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Acute high-intensity interval exercise is superior to moderate-intensity continuous exercise in enhancing endothelial function and its associated biomarkers in sedentary young individuals: the possible involvement of lactate

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ABSTRACTS

Objectives: Our study investigated the effects of acute high-intensity interval exercise (HIIE) and moderate-intensity continuous exercise (MICE) on endothelial function and its associated biomarkers in sedentary young individuals.

Methods: Fifteen subjects (10M / 5F; 22 ± 2 years; BMI: 23.07 ± 4.12 kg/m^2) participated in a crossover trial including three experimental conditions: HIIE, MICE, and a control session of rest (CON) in random order separated by a 7-day washout period. Endothelial function was assessed using flow-mediated dilation (FMD), mean shear rate (MSR), and circulating levels of blood lactate, VEGF, IGF-1, and irisin.

Results: Both HIIE and MICE significantly enhanced FMD% (both $P < 0.001$ and $P < 0.01$, respectively), lactate (both $P < 0.001$), VEGF ($P < 0.001$ and $P < 0.01$, respectively), IGF-1 (both $P < 0.001$), and irisin ($P < 0.001$ and $P < 0.05$, respectively), with a greater extent after HIIE compared to MICE in FMD% ($P < 0.001$), MSR ($P < 0.05$), lactate ($P < 0.001$), VEGF ($P < 0.05$), and IGF-1 ($P < 0.05$). Additionally, change (post-pre) in FMD% was positively correlated with changes in MSR, lactate, and VEGF in both HIIE and MICE conditions. Change in MSR was positively associated with changes in lactate and VEGF in both HIIE and MICE conditions. Furthermore, enhancement in lactate was correlated with enhancements in VEGF in both HIIE and MICE conditions.

Conclusions: Acute HIIE is a more effective method than MICE at improving endothelial function in sedentary young individuals and increases in lactate and its mediated VEGF release, attributed to increase in shear rate after exercise, are involved in regulatory mechanisms.

1. Introduction

Sedentary behavior (SB) involves prolonged sitting during leisure and recreation, commuting, and in the workplace and at home. According to the Sedentary Behavior Research Network (SBRN), SB is defined as "a behavior in which an adult's energy expenditure is less than or equal to 1.5 metabolic equivalents (MET) in a sitting or lying position while awake".[1] It is of interest to note that SB contributes to the risk of cardiovascular diseases (CVD).[2] The scientific report of the Physical Activity Guidelines Advisory Committee (PAGAC) provides

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strong evidence for a dose-response relationship between SB and CVD mortality,[3] with increased all-cause mortality, CVD morbidity, and mortality rates among those with high levels of SB (≥ 8 h/day).[4,5] SB leads to endothelial dysfunction, which has been recognized as a critical early step in the pathogenesis of CVD.[6]

The prevalence of SB in young people is increasing in recent years and CVD risk factors, even CVD, are emerging earlier and more frequently in young people.[7] Prolonged SB can adversely affect cardiovascular function in young individuals.[8] However, due to their current sedentary lifestyles in work and study environments, it is difficult for young people to reduce their sedentary time. Therefore, it is essential to identify effective modalities to prevent or reduce the CVD risk associated with SB in young individuals.

Nowadays, there is growing evidence that appropriate exercise can prevent or treat endothelial dysfunction associated with SB[9-10] however, the effect is inconsistent among different exercise modalities. While moderate-intensity continuous exercise (MICE) is a well-known exercise regime for improving endothelial function,[11] it can be time-consuming and monotonous. Recently, high-intensity interval exercise (HIIE) has become popular among young individuals due to its time efficiency.[12]

In recent years, empirical studies on the effects of HIIE and MICE on endothelial function have been inconclusive, with some studies suggesting that long-term HIIE has yielded more favorable outcomes than MICE in enhancing vascular function.[13–15] However, some studies have found no significant difference in the improvement of endothelial function between HIIE and MICE.[16,17] This discrepancy may be due to a number of factors, including different exercise protocols, study populations, measuring methods, etc. Most studies have focused on the effects of HIIE and MICE on endothelial function in menopausal women,[18] obese population,[19] and older populations[20] so far, whereas, studies on sedentary young people are still scarce. Furthermore, few studies compare the acute effects of HIIE with MICE on endothelial function in sedentary young individuals. Therefore, it is important to study the changes in endothelial function after a single bout of HIIE or MICE, as the chronic benefits of exercise may be associated with repeated responses to acute exercise.

Studies on the mechanisms by which exercise improves endothelial function have identified changes in shear stress as the primary factor.[21] In addition, several key biomarkers, such as IGF-1,[22] VEGF,[23] and irisin,[24] which have also been suggested to play important role in improving vascular function through exercise. Nitric oxide (NO) is considered as the most important molecule in the maintenance of endothelial function and has a strong vasorelaxant effect on vascular smooth muscle.[25] Irisin promotes NO production in vascular endothelial cells via the AMPK-Akt-eNOS pathway to improve vascular endothelial function.[26] VEGF level can rise during exercise, binding to its receptor and thereby activating eNOS via the PI3K-Akt pathway, leading to NO production.[27] In addition, IGF-1 interacts with endothelial high-affinity binding sites to increase NOS activity, promoting endothelial NO production and inhibiting endothelial cell apoptosis.[28]

Lactate, the end product of anaerobic or aerobic glycolysis, was traditionally considered a byproduct or waste of glycolysis. Recently, lactate is increasingly being shown to play a specific role in the regulation of vascular smooth muscle cells,[29] the promotion of angiogenesis,[30,31] the modulation of haemodynamics,[32] and the electrophysiological activity of the heart,[33,34] all of which are essential for the maintenance of cardiovascular homeostasis. Lactate is associated with changes in VEGF and IGF-1 levels,[35,36] suggesting that it may be involved in the process by which exercise improves vascular function. In addition, lactate is a metabolite released from skeletal muscle during and after strenuous exercise and the level of lactate after exercise is largely dependent on exercise intensity. HIIE has been demonstrated to increase higher concentration of lactate than MICE.[37] However, there were currently no studies investigating the role of lactate in the improvements of endothelial function after acute HIIE and MICE. We hypothesized that acute HIIE is more effective at improving endothelial function than MICE, and the underlying mechanism involves the greater change in lactate after HIIE.

