Aerobic exercise acutely prevents the endothelial dysfunction induced by mental stress among subjects with metabolic syndrome: the role of shear rate


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Sales AR, Fernandes IA, Rocha NG, Costa LS, Rocha HN, Mattos JD, Vianna LC, Silva BM, Nóbrega AC. Aerobic exercise acutely prevents the endothelial dysfunction induced by mental stress among subjects with metabolic syndrome: the role of shear rate. Am J Physiol Heart Circ Physiol 306: H963-H971, 2014; First published February 15, 2014; doi:10.1152/ajpheart.00811.2013—Mental stress induces transient endothelial dysfunction (MetS) and whether an increase in shear rate during exercise plays a role in this phenomenon. Subjects with MetS participated in two protocols. In protocol 1 (n = 16), endothelial function was assessed using brachial artery flow-mediated dilation (FMD). Subjects then underwent a mental stress test followed by either 40 min of leg cycling or rest across two randomized sessions. FMD was assessed again at 30 and 60 min after exercise or rest, with a second mental stress test in between. Mental stress reduced FMD at 30 and 60 min after the rest session (baseline: 7.7 ± 0.4%, 30 min: 5.4 ± 0.5%, and 60 min: 3.9 ± 0.5%, P < 0.05 vs. baseline), whereas exercise prevented this reduction (baseline: 7.5 ± 0.4%, 30 min: 7.2 ± 0.7%, and 60 min: 8.7 ± 0.8%, P > 0.05 vs. baseline). Protocol 2 (n = 5) was similar to protocol 1 except that the first period of mental stress was followed by either exercise in which the brachial artery shear rate was attenuated via forearm cuff inflation or exercise without a cuff. Noncuffed exercise prevented the reduction in FMD (baseline: 7.5 ± 0.7%, 30 min: 7.0 ± 0.7%, and 60 min: 8.7 ± 0.8%, P > 0.05 vs. baseline), whereas cuffed exercise failed to prevent this reduction (baseline: 7.5 ± 0.6%, 30 min: 5.4 ± 0.8%, and 60 min: 4.1 ± 0.9%, P < 0.05 vs. baseline). In conclusion, exercise prevented mental stress-induced endothelial dysfunction among subjects with MetS, and an increase in shear rate during exercise mediated this effect.

Flow-mediated dilation; shear rate; mental stress test; aerobic exercise

ACUTE EXPOSURE to mental stress activates the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis (26). This activation results in the secretion of hormones and neurotransmitters such as cortisol, adrenaline, and noradrenaline (4, 12, 26) that can trigger the secretion of endothelin-1, the release of cytokines, and the production of reactive oxygen species, thereby leading to transient endothelial dysfunction (4, 12, 29). This deleterious process begins during mental stress and can last up to 90 min (12), and its magnitude is considered clinically meaningful (26). Consequently, preventing this process might be important with regard to cardiovascular health protection, particularly among subjects with a cluster of risk factors, such as those with metabolic syndrome (MetS) (1, 10).

Moderate aerobic exercise of the lower limbs acutely increases endothelium-dependent flow-mediated dilation (FMD) of the brachial artery among subjects with cardiometabolic risk factors (9, 34). This beneficial effect of exercise has been applied successfully, for example, to prevent the transient endothelial dysfunction provoked by the ingestion of a high-fat meal (25, 35). Therefore, aerobic exercise might also attenuate or even prevent the transient endothelial dysfunction induced by mental stress; however, this hypothesis currently remains untested.

The increase in shear rate (SR) that occurs during exercise is a key mechanism that mediates the increase of brachial artery FMD after aerobic exercise (3, 32, 33). This result occurred in a forearm with undisturbed SR during leg cycling, whereas attenuating the mean SR during exercise (i.e., reducing antegrade SR, augmenting retrograde SR, or both) via cuff inflation on the contralateral forearm abolished the FMD increase (3, 19, 32). Therefore, if aerobic exercise acutely attenuates or prevents the transient endothelial dysfunction induced by mental stress, then the increase in SR that occurs during exercise might mediate this effect.

