), with a decline in FMD after I/R for control and endurance exercise sessions but not when interval exercise preceded I/R.

Impact of Exercise on Local Oxygenation Status

NIRS data showed no significant differences between endurance and interval exercise bouts for the total area under the curve for HbO2 ($63.311 \pm 18.048$ and $60.008 \pm 27.941$ arbitrary units, respectively, $P = 0.21$) and the area below baseline ($-1.24 \pm 1.33$ and $-1.72 \pm 0.96$ arbitrary units, respectively, $P = 0.13$). Endurance exercise was associated with a significantly smaller area above baseline compared with the interval exercise bout ($1.28 \pm 1.67$ and $3.72 \pm 2.38$ arbitrary units, respectively, $P = 0.03$). Nonetheless, clear differences in the pattern of local HbO2 could be observed between endurance and interval exercise bouts (Fig. 2).
thelial nitric oxide synthase and/or K<sub>ATP</sub> channels remains unclear and should be subject of future research.

**Study Limitations**

A limitation of our study is that we did not include measures to explore the potential mechanisms involved underlying the protective effects of (high-intensity interval) exercise on endothelial I/R. However, the study was designed to explore whether (different forms of) excise could prevent endothelial I/R injury. Another limitation is that we have included healthy young individuals only and did not assess exercise bouts of different duration and/or intensity. Ischemic events typically occur in an elderly population with cardiovascular risk and/or diseases. Whether exercise has similar preconditioning effects in groups with cardiovascular disease or risk is currently unknown and should be subject for future research. In this light, it is important to realize that recent papers have questioned the efficacy of “traditional” IPR in older subjects and heart failure patients (11, 32). Exercise may represent a suitable, effective, and safe alternative as a preconditioning stimulus in these groups. Furthermore, previous work has highlighted the impact of duration and intensity of exercise on the vasculature. Therefore, we cannot exclude the possibility that endurance exercise of different intensity (i.e., above lactate threshold) or duration has preconditioning effects. Finally, we used brachial artery endothelial function as a model to study I/R injury in the forearm. Although this model has been frequently used by others (14, 16, 32) and strong correlations have been reported between brachial artery FMD and coronary endothelial function (1, 31), caution should be taken when extrapolating our findings to other vascular beds, such as the coronary circulation. Future studies are recommended to further validate this technique.

**Clinical Relevance**

Exercise training has strong cardioprotective effects. Approximately 40% of the beneficial effects of exercise training can be explained by improvement in cardiovascular risk factors (22). Possibly, the preconditioning effects of a single bout of (interval) exercise may contribute to the cardioprotective effects of exercise. Moreover, repeatedly performing this type of exercise (and therefore preconditioning) may protect against I/R injury. Previous work found that habitual endurance (9) or resistance (10) exercise (partly) prevented endothelial I/R injury. A potential implication of our results is that exercise training may possess preconditioning effects that ultimately protect against I/R injury. Future studies are needed to explore this hypothesis.

**Conclusions**

Our study showed the ability of interval exercise to prevent endothelial I/R injury in a group of healthy young subjects, whereas this effect of exercise was absent when I/R injury was preceded by a single bout of short-duration, moderate-intensity endurance exercise. These protective effects of lower limb interval exercise were observed in upper limb arteries, which suggests that the preconditioning effects represent a remote, rather than local, effect of interval exercise. Our findings may have potential clinical relevance for the protection of the heart and other tissues against I/R injury by (interval) exercise.

**GRANTS**

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**DISCLOSURES**

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

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