Thus, the purpose of our study was to compare the effects of acute HIIE and MICE on endothelial function with its associated circulating biomarkers and to investigate the possible mechanisms in sedentary young individuals. We aimed to establish a theoretical foundation for understanding the effects of exercise on endothelial function and develop effective exercise programs for sedentary young individuals.

2. Methods

2.1. Participants

The total sample size was calculated by G*power and analyzed by repeated measures ANOVA under F-test. The effect sizes from previous similar studies are ranged from 0.31 to 1.35, and the present study set the effect size at 0.31, confidence interval at 0.05, test efficacy at 0.80, and parameter setting at 3 visits and two measurements (pre- and post-visits). The required sample size was at least 30 participants. Therefore, under the randomized crossover experimental design, at least 10 participants needed to be recruited in the present experiment. All participants were required to meet the following inclusion criteria: (1) 18–25 years, regardless of sex; (2) sedentary behavior (cumulative sedentary time ≥ 8 h per day)[38,39]; (3) irregular exercise habits (< 150 min of moderate-to-vigorous physical activity in a typical week in past 6 months); (4) no contraindications to exercise, no CVD such as hypertension; (5) willingness to participate in this study by signing an informed consent form. A total of 15 participants attended and signed the written informed consent, with approval from the Guangzhou Sport University Ethics Committee (2021LCLL-26).

2.2. Experimental design

This experiment was a randomized crossover trial. Basic characteristics of all participants such as height, weight, body mass index (BMI), resting blood pressure (BP), and heart rate (HR) were collected prior to the formal experiment. Then, they underwent a maximal oxygen uptake test ($VO_{2\ max}$ test) to determine the intensity of exercise. Finally, all participants completed three visits: HIIE, MICE, and a control session of rest (CON) in random order separated by a 7-day washout period (Fig. 1). All participants abstained from alcohol, caffeine, and strenuous physical activity 24 h prior to the experiments. In addition, they were asked to maintain the same diet before each experiment and fast 2 h

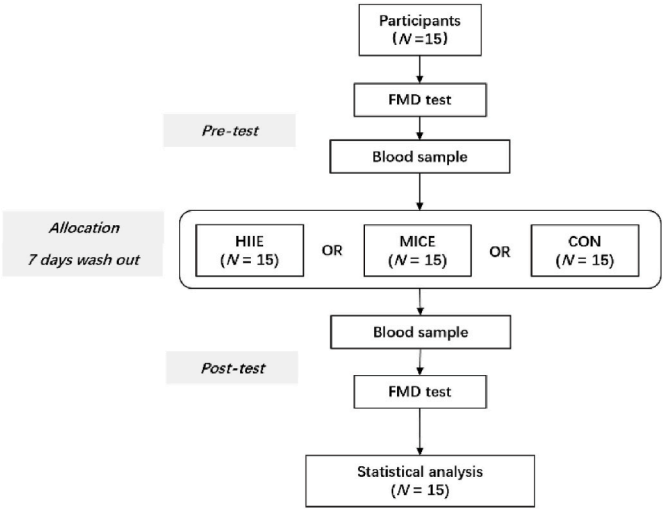

Fig. 1. Experimental design
HIIE: high-intensity interval exercise; MICE: moderate-intensity continuous exercise; CON: control.

prior to the experiments. To minimize variance, they were instructed to conduct the experiments at the same time of day of testing.

2.3. Exercise protocols

The HIIE protocol used in this study was modified from the protocol of Gillen et al., which was widely used in participants with SB, type 2 diabetes, obesity, or overweight,[12] and is more likely to be adhered by the participants. HIIE was conducted using a cycle ergometer, consisting of 40% VO_{2max} intensity warm-up for 2 min, 8 × 1-min 80% VO_{2max} high-intensity exercise interspersed with 7 × 1-min 40% VO_{2max} active rest, and 3-min 40% VO_{2max} rest for recovery. MICE was also conducted using a cycle ergometer, consisting of a 20% VO_{2max} intensity warm-up for 2 min, 60% VO_{2max} exercise for 30 min, and 3-min 20% VO_{2max} recovery rest. The amounts of total power during the training sessions were equal for both exercise protocols. Participants in the control session of rest (CON) maintained their sedentary behavior for 1 h (Fig. 2).

2.4. Measurements

2.4.1. Measurement of VO_{2max}

Participants completed a progressive exercise test on a cycle ergometer (Ergoselect 100, Ergoline, Germany) following the previous test criteria.[40] In the progressive loading test, participants pedaled at a starting speed of 55 W for 2 min and then increased the load by 15 W every 2 min until exhaustion. The participants' maximal oxygen uptake during the last 1 min of each phase and the exercise load were used to generate linear equations using standard curves to calculate the load values.[41] To ensure exercise intensity and safety, heart rate (Polar, Finland) and exhaled gas (Vyntus CPX, Jaeger, CareFusion, Germany) were monitored during all exercise sessions and were used to calculate oxygen and energy expenditure. The participant's maximal oxygen uptake was determined while 2 of the following 4 criteria were met[42]: (1) oxygen consumption plateaued and did not increase continuously; (2) respiratory exchange ratio ≥ 1.1; (3) heart rate was higher than the predicted maximum heart rate (220 - age); (4) RPE ≥ 19.