Thus, this study tested the hypotheses that 1) aerobic exercise acutely attenuates or prevents the endothelial dysfunction induced by mental stress among subjects with MetS and 2) the increase in SR during aerobic exercise contributes for this attenuation/prevention. To test these hypotheses, we evaluated the effect of exercise on brachial artery FMD when subjects were exposed to mental stress and either exercised or remained at rest. The isolated effect of exercise and time on FMD were evaluated in a portion of the sample. Finally, the effect of SR on brachial artery FMD was assessed when subjects were exposed to mental stress and exercised with or without a forearm cuff.

MATERIALS AND METHODS

Subjects

Subjects were recruited from the local community via the distribution of posters and pamphlets as well as print and electronic media releases. Sixteen subjects with MetS (14 men and 2 women) were enrolled in the study after a screening for the eligibility criteria. The initial screening consisted of a clinical assessment composed of a biochemical blood analysis (venous blood sample collected after 12-h fasting) and physical examination. The physical examination included resting blood pressure (BP) measurement (sphygmomanometry), a resting electrocardiogram, anthropometry (i.e., body weight, waist circumference, and dual-energy X-ray absorptiometry), and cardio-
pulmonary exercise testing. The inclusion criteria consisted of being between 18 and 49 yr old, no smoking history, a sedentary lifestyle for at least 3 mo, the absence of chronic diseases (except those disturbances associated with MetS), not regularly taking prescription drugs, and normal resting and exercise electrocardiograms. The included women had regular menstrual cycles, and they attended the experimental visits during their early follicular phase (up to 5 days after the onset of menstruation). MetS was diagnosed in accordance with the Joint Interim Statement (1) when at least three of the following five criteria were met: a waist circumference of \( \geq 90 \) cm in men and \( \geq 80 \) cm in women, systolic BP \( \geq 130 \) mmHg or diastolic BP \( \geq 85 \) mmHg, high-density lipoprotein-cholesterol <40 mg/dl in men and <50 mg/dl in women, triglycerides \( \geq 150 \) mg/dl, and fasting glucose \( \geq 100 \) mg/dl.

The local ethics committee (CEP-CCM/HUAP 013/2010) approved this study that conformed with standards set by the Declaration of Helsinki. All subjects provided written consent after being informed of the experimental procedures.

Study Design

The experimental visits were conducted in the morning in a quiet, air-conditioned room (22–24°C) at least 1 h after a standardized light breakfast. Repeated visits were conducted at the same time of day, with an interval of at least 48 h. Before each visit, subjects abstained from alcohol and caffeine for 24 h and from intense physical activities 48 h.

The study had two protocols (Fig. 1). Protocol 1 investigated whether a mental stress test induces endothelial dysfunction among subjects with MetS and whether aerobic exercise attenuates or prevents this dysfunction. Subjects (n = 16) reported to the laboratory twice to perform either an exercise session or a rest session based on random assignment (Fig. 1, visits A and B). In the exercise session, endothelial function was assessed using brachial artery FMD. Subjects were then submitted to a mental stress test followed by 40 min of aerobic exercise. FMD was assessed again at 30 and 60 min after exercise, with a second mental stress test in between. The rest session consisted of the same protocol; however, subjects remained seated for 40 min rather than exercising. To examine the isolated effect of exercise and time on endothelial function (i.e., without the effect of mental stress), a subgroup of subjects (five men) returned to the laboratory for two additional randomized visits. During these visits, there was no mental stress test. FMD was initially assessed and followed by either exercise or a rest period (Fig. 1, visits C and D).

