Effects of Submaximal Exercise on Blood Rheology and Sympathetic Nerve Activity

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Background: To explore the acute effects of submaximal exercise on blood rheology and sympathetic nerve activity.

Methods and Results: The effects of exercise (20 or 80 Watts (W)) on blood rheology and sympathetic nerve activity were assessed in 10 healthy Japanese men. Blood sampling and heart rate variability (HRV) recording were performed during 20-min supine rest and standing ergometric exercise (20W for 10 min, 80W for 10 min) and recovery. Blood passage time across the microchannels (diameter, 7 μm) as a parameter of blood rheology, and the number of adhesive leukocytes on microchannel terraces as a parameter of leukocyte activation were measured. Sympathetic nerve activity was evaluated by plasma noradrenalin levels and the ratio of low-frequency (LF)/high-frequency (HF) by spectral analysis of HRV. Compared with values while supine at rest, significant increases in hematocrit, leukocyte count, noradrenalin level and blood passage time were seen after strenuous ergometer exercise at 80W (P<0.01 each). The LF/HF ratio and nitric oxide metabolites tended to be increased with 80W exercise.


Key Words: Exercise; Leukocytes; Microcirculation; Rehabilitation; Sympathetic nerves

Exercise training has become an accepted therapeutic modality for patients with chronic heart failure and ischemic heart disease. However, the effects of exercise on the rheological properties of blood have not received much research attention, despite the potential clinical importance. Limited evidence has recently suggested that acute coronary syndrome can occur during strenuous exercise, because of platelet activation, hemoconcentration and hypercoagulability. Strenuous exercise is thought to activate blood cells by catecholamine stimulation and oxidative stress, although increased shear stress during exercise upregulates endothelial nitric oxide synthetase (eNOS) expression at the transcriptional level, thereby increasing endothelium-derived nitric oxide (NO) production. Endothelium-derived NO plays an important role in the regulation of vascular tone, inhibition of platelet aggregation, and prevention of leukocyte recruitment to the vessel wall. In addition, changing to an upright posture leads to rapid pooling of blood in the lower extremities and shifts plasma into surrounding tissues. Exercise also decreases plasma volume by shifting plasma from the intravascular space to muscle tissues, consequently leading to hemoconcentration.

Because of methodological limitations, the effects of exercise on blood rheology remain unclear. Kikuchi et al have developed optically assessable microchannels formed in a single-crystal silicon substrate for ex vivo studies of blood rheology. The microchannel flow analyzer provides reliable quantitative blood rheological data for animals and humans. The aim of this study was to explore the acute effects of posture change and exercise on sympathetic nerve activity and blood rheology using the ex vivo microchannel flow analyzer.

Methods

Subjects
Subjects were 10 healthy, non-smoking Japanese male volunteers (age range, 27–47 years). They had normal findings on routine physical examination and standard laboratory tests (Table 1) and all gave written informed consent prior to enrolment. All subjects fasted for 5 h and abstained from drinking beverages containing alcohol or caffeine for ≥12 h.
before the study. All studies were performed in an air-conditioned room at 24°C in Saitama Medical Center, Jichi Medical University.

Protocol

The study protocol was approved by the Ethical Committee of Jichi Medical University.

In a pilot study, all subjects underwent a cardiopulmonary exercise test to determine workload and oxygen consumption at the anaerobic threshold (AT), with an electronically braked cycle ergometer (Ergometer 2320; Minato Medical Science, Osaka, Japan) at a constant rate of 80 rpm in an upright position, followed by ergometric exercise at 80 W for the fourth 10-min period, as the work load beyond the AT, and finally recovery while standing for the last 10 min. At the end of each phase, blood sampling was repeated through the catheter. Blood pressure was recorded each minute by the manchette method (STBP-780; NIPPON COLIN, Aichi, Japan). At the end of the each phase, the subjects were asked to indicate their level of physical fatigue using the Borg scale (6–20 point scale).