2.4.2. Measurement of endothelial function

The details for brachial artery flow-mediated dilation (FMD) measurement were previously described.[43,44] In brief, a non-invasive vascular endothelial function ultrasound detector (UNEXEF38G, UNEX, Nagoya, Japan) was used to monitor changes in vascular intimal diameter in real time by Doppler ultrasonography as well as an automatic tracking function. While using the auto-calibration modes, the computer-assisted analysis software in the device can automatically generate a distinct 2D-image of the vessel, consisting of two cross-sectional images and one longitudinal image. A 10 MHz H-type probe was used to scan the brachial artery 5–10 cm above the right elbow. This location was marked on the skin of each participant and all subsequent measurements were performed at the same location. The menstrual cycle of female participants was recorded and they were not menstruating during the conduct of each experiment.

FMD tests were performed on each participant before and immediately at the end of each visit by the same operator. Our previous results of repeated measurements showed that the correlation coefficient was 0.88 and the coefficient of variation was 11.4%, which satisfies the validity requirements of the test.[45] FMD and mean shear rate (MSR) were calculated according to the following equations: allometric scaling FMD (%) = peak diameter / baseline diameter ^ b, b the slope of the relationship between log (baseline diameter) and log(peak diameter); absolute FMD (AbsFMD) = peak diameter - baseline diameter; MSR (s^{-1}) = (4 × mean blood flow velocity) / mean baseline diameter.

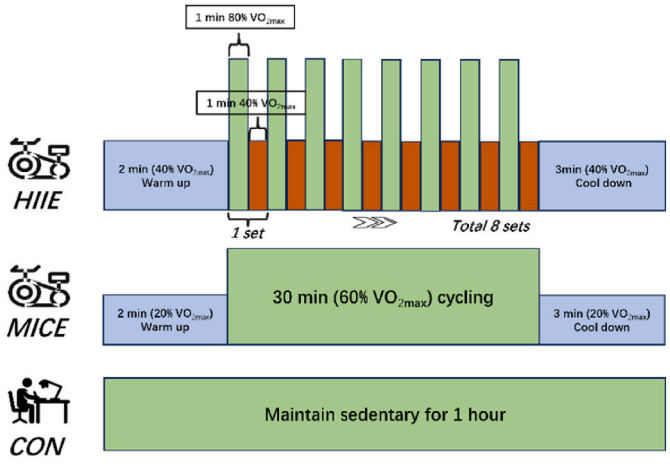

Fig. 2. Exercise protocols
HIIE: high-intensity interval exercise; MICE: moderate-intensity continuous exercise; CON: control.

2.4.3. Measurements of circulating biomarkers

Blood samples were collected before and immediately after (within 5 min) each visit using K^+-EDTA anticoagulant tubes. The level of lactate was measured using a handheld lactate tester (Lactate Scout, SensLab, Leipzig, Germany). Plasma was separated by centrifugation (3500 rpm for 10 min at 4°C) and stored in 1 ml aliquots at -80°C until further analysis. The concentrations of VEGF, IGF-1, and irisin were analyzed using the enzyme-linked immunosorbent assays (ELISA) kits (Cusabio, Wuhan, China) according to the manufacturer's instructions. The optical density at 450 nm wavelength was evaluated using a microplate reader (Bio Tek Instruments, Vermont, USA).

2.5. Statistical analyses

Data were statistically analyzed using SPSS 22.0. The results are expressed as mean and standard deviation of mean (SD). One-way ANOVA and the Bonferroni post-hoc test were used for between-group comparisons in basic characteristics. Other data were analyzed using a two-way (time × condition) repeated-measures analysis of variance after normal distributions were confirmed, and specific differences were identified with a Bonferroni post-hoc test. Given the possible change in baseline brachial artery diameter and post-deflation mean shear rate following exercise, we used allometric scaling technique to eliminate this effect.[46,47]

In addition, Spearman correlation analysis was used to analyze the correlation between the tested indicators, and the degree of correlation was determined based on the absolute value of Spearman's correlation coefficient and *P* value.[48] Mediation analysis was performed to understand the relationship between changes in variables. We used bootstrapping (5000 samples) to calculate bias-corrected 95% confidence intervals (CI) of the explained associations using the PROCESS statistical package. The indirect effect of the mediation analysis was interpreted as significant if zero was not included in the 95% CI.

3. Results

3.1. Participants' characteristics

A total of 15 healthy subjects (10 males and 5 females) volunteered to participate and complete all the experiments. The basic information of the participants in this experiment is showed in Table 1.

3.2. Endothelial function

As shown in Fig. 3A and B, baseline diameter and peak diameter only significantly enhanced in HIIE condition ($P < 0.05$ and $P < 0.001$, respectively) but not MICE and control conditions after visits. MBP

Table 1
Participants' characteristics

Basic characteristics	Mean ± SD
Age (years)	22.9 ± 2.7
Height (cm)	171.0 ± 8.2
BMI (kg/m^2)	23.1 ± 4.1
VO_{2max} (ml/kg/min)	36.0 ± 6.3
Heart rate (bpm)	64.9 ± 6.0
SBP (mmHg)	112.3 ± 7.6
DBP (mmHg)	61.2 ± 6.3

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

significantly enhanced in HIIE and MICE conditions but not in control condition after visits compared to the baseline value (both $P < 0.001$). Moreover, a significant enhancement in MBP was seen in both HIIE and MICE groups compare to control condition (both $P < 0.001$). Meanwhile, MBP in HIIE condition was significantly higher than that in MICE condition ($P < 0.01$) (Fig. 3C).