Protocol 2 investigated whether an increase in SR during aerobic exercise mediates the prevention of the endothelial dysfunction induced by mental stress among subjects with MetS. Hence, subjects (five men) underwent two randomized exercise sessions on visits separated by at least 48 h (Fig. 1, visits E and F). At one session, the SR in the brachial artery was attenuated during exercise using a pneumatic cuff placed around the left forearm, immediately below the cubital crease. One minute before the onset of exercise, the cuff was inflated to 70 mmHg and remained inflated throughout the exercise. The cuff was not used during the other session. A similar cuff protocol previously attenuated the rise of SR in the brachial artery during exercise (3, 32, 33).

FMD

Subjects rested for 10 min in the supine position. Brachial artery FMD was then measured in the left arm, with the shoulder abducted at \( \sim 80° \) and the forearm supinated. In accordance with the most recent FMD guidelines (16, 31), an appropriately sized rapid inflation/deflation pneumatic cuff (E-20 Rapid Cuff Inflator, D.E. Hokanson) was placed around the left forearm, immediately distal to the olecranon process. Brachial artery imaging was obtained from the distal third of the arm (2–12 cm above the antecubital fossa) using a multifrequency linear-array probe coupled to a high-resolution Doppler ultrasound system (Vivid 7, General Electric, Horten, Norway). The contrast resolution, depth, and gain were adjusted to optimize the longitudinal images of the lumen/arterial wall interface. Brachial artery diameter and insonation angle-corrected (\( \pm 60° \)) blood velocity spectra were simultaneously recorded via the pulsed-wave mode at linear frequencies of 13 and 6.0 MHz, respectively. The sample volume was located at the center of the brachial artery and then adjusted to cover vessel width. The probe location was marked on the skin to reproduce the position throughout the experiments. Baseline diameter and blood velocity waveforms were continuously recorded over 60 s. The cuff was then rapidly inflated to 200 mmHg for 5 min. After this period, the cuff was rapidly deflated. Doppler recordings resumed 10 s before cuff deflation and continued for 3 min. FMD reliability was evaluated through the comparison of the baseline value between days. The intraclass correlation coefficient was 0.93 (P < 0.05), and the coefficient of variation was 4.5%.

Mental Stress Test

Mental stress was elicted over a 3-min period using an adapted, computerized version of the Stroop color-word test (30). The test consisted of a slideshow projected on the ceiling in front of the subjects. Slides changed every 2 s. Auditory conflicts were continuously delivered via earphones using a standardized audio clip integrated into the slideshow. Two slideshow versions were used to avoid subject adaptation; the versions differed by the sequence of the slides, and the order of versions was randomized within the experimental visit. Beat-to-beat BP was recorded via finger photoplethysmography (Finometer, Finapres Medical Systems). Perceived stress level was recorded after each test using a five-point scale as follows: 0 = not stressful, 1 = somewhat stressful, 2 = stressful, 3 = very stressful, and 4 = extremely stressful (5).

Exercise

Cardiopulmonary exercise testing. The cardiopulmonary exercise test was performed on an electromagnetic leg cycle ergometer (protocol 1: CG400, Inbramed; protocol 2: RB300, AIBI GYM). The protocol consisted of the following stages: 1) 3 min of rest, 2) 3 min of warmup at 30 W, 3) a progressive increase in workload until exhaustion, and 4) 5 min of recovery at 30 W. The increase in

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Fig. 1. Design of protocol 1 (visits A and B, n = 16; visits C and D, n = 4) and protocol 2 (visits E and F, n = 5). FMD, flow-mediated dilatation; MS, mental stress; noncuffed exercise, exercise without attenuation of shear rate (SR); cuffed exercise, exercise with attenuation of SR.
Ventilation, O₂ uptake (V˙O₂), and CO₂ output (V˙CO₂) were measured.

To determine the ventilatory threshold, V˙O₂ was identified by

1. The first inflection of the ventilation versus time curve.

2. A consistent increase in the ventilatory equivalent of O₂ (V˙E/V˙O₂) without a concomitant increase in the ventilatory equivalent of CO₂ (V˙E/V˙CO₂) (2, 27, 37). The electrocardiogram was continuously monitored during the whole test. BP was measured every 2 min. Perceived effort was assessed every minute.