Blood Kinetics Through Narrow Microchannels Ex Vivo

Immediately after blood sampling, the passage time of 0.1 ml of blood through the narrow microchannels (<0.01 ml) was determined using a microchannel flow analyzer (Kowa) as an ex vivo rheological parameter.17–19 Saline passage time was determined before each blood measurement for calibration. Microscopic images of blood passing through the micro ditches were monitored on a television screen with a charge-coupled device camera. Images were stored on a digital videocassette recorder (WV-DR9; Sony, Tokyo, Japan) for off-line analysis. The video vertical frame rate of the camera was 30 frames/s. Overall magnification on the TV monitor was approximately ×900. An investigator who was unaware of the subjects’ backgrounds selected 5 still images at 30–33 s for off-line VTR analysis. The number of adhesive leukocytes on the microchannel terrace and the percentage of microchannels obstructed were then counted. At ex vivo hemorheological analysis, some microchannels were obstructed by blood cells because of rheological worsening, and there was “no reflow”. To minimize unevenness, passage times greater than 120 s (showing obstruction of almost all microchannels) were considered as 120 s.

Measurement of Plasma Levels of NA and NO Metabolites

Assays for plasma NA level were conducted according to established methods (SRL, Tokyo, Japan).22 NO metabolites (nitrite, nitrate) in plasma were measured using an NO analyzer (ENO-20; Eicom, Tokyo, Japan), as described previously.14,23,24 the minimum detectable concentration of nitrite or nitrate was 0.01 mmol/L.

Evaluation of HRV

Qualifying recorded tapes were subsequently analyzed to measure HRV using validated HRV software (TM-2025-15; A&D, Tokyo, Japan). We assessed frequency domain variability with spectral analysis using the fast Fourier transformation method. The power spectrum of HRV was divided into a low-frequency (LF) band of 0.04–0.15 Hz and a high-frequency (HF) band of 0.15–0.40 Hz. Sympathetic nerve activity was shown by the ratio LF/HF.

Table 1. Baseline Characteristics of the Healthy Male Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>41.7±10.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.1±6.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.8±7.8</td>
</tr>
<tr>
<td>White blood cells (µl)</td>
<td>5.64±1.341</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>42.6±2.3</td>
</tr>
<tr>
<td>Platelets (×10^3/µl)</td>
<td>243.2±39.5</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>195.3±29.2</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>50.2±8.1</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>98.5±50.4</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dl)</td>
<td>91.7±8.7</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.79±0.15</td>
</tr>
<tr>
<td>Anaerobic threshold (ml·kg⁻¹·min⁻¹)</td>
<td>15.5±3.8</td>
</tr>
<tr>
<td>Peak VO₂ (ml·kg⁻¹·min⁻¹)</td>
<td>31.7±4.1</td>
</tr>
<tr>
<td>Work load at AT (W)</td>
<td>69±14</td>
</tr>
<tr>
<td>Work load at AT-1 min (W)</td>
<td>59±14</td>
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</tbody>
</table>

HDL, high-density lipoprotein; AT, anaerobic threshold; W, Watts.

Table 2. BP, HR and Borg Scale (6–20 Point Scale) at Each Phase of the Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>20 W exercise</th>
<th>80 W exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>124±9</td>
<td>133±16</td>
<td>174±22</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>76±8</td>
<td>86±12</td>
<td>87±7</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>79±11</td>
<td>100±13</td>
<td>140±17</td>
</tr>
<tr>
<td>Borg scale</td>
<td>8.4±0.9</td>
<td>15.3±1.3</td>
<td></td>
</tr>
</tbody>
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BP, blood pressure; HR, heart rate.
Statistical Analysis
Data are presented as mean ± standard deviation. Mean values were compared among serial data using analysis of variance, followed by Bonferroni/Dunn’s multiple comparison test. Probability values of P<0.05 were considered indicative of statistical significance. All statistical analyses were performed using StatView version 5.0 software (SAS Institute, Cary, NC, USA).