Compared to the baseline values, MSR significantly increased in both HIIE and MICE conditions ($P < 0.001$ and $P < 0.01$, respectively) but not in control condition after visits. Moreover, MSR in HIIE condition was significantly higher than that in MICE condition as well as that in control condition ($P < 0.05$ and $P < 0.001$, respectively) (Fig. 3D).

FMD% significantly increased in both HIIE and MICE conditions (both $P < 0.001$). In addition, the enhancement in FMD% was significantly greater after HIIE than MICE ($P < 0.001$) (Fig. 3E).

AbsFMD significantly enhanced in both HIIE and MICE conditions ($P < 0.001$ and $P < 0.01$, respectively) but not in control condition after visits compared to the baseline values. Moreover, AbsFMD in HIIE condition was significantly higher than that in MICE condition as well as that in control condition ($P < 0.01$ and $P < 0.001$, respectively) (Fig. 3F).

3.3. Circulating biomarkers

As seen in Fig. 4A, circulating lactate levels significantly increased in both HIIE and MICE conditions but not in control condition after visits compared to the baseline values (both $P < 0.001$). Moreover, significant changes in lactate were observed in both HIIE and MICE conditions compared to control condition (both $P < 0.001$). In addition, the change in lactate was significantly greater after HIIE than MICE ($P < 0.001$). Circulating VEGF levels significantly increased in both HIIE and MICE conditions but not in control condition after visits compared to the baseline values ($P < 0.001$ and $P < 0.01$, respectively). Furthermore, VEGF in HIIE condition was significantly higher than that in MICE condition as well as that in control condition ($P < 0.05$ and $P < 0.01$, respectively) (Fig. 4B). Similarly, HIIE and MICE significantly increased circulating IGF-1 levels compared to the baseline level (both $P < 0.001$). Moreover, a significant increase in IGF-1 was seen in HIIE condition compared to MICE and control conditions ($P < 0.05$ and $P < 0.001$, respectively) (Fig. 4C). In addition, circulating irisin levels significantly increased in both HIIE and MICE conditions but not in control condition after visits compared to the baseline values ($P < 0.001$ and $P < 0.05$, respectively) (Fig. 4D).

3.4. Correlation analyses and mediation analyses

As shown in Fig. 5, our correlation analyses showed that change in FMD was positively correlated with changes in MSR, blood lactate, and