Exercise bout. Subjects performed the exercise bout on the same ergometer used in the cardiopulmonary exercise test (protocol 1: CG400, Inbramed; protocol 2: RB300, AIBI GYM). The exercise bout consisted of the following stages: 1) 5 min of warmup at 30 W, 2) 40 min of exercise at 80% of the ventilatory threshold workload, and 3) 5 min of recovery at 30 W. The intensity and duration of the exercise bout were set to follow recommendations of exercise prescription for sedentary adults (11). They were also based on the configuration of the exercise bout from previous studies, which showed that an exercise session acutely decreases the BP response to mental stress (15) and increases FMD (9, 34). V˙O₂, BP, HR, and perceived effort were measured to assess whether the subjects maintained a steady-state condition. If there was no steady state over time (i.e., progressive increase in V˙O₂, BP, HR, and perceived effort), then the workload was reduced to adjust exercise intensity. In addition to the aforementioned measurements, in protocol 2, brachial artery diameter and blood velocity were measured over 12-s periods every 5 min throughout the 40-min exercise using a high-resolution Doppler ultrasound system (Vivid 7, General Electric). This protocol was conducted using a semirecumbent cycle ergometer (RB300, AIBI GYM) to ensure vascular measurement quality.

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>39.0 ± 3.0</td>
</tr>
<tr>
<td>Sex</td>
<td>2 women/14 men</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>95.6 ± 3.0</td>
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<tr>
<td>Height, cm</td>
<td>174.4 ± 2.2</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>31.4 ± 0.8</td>
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<tr>
<td>Waist circumference, cm</td>
<td>105.0 ± 2.3</td>
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<tr>
<td>Body fat mass, kg</td>
<td>31.4 ± 1.5</td>
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<tr>
<td>Body lean mass, kg</td>
<td>64.2 ± 2.2</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>126.0 ± 3.0</td>
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<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>83.0 ± 2.4</td>
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<tr>
<td>Total cholesterol, mg/dl</td>
<td>205.0 ± 7.7</td>
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<tr>
<td>High-density lipoprotein-cholesterol, mg/dl</td>
<td>34.8 ± 1.6</td>
</tr>
<tr>
<td>Low-density lipoprotein-cholesterol, mg/dl</td>
<td>128.0 ± 7.7</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>230.3 ± 3.2</td>
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<tr>
<td>Fasting glucose, mg/dl</td>
<td>108.2 ± 7.2</td>
</tr>
<tr>
<td>Glycated hemoglobin, %</td>
<td>5.9 ± 0.2</td>
</tr>
<tr>
<td>Ventilatory threshold V˙O₂, ml/kg⁻¹·min⁻¹</td>
<td>14.0 ± 0.8</td>
</tr>
<tr>
<td>Peak V˙O₂, ml/kg⁻¹·min⁻¹</td>
<td>23.1 ± 1.4</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE. V˙O₂, O₂ uptake.

Fig. 2. A: FMD at baseline (BL; −60 min) and 30 and 60 min after exercise (EX) and rest (RE) (results from protocol 1, visits A and B, n = 16). MS was elicited before exercise and rest and between 30 and 60 min. B: individual FMD in the exercise session visit. C: individual FMD in the rest session visit. 

Data Analysis

The Doppler ultrasound video signal was real time encoded and captured at a frequency of 30 Hz using a video capture board with an audio USB 2.0 (EasyCap DC60, Leadership) connected to a laptop computer. The video files were compatible with commercial automated edge-detection and wall-tracking software (Vascular Research Tools 5, Medical Imaging Applications), which was used for offline analysis. The initial phase of the software analysis consisted of identifying regions of interest on the optimal portion of the brachial artery image and its blood velocity spectra. An R-wave gaiting function was not applied to continuously assess brachial artery diameter or blood velocity. Brachial artery diameter and blood velocity were averaged into 3-s averaged time bins. FMD was calculated as the...
absolute change (in mm) and relative change (in %) in the postcuff deflation peak diameter from baseline. SR, a proxy of shear stress, was calculated as four times the ratio between mean blood velocity (V\text{mean}; in cm/s) and artery diameter (in cm) [i.e., SR = 4 × (V\text{mean}/diameter)]. The cumulative SR from the FMD was considered the area under the curve (AUC) of these variables, from postcuff deflation until peak diameter.