Results
Blood pressure, heart rate and Borg scale at the end of each phase are shown in Table 2. After the end of 10min of 80W ergometric exercise, blood pressure rose to 174±22 mmHg and the Borg scale was 15.3±1.3 (hard).

Effects of Posture Change on Hemorheological Parameters
Posture change from supine to standing tended to increase the hematocrit (Figure 1a), whole blood passage time through the microchannels (Figure 2a) and NA concentration (Figure 3a).

Effects of Exercise on Hematocrit, Leukocyte and Platelet Counts
After strenuous ergometer exercise at 80W, hematocrit (42.6±2.2% to 47.4±3.2%, a) and leukocyte count (5,648±1,341/μl to 7,584±1,860/μl, c) were significantly increased compared with values at rest while supine, but platelet count was not. *P=0.0001 vs while supine; #P=0.005 vs while supine. EX, exercise.
Effects of Exercise on Hemorheology

Effects of Exercise on Hemorheology

Microchannels was significantly increased after 10 min of 80 W exercise (71.3±27.0 s) compared with the value at rest while supine (47.1±11.4 s, P=0.004, Figure 2a). The number of obstructed microchannels tended to be increased while standing and with 80 W exercise compared with resting while supine (Figure 2b). The number of adherent leukocytes on the terrace was unchanged through all the study phases (Figure 2c).

Effects of Exercise on Sympathetic Nerve Activity and NO Metabolites

Plasma levels of NA were significantly increased after 80 W exercise (994±391 pg/ml, Figure 3a) compared with resting while supine (306±130 pg/ml, P<0.0001). The LF/HF ratio and NO metabolites also tended to increase with 80 W exercise (Figures 3b, c).

Discussion

The present data indicate that strenuous, seated ergometer exercise induced hemococoncentration and sympathetic nerve activation, thus transiently worsening hemorheological parameters even in healthy men, although NO production tended to be increased. We believe that the exercise work rates at 20 W and 80 W were appropriate as light exercise under the AT and strenuous exercise over the AT, because averaged Borg scales at 20 W and 80 W ergometer exercise were 8.4 (very light) and 15.3 (hard), respectively.

Dynamic Changes in Blood Rheology by Posture Change and Exercise

Posture change and exercise induce a shift in water from the intravascular space to the extravascular space such as muscle and the interstitial spaces. The resulting hemoconcentration caused by this water shift increases blood viscosity and worsens hemorheological parameters, although eNOS activity may be enhanced by the increased shear stress during exercise. Standing and strenuous exercise increase sympathetic nerve activity and catecholamine spillover, leading to activation of platelets and leukocytes both in vitro and in vivo.

Strenuous exercise is rapidly followed by an increase in blood cell count, not only by hemoconcentration, but also by altered hemodynamic conditions; that is, increased flow and shear forces within the circulation would be expected to lead to recruitment of both sequestered red blood cells in various circulatory beds and of leukocytes from the marginal pool.

Leukocyte Activation, Sympathetic Nerve Activity and NO

No significant increase in the number of adherent leukocytes was seen after exercise in the healthy men. Previous reports have shown that strenuous exercise contributes to hemorheological deterioration as a proinflammatory factor. The most likely causes of the inflammatory response after strenuous exercise are generalized muscle damage and oxidative stress. Leukocytes activated in this manner may block microvascular circuits and result in further oxidative stress. In patients with ischemic heart disease, leukocyte activation may represent the most important factor in hemorheological deterioration. Exercise at 80 W for 10 min might not reach the level required to activate leukocytes in healthy subjects. Serum levels of NO metabolites tended to be increased after exercise, but this change was not significant. Exercise increases the production of NO from the endothelium following increases in shear stress, particularly in the vessels of the working muscles. At the same time, exercise increases the formation of reactive oxygen species. The bioavailability of endothelial NO mainly depends on the balance between eNOS activity and inactivation of NO by reactive oxygen species. We are currently unable to determine which of these factors represent the most important contributors to the observed changes, because we did not assess reactive oxygen species or endothelial function using plethysmography or ultrasound techniques.

Study Limitations