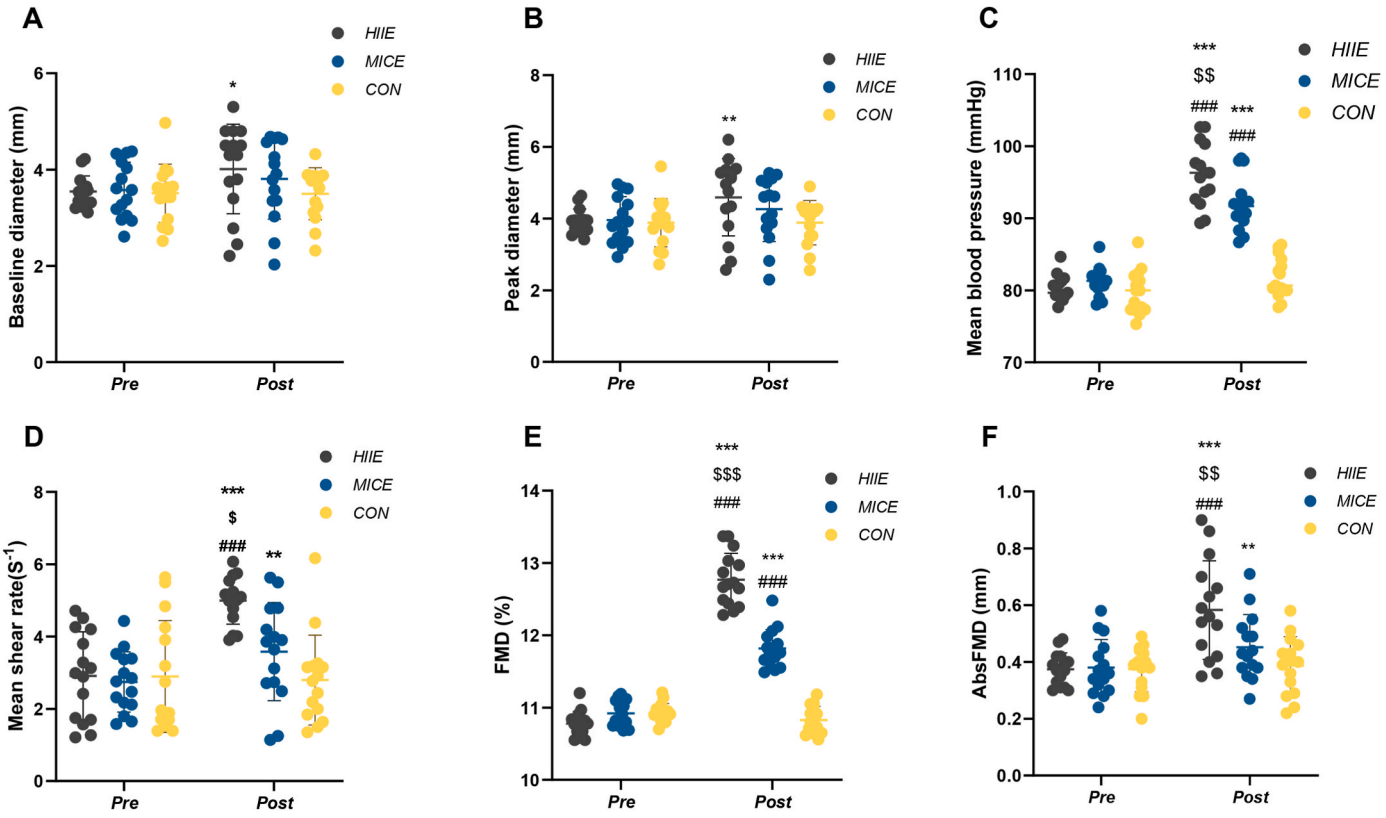

Fig. 3. Effects of acute HIIE and MICE on endothelial function-related indicators in sedentary young individuals
The statistical analyses showed the levels of baseline diameter (A), peak diameter (B), mean blood pressure (C), MSR (D), FMD% (E), and absolute FMD (F) in the pre- and post-visits of HIIE, MICE, and CON conditions. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs pre-visit; $^{\#\#\#}P < 0.001$ vs CON; $^{\$}P < 0.05$, $^{\$\$}P < 0.01$, $^{\$\$\$}P < 0.001$ vs MICE. Data are the Mean ± SD. HIIE: high-intensity interval exercise; MICE: moderate-intensity continuous exercise; CON: control; FMD%: percent flow-mediated dilation; AbsFMD: absolute FMD; MSR: mean shear rate.

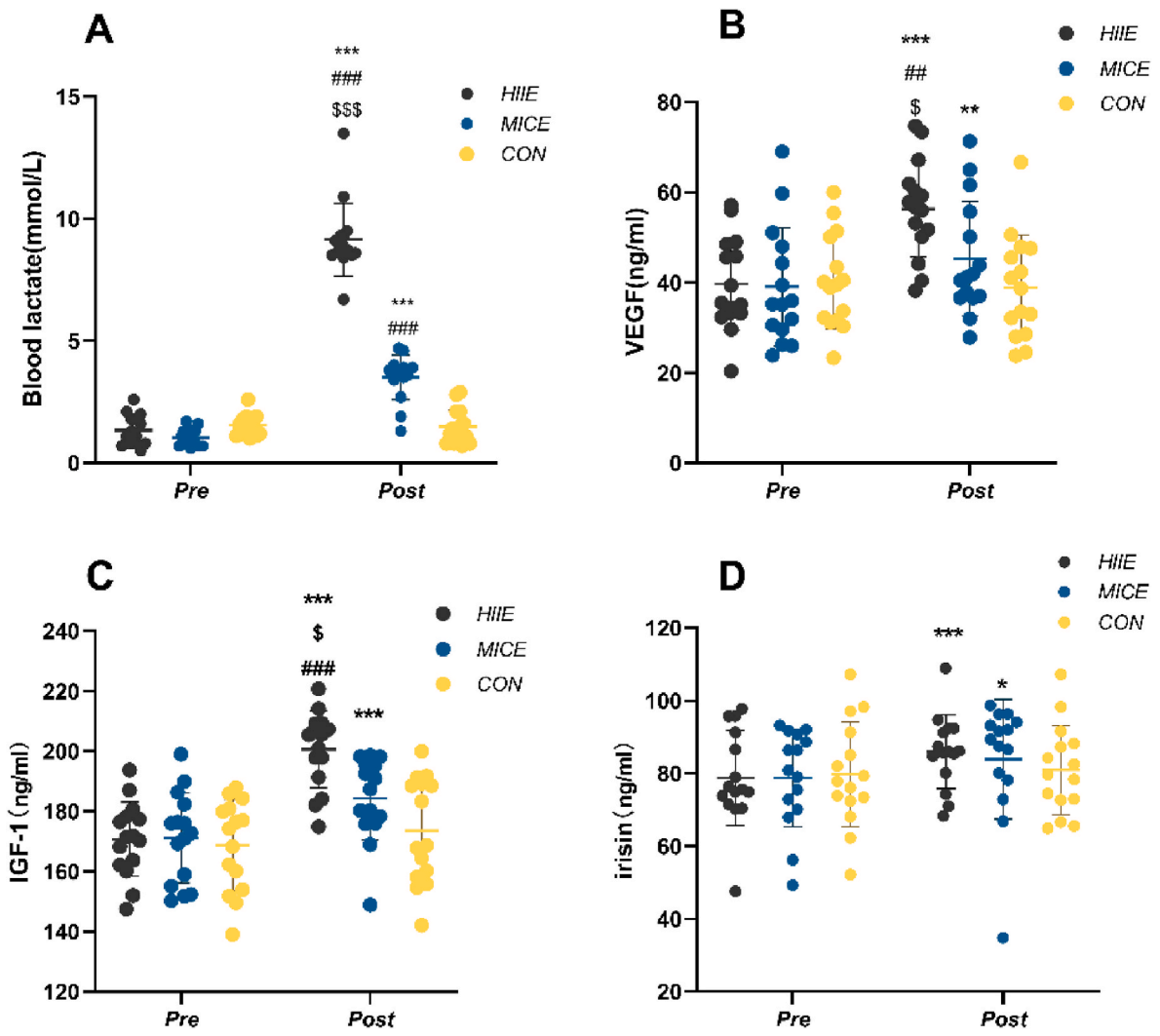

Fig. 4. Effects of acute HIIE and MICE on blood biomarkers in sedentary young individuals
The statistical analyses showed the levels of blood lactate (A), VEGF (B), IGF-1 (C), and irisin (D) in the pre- and post-visits of HIIE, MICE, and CON conditions. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs pre-visit; $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs CON; $^{\$}P < 0.05$, $^{\$\$\$}P < 0.001$ vs MICE. HIIE: high-intensity interval exercise; MICE: moderate-intensity continuous exercise; CON: control; VEGF: vascular endothelial growth factor; IGF-1: insulin-like growth factor.