The data obtained during the exercise in protocol 2 were averaged to generate one mean for the entire period. The SR pattern during exercise was assessed by measuring the AUC for all antegrade and retrograde blood velocity recordings. This measurement enabled the calculation of antegrade and retrograde shear.

**Statistical Analysis**

The Shapiro-Wilk test was used to verify data distribution, and Mauchly’s test was used to verify sphericity. The normality and sphericity assumptions were not violated. Two-way repeated-measures ANOVA was used to analyze the FMD variables, SR patterns, when significant F values were found. Data are presented as mean ± SE. Significance was set at P < 0.05. The obtained power of the ANOVA interaction on the relative FMD analysis for protocol 1, protocol 1 subgroups, and protocol 2 was 100%, 96%, and 98%, respectively. Pearson’s correlation was used to determine the association between the change in the relative FMD (change = 60 min FMD - baseline FMD/baseline FMD × 100) and the change in the mean SR (change = exercise SR - baseline SR/baseline SR × 100) from data obtained in the noncuffed exercise visit (visit E). All analyses were performed using STATISTICA 10.0 (StatSoft).

**RESULTS**

Table 1 shows subject characteristics. As expected, subjects presented high values of body mass index, body fat mass, waist circumference, total cholesterol, triglycerides, fasting plasma glucose, and glycated hemoglobin as well as low levels of high-density lipoprotein-cholesterol, V\text{O}_2 at the ventilatory threshold, and peak V\text{O}_2 (V\text{O}_2\text{peak}). The number of subjects that met each of the criteria for MetS was as follows: waist circumference, n = 16 subjects; blood pressure, n = 6 subjects; high-density lipoprotein-cholesterol, n = 9 subjects; triglycerides, n = 12 subjects; and fasting glucose, n = 8 subjects.

**Protocol 1**

After the rest session, mental stress significantly reduced the relative and absolute FMD at 30 and 60 min compared with baseline (Fig. 2 and Table 2; P < 0.05). Conversely, FMD did not change from baseline at 30 min after the exercise session (P > 0.05), although it significantly increased from 30 to 60 min (P < 0.05). Thus, FMD was significantly greater after the exercise session than the rest session at 30 and 60 min (P < 0.05). No difference was observed in perceived stress within or between visits (P > 0.05). Mean BP (MBP) increased each time the mental stress was elicited (visit A: first mental stress = 12 ± 2 mmHg and second mental stress = 7 ± 1 mmHg; visit visit A–C:O\text{2} uptake (V\text{O}_2; A), mean blood pressure (MBP; B), and heart rate [HR; in beats/min (bpm); C] during the exercise and rest sessions of protocol 1 (n = 16). *P < 0.05 vs. BL; ‡P < 0.05 vs. the same moment between sessions.

Data are presented as means ± SE; n = 16 subjects. FMD, flow-mediated dilatation; AUCsr, area under the shear rate curve. *P < 0.05 vs. baseline within session; †P < 0.05 vs. 30 min within session; ‡P < 0.05 vs. the same moment between sessions.