VEGF in HIIE and MICE conditions but not in control condition (Fig. 5A–C). Notably, change in MSR was positively associated with changes in blood lactate, VEGF, and IGF-1 in HIIE and MICE conditions but not in control condition (Fig. 5D–F). Furthermore, enhancement in blood lactate was positively correlated with enhancements in VEGF in HIIE and MICE conditions but not in control condition (Fig. 5G). In addition, change in blood lactate was positively associated with change in IGF-1 only in HIIE condition (Fig. 5H). Additionally, a significant positive correlation between change in IGF-1 and change in VEGF was observed in HIIE and MICE conditions but not in control condition (Fig. 5I).

As shown in our mediation analyses, MSR had no direct effect on FMD in HIIE condition but influenced FMD indirectly through VEGF in HIIE condition (Fig. 6A). However, MSR influenced FMD directly and indirectly through VEGF in MICE condition (Fig. 6B). In addition, lactate had no direct effect on FMD but influenced FMD indirectly through VEGF in both HIIE and MICE conditions (Fig. 6C and D).

4. Discussion

The present study aimed to compare the effects of acute HIIE and MICE on endothelial function and its associated biomarkers and to investigate the possible mechanisms in sedentary young individuals. The main finding of this study is that acute HIIE has a greater positive influence on endothelial function and its associated biomarkers than MICE in sedentary young individuals while the total power of these two protocols is equal. Importantly, the increases in lactate and its mediated VEGF release, attributed to the increase in blood flow shear stress after exercise, are involved in the regulatory mechanisms of improved endothelial function.

Although previous studies have investigated the effects of HIIE and MICE on endothelial function and indicated long-term HIIE has yielded more favorable outcomes than MICE in enhancing vascular function,[15] few studies compare the acute effects of HIIE with MICE on endothelial function and its associated biomarkers especially in sedentary young individuals.[49,50] Thus, the present study compared the effects of acute HIIE and MICE on brachial artery FMD, the non-invasive gold-standard used to assess endothelial function, in sedentary young people. The present study demonstrated that both acute HIIE and MICE could enhance endothelial function in sedentary young individuals, and HIIE seems to be superior to MICE in improving endothelial function in this population due to the fact that FMD increased at a greater extent in HIIE condition compared to MICE condition. These findings highlight that HIIE is a more effective method than MICE at acutely improving

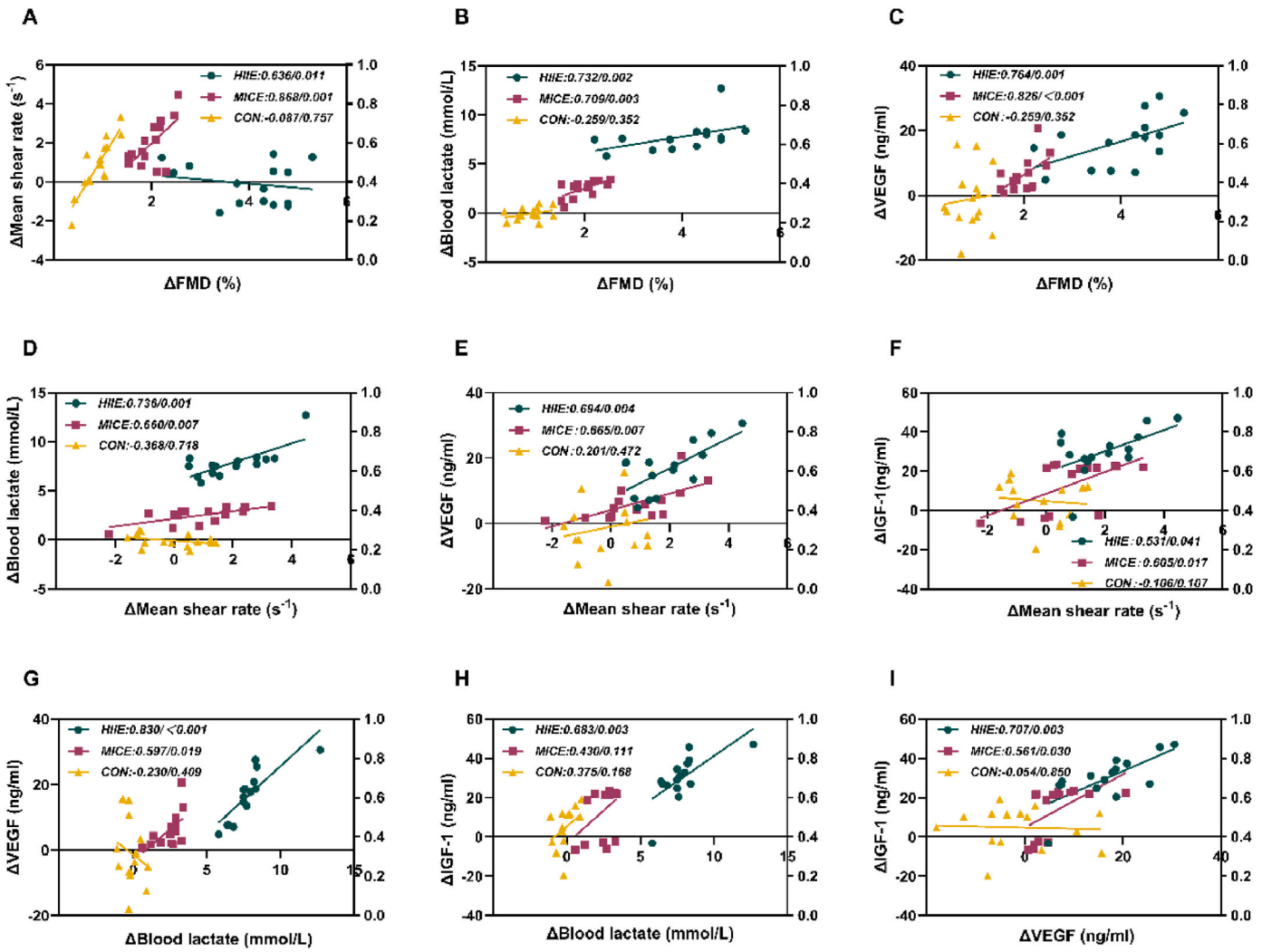

Fig. 5. Correlation analyses of vascular endothelial function variables
Spearman correlation analyses showed a correlation between change in FMD% and change in mean shear rate (A), change in blood lactate (B), or VEGF (C). Spearman correlation analyses showed a correlation between change in mean shear rate and change in blood lactate (D), change in VEGF (E), or change in IGF-1 (F). Spearman correlation analyses showed a correlation between change in blood lactate and change in VEGF (G) or change in IGF-1 (H). Spearman correlation analysis showed a correlation between change in VEGF and change in IGF-1 (I). Values are the Spearman's correlation coefficients/*P* value. FMD%: percent flow-mediated dilation; VEGF: vascular endothelial growth factor; IGF-1: insulin-like growth factor.

endothelial function in sedentary young individuals.

A significant increase in baseline diameter after HIIE was found in our study, which is consistent with a previous finding reporting that both of baseline diameter and FMD increased after an acute bout of aerobic exercise in sedentary young individuals.[51] It is worth mentioning that we have handled this result with caution because changes in FMD could be influenced by baseline diameter, and acute exercise leads to an increase in blood flow ultimately causing change in baseline diameter. So there has been an effort to standardize FMD according to the shear rate, for example, Pyke et al. and Harris et al. proposed a method of standardization of the shear rate,[52–54] which has been accepted as one of the appropriate methods for interpreting FMD. However, since FMD and shear rate are weakly related after acute exercise, so this normalization method should not be used for post-exercise data.[55] Instead, we adopted the well-recognized allometric scaling FMD % to demonstrate changes in endothelial function before and after acute exercise.[46,47]

It is well known that hemodynamic changes are one of the most fundamental causes of exercise-induced changes in endothelial function.[56] The result of this study showed that the increase in MSR showed a significant positive correlation with the increase in FMD after exercise, in consistent with the result from a previous study which demonstrated that an increase in shear rate during exercise was involved in acute exercise-induced improvement of endothelial function in subjects with metabolic syndrome.[57] Moreover, our study reported that HIIE is more effective than MICE at increasing MSR as well as FMD in sedentary young individuals, indicating that HIIE exerts a greater impact than MICE at improving endothelial function might be due to the fact that HIIE is a more potent stimulus than MICE in elevating MSR. The shear stress generated by blood flow on the vascular endothelium during exercise induces NO production by endothelial cells (EC), resulting in vascular smooth muscle cell relaxation, arteriolar vasodilation, and a decrease in vascular resistance.[58,59] Enhanced endothelial function in response to acute exercise may be the result of exercise-increased shear stress on endothelium to enhance NO bioavailability.[60] Furthermore, the increase in peripheral shear stress is greater after acute high-intensity exercise,[61,62] so it is reasonable that HIIE is more effective than MICE in improving MSR.

In addition to increasing NO bioavailability, increase in MSR might promote FMD by altering the levels of circulating vascular markers.[63] The results of the present study showed that both lactate and VEGF significantly increased after acute HIIE and MICE, and their levels in

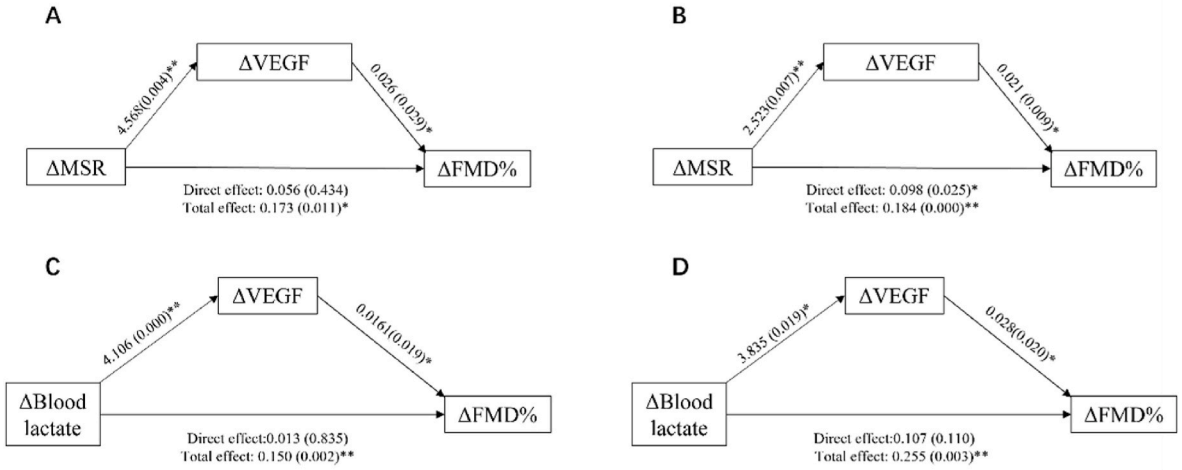

Fig. 6. Mediation analyses
Mediation models showed the relationship between change in MSR and change in FMD% induced by HIIE (A) or MICE (B) with VEGF as a mediator. Mediation models showed the relationship between change in lactate and change in FMD% induced by HIIE (C) or MICE (D) with VEGF as a mediator. Data are unstandardized regression coefficient (*P*-value). FMD%: percent flow-mediated dilation; MSR: mean shear rate; VEGF: vascular endothelial growth factor.