### Table 2. Brachial artery characteristics at baseline and 30 and 60 min after rest and exercise (results from protocol 1, visits A and B)

<table>
<thead>
<tr>
<th>Brachial Artery Characteristic</th>
<th>Rest Session</th>
<th>Exercise Session</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>30 min postsession</td>
</tr>
<tr>
<td>Resting diameter, mm</td>
<td>4.25 ± 0.15</td>
<td>4.20 ± 0.15</td>
</tr>
<tr>
<td>Peak diameter, mm</td>
<td>4.57 ± 0.15</td>
<td>4.41 ± 0.15</td>
</tr>
<tr>
<td>FMD, mm</td>
<td>0.32 ± 0.02</td>
<td>0.22 ± 0.02</td>
</tr>
<tr>
<td>AUCsr, 10^{-4} s^{-1}</td>
<td>3.86 ± 0.36</td>
<td>2.77 ± 0.38</td>
</tr>
<tr>
<td>FMD%/AUCsr, %</td>
<td>2.27 ± 0.23</td>
<td>2.26 ± 0.30</td>
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</table>
exercise tended to attenuate this increase in MBP (interaction: $P < 0.05$; Fig. 3) and were higher during the exercise session than the rest session ($P < 0.05$). The exercise was performed at $48 \pm 2\%$ of $\dot{V}O_2$ peak.

One subject did not complete visit C (exercise session but no mental stress). Therefore, the sample size used in the inferential analysis to compare the exercise session (without mental stress) with the rest session (without mental stress) was four subjects. Relative FMD did not change from baseline at 30 min after the exercise session; however, this value increased significantly from 30 to 60 min ($P < 0.05$; Fig. 4). As a result, the FMD value at 60 min was significantly greater after the exercise session compared with the rest session ($P < 0.05$), and absolute FMD showed the same response (Table 3). $\dot{V}O_2$, MBP, and HR increased from baseline to exercise ($P < 0.05$) and were higher during the exercise session than the rest session ($P < 0.05$). The exercise was performed at $48 \pm 1\%$ of $\dot{V}O_2$ peak.

**Protocol 2**

Mean and antegrade SR increased during the noncuffed exercise ($P < 0.05$; Fig. 5), whereas retrograde SR did not change from baseline ($P > 0.05$). Mean SR was maintained at the baseline level during the cuffed exercise ($P > 0.05$), whereas antegrade and retrograde SR increased from baseline ($P < 0.05$). Consequently, mean SR was significantly higher ($P < 0.05$) and retrograde SR was significantly lower ($P < 0.05$) during the noncuffed exercise versus the cuffed exercise.

Relative and absolute FMD values did not change over time after the noncuffed exercise session ($P > 0.05$; Fig. 6 and Table 4). In contrast, FMD was significantly reduced at 60 min from baseline after the cuffed exercise session ($P < 0.05$). As a result, FMD at 60 min was significantly lower after the cuffed exercise than after noncuffed exercise ($P < 0.05$). Pearson’s correlation revealed a positive association between the change in relative FMD and the change in mean SR during the noncuffed exercise visit ($r = 0.96$, $P = 0.008$; Fig. 7).

Neither within- nor between-visit differences were observed in the MBP increase (visit E: first mental stress $= 7 \pm 2$ mmHg and second mental stress $= 7 \pm 2$ mmHg; visit F: first mental stress $= 5 \pm 2$ mmHg and second mental stress $= 4 \pm 2$ mmHg; mental stress main effect: $P < 0.01$, interaction: $P > 0.05$) or perceived stress during the mental stress test ($P > 0.05$). $\dot{V}O_2$, MBP, and HR increased from baseline to exercise ($P < 0.05$), and there were no differences in these variables between cuffed and noncuffed exercise ($P < 0.05$). Cuffed and noncuffed exercises were performed at $49 \pm 7\%$ and $47 \pm 3\%$ of $\dot{V}O_2$ peak, respectively.

![Fig. 4](http://ajpheart.physiology.org/)

**Table 3.** Brachial artery characteristics at baseline and 30 and 60 min after rest and exercise (results from protocol 1, visits C and D)

<table>
<thead>
<tr>
<th>Brachial Artery Characteristic</th>
<th>Rest Session</th>
<th>Exercise Session</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>30 min postsession</td>
</tr>
<tr>
<td>Resting diameter, mm</td>
<td>4.00 ± 0.10</td>
<td>4.00 ± 0.10</td>
</tr>
<tr>
<td>Peak diameter, mm</td>
<td>4.32 ± 0.10</td>
<td>4.32 ± 0.10</td>
</tr>
<tr>
<td>FMD, mm</td>
<td>0.32 ± 0.01</td>
<td>0.34 ± 0.01</td>
</tr>
<tr>
<td>AUC$_{SR}$, 10$^3 \cdot $s$^{-1}$</td>
<td>5.86 ± 1.03</td>
<td>4.06 ± 0.12</td>
</tr>
<tr>
<td>FMD%/AUC$_{SR}$, %/10$^4 \cdot $s$^{-1}$</td>
<td>1.55 ± 0.33</td>
<td>3.82 ± 0.20</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE; $n = 4$ subjects. *$P < 0.05$ vs. 30 min within session.
Acute exposure to mental stress tends to provoke transient endothelial dysfunction (12, 26, 29), and this condition is particularly relevant for subjects with cardiometabolic risk factors (1, 10). However, moderate aerobic exercise might acutely enhance endothelium-dependent vasodilation (8). To the best of our knowledge, no previous study has investigated whether exercise attenuates or prevents the transient endothelial dysfunction induced by mental stress. Hence, the present study investigated this issue. Our major findings were that 1) a single moderate aerobic exercise session prevented the endothelial dysfunction induced by mental stress among subjects with MetS and 2) an increase in SR during exercise was associated with protection against the effect of mental stress on the endothelium.

The magnitude and extent of the transient endothelial dysfunction induced by mental stress are heterogeneous (26) and depend on factors such as the type of mental stress and its duration (26), the subject’s degree of responsiveness to mental stress (18), and the baseline level of endothelial function (12). In our study, a significant reduction in FMD was observed 100 min after the Stroop color test when subjects were exposed to 3 min of mental stress before the rest session. This result is consistent with a previous study (12) that showed that the deleterious effect of 5 min of mental stress on endothelial function was present for 90 min among healthy subjects. Furthermore, a second exposure to mental stress reduced FMD to half of its baseline value. This finding indicates that a robust deleterious effect of mental stress was induced on endothelial function after only 3 min of the Stroop test among subjects with MetS, which is clinically meaningful, since it has been shown that the summation of repeated mental stress events contributes to the development of cardiovascular diseases, probably in part via endothelial dysfunction (7, 36).

Previous studies have shown that aerobic exercise acutely reduces BP reactivity (15) and improves hemodynamic responses during mental stress (21). In our study, FMD significantly increased when exercise was used without mental stress among subjects with MetS, which corroborates the findings from other studies in subjects with MetS (34) and in patients with coronary heart disease (9). Most importantly, our study also provides evidence that moderate aerobic exercise success-
fully prevented the endothelial dysfunction induced by mental stress. Notably, no changes were observed in subjects’ perceived stress or baseline diameter throughout the protocol. In addition, FMD did not change over time when mental stress and exercise were not present. Therefore, these factors did not interfere with the effects of mental stress and exercise on FMD. Moreover, despite variations in the area under the SR curve (AUCSR) when the FMD-to-AUCSR ratio was taken into account (31) (or when AUCSR was considered a covariate in the FMD repeated-measures ANOVA; data not shown) (31), the effects of mental stress and exercise on FMD were maintained throughout the protocol.

Studies (20, 24) of cultured endothelial cells, endothelial cells from isolated arteries, and endothelial cells within the arteries of living animals have shown that the magnitude and pattern of shear stress modulate vascular phenotype. Increases in mean shear stress via higher antegrade, lower retrograde, or both types of shear decrease the expression of endothelin-1, VCAM-1, and enzymes that produce reactive oxygen species (i.e., NADPH oxidase), whereas they increase the expression of endothelial nitric oxide (NO) synthase (20, 24, 38). Moreover, these findings were recently translated to humans by attenuation of the increase in SR during exercise by inflating a cuff on one forearm at a subdiastolic pressure (3, 20, 24, 38). This approach indicated that increases in SR during exercise mediate the acute and long-term beneficial effects of exercise on the vascular function of humans (32, 33), which is mediated in part by a systemic increase in the production of NO (14). Given that SR plays an important role in improving the endothelial function that results from exercise, the present study investigated whether increased SR during exercise mediates the prevention of the endothelial dysfunction induced by mental stress among subjects with MetS. This goal was accomplished using the forearm cuff inflation method to attenuate increases in SR during exercise. Cuff inflation to 70 mmHg maintained mean shear at a resting level by maintaining antegrade shear but elevating retrograde shear. As a result, the prevention of transient endothelial dysfunction through exercise was abolished by mean SR attenuation. Moreover, the correlation analysis indicated that the magnitude of the increase in SR during exercise was proportionally related to the magnitude of FMD after exercise.

No between- or within-group differences were observed in the perceived stress level across cuffed and uncuffed exercise sessions. Moreover, we did not observe between-condition differences in terms of MBP reactivity to mental stress. Thus, these factors did not weaken our interpretation. The forearm cuff inflation leads to two different effects: 1) a reduction in mean SR in the brachial artery (3, 6, 19, 23, 32, 33) and 2) mild ischemia in the forearm circulation secondary to venous pooling (17). However, we evaluated endothelial function in the brachial artery, which was exposed only to less SR but not to mild ischemia. In addition, AUCSR during the FMD evaluation was not altered by the cuff inflation (Table 4), which is a variable directly dependent on the forearm hyperemia that occurs during the FMD evaluation (28). Finally, the brachial artery blood flow (data not shown), similarly to the mean SR, was maintained at resting level during the cuffed exercise, which indicates that there was no ischemia in the arm. Thus, the mild ischemia in the forearm did not interfere with our interpretation about the contribution of SR during exercise on brachial artery FMD. One could also argue that the cuff inflation per se might reduce FMD; therefore, a mechanism other than SR might have protected the endothelium against mental stress. Nevertheless, a previous study (32) found that FMD was maintained at a baseline level after a cuffed exercise, which refutes this interpretation.

There are some technical issues regarding this study that should be mentioned. First, our study did not involve a group of healthy subjects, which did not allow us to determine whether basal endothelial function was altered in subjects with MetS. In addition, based on the design of the study, it was not possible to determine the time taken by the subjects with MetS to recovery from the transient endothelial dysfunction. We recognize that attempts to overcome these limitations would
AERobic exercise acutely prevents ENDOTHELIAL dysfunction

provide valuable insights into the impact of MetS on endothelial function. However, it is worth noting that these limitations did not weaken the test of our hypothesis. Second, the sample size for protocol 2 was modest. Nonetheless, the results were consistent between and within subjects, and even a small sample size was sufficient to guarantee an adequate statistical power. The small number of women in our study also precluded us from evaluating sex differences. However, when we analyzed the data for men only, the results were identical (data not shown). Third, we did not investigate the mechanisms by which the increase in SR during exercise prevents the endothelial dysfunction induced by mental stress. However, the systemic increase in NO production is probably involved (14). Finally, our study did not evaluate endothelium-independent vasodilatation. Nevertheless, previous evidence supports the notion that subjects with incipient vascular dysfunction (e.g., those with MetS) do not have altered smooth muscle function (13). In addition, no evidence exists that nitroglycerin-mediated vasodilatation is acutely altered after exercise (32, 33) or mental stress (12, 29).

In summary, the present study demonstrated that aerobic exercise acutely prevents mental stress-induced endothelial dysfunction among subjects with MetS, and the increase of SR during exercise is a mechanism that contributed to that.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS


REFERENCES