HIIE condition were significantly higher than in MICE condition. Interestingly, change in lactate was associated with change in VEGF, and they also had positive correlations with changes in FMD and MSR. In addition, our mediation analyses suggested that MSR influenced FMD directly and indirectly through VEGF, and lactate may indirectly influence FMD through VEGF. These results indicate that increase in MSR after acute HIIE and MICE to promote the improvement of FMD in sedentary young people may be mediated by lactate and VEGF. A study has demonstrated that lactate may have a beneficial effect on endothelial function, which has been reported that hypoxic conditions, such as those induced by HIIE, can increase lactate, resulting in decreased neuronal prostaglandin E2 uptake and consequent brain vasodilation.[64] Furthermore, previous animal experiments have found that exercise induces VEGF and angiogenesis in the brain via the lactate receptor HCAR1.[65] In experimental studies with human umbilical vein endothelial cells and human microvascular endothelial cells, it was found that lactate indirectly enhanced endothelial cell migration by stimulating VEGF production.[36] Similarly, Zhu et al. demonstrated that an increase in retinal lactate contributes to the production of retinal VEGF in pathological states.[66] The present study suggests that lactate-induced increase in VEGF production is involved in the process of MSR to improve FMD in sedentary young people. Importantly, to the best of our knowledge, this study for the first time reported that the more potent influence of HIIE on endothelial function is perhaps due to its greater induction at lactate release than MICE. Our results highlight the important role of lactate in exercise-induced improvement in endothelial function.

Furthermore, the results of this study showed that HIIE and MICE significantly increased IGF-1 levels in a sedentary young individuals. Although IGF-1 did not have a direct correlation with FMD in this study, IGF-1 had a strong positive correlation with lactate in HIIE condition, and a strong positive correlation with VEGF in both HIIE and MICE conditions. Indeed, related animal studies have shown that IGF-1 enhanced VEGF synthesis to mediate exercise-induced angiogenesis.[67,68] IGF-1 and its receptor IGF-1R induced cell proliferation, and both IGF-1 and IGFBP-3 could promote angiogenesis by increasing the transcription of the VEGF gene.[69] In addition, lactate has been demonstrated to increase the expression of IGF-1 mRNA by activating the somatotropic axis.[35] Our results suggest that increase in lactate-induced IGF-1 release after HIIE may indirectly improve endothelial function by increasing VEGF expression.

In addition to its function in regulating glycolipid metabolism, irisin, an exercise-induced myokine, has a role in reducing oxidative stress and inflammation and increasing eNOS and NO and is expected to be a target for the treatment of cognitive dysfunction and CVD.[70] In the present study, both of HIIE and MICE in an acute manner could induce significant changes in circulating irisin levels in sedentary young individuals, suggesting that acute HIIE and MICE had positive effects on irisin secretion in sedentary young individuals. In addition, a meta-analysis study reported that peripheral irisin levels may be significantly elevated immediately after acute exercise in young and middle-aged adults.[71] However, some inconsistent results had also been reported. For example, plasma irisin level decreased after acute HIIE in taekwondo athletes.[70] Moreover, in overweight female adolescents, a single session of HIIE increased irisin levels in skeletal muscle but not in plasma.[72] In addition, a meta-analysis including a total of 921 participants reported that although exercise significantly increased circulating irisin levels, subgroup analysis demonstrated that irisin levels significantly raised only when resistance training and combined aerobic and resistance training were applied, suggesting that irisin is more sensitive to resistance training than aerobic training.[73] These discrepancies may be attributed to the variability in the exercise modalities, durations, intensities, populations, etc. The exact impacts and underlying mechanisms of exercise on irisin secretion need further investigation.

A significant enhancement in MBP after acute exercise was observed in the present study, which is in line with a randomized crossover trial reported that FMD enhanced after acute exercise with a significant increase in MBP.[74] However, a previous study by Gonzales et al. concluded that high MBP during acute exercise, characterized by high contractile activity (time spent in contraction and contractile work), was associated with decreased FMD following exercise. This finding seems to support that increased blood pressure after acute exercise is associated with decreased FMD, since high blood pressure could stimulate vascular endothelium to release the vasoconstrictor, endothelin-1.[75] This discrepancy may be due to the FMD measurement time following exercise. The present study measured FMD within 10 min after exercise, and it has been shown that circulating NO level is elevated 10 min after exercise.[76] However, the study by Gonzales et al. measured FMD 30 min after exercise, allowing adequate time for clearance of vasoactive metabolites or recovery of enhanced level of NO and the vasoconstrictors such as endothelin-1 increased by elevated blood pressure may mediate the decrease in FMD following exercise.[75]

Our study also had some limitations, Firstly, our study did not consider sex differences because of the small sample size. Secondly, our

study only evaluated the acute impacts of HIIE and MICE on endothelial function in sedentary young individuals. Finally, due to practical constraints, we could only ask participants to fast 2 h prior to the experiments and did not strictly follow the guidelines. Future studies ought to examine the temporal progression of the effects of HIIE and MICE on endothelial function in sedentary young individuals, determining whether prolonged exercise training could lead to a persistent improvement in endothelial function.

5. Conclusion

In conclusion, both acute HIIE and MICE have a positive influence on endothelial function in sedentary young individuals, and acute HIIE has a greater impact than MICE at improving endothelial function in this population, which is due to the fact that acute HIIE is more effective in improving shear rate, lactate, VEGF, and IGF-1. Mechanistically, the increase in shear rate induced by exercise to promote the improvement of endothelial function in sedentary young individuals may be induced by lactate-mediated VEGF release. These findings highlight that acute HIIE is a more effective method than MICE at improving endothelial function in sedentary young individuals. Our results from an acute model of HIIE and MICE provide insight for understanding the beneficial effects of prolonged exercise on endothelial function, since repeated acute changes may result in chronic adaptations.

Author contribute statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Junhao Huang reports was provided by Guangzhou sport university. Junhao Huang reports a relationship with Guangzhou Sport University that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jesf.2024.12.006.

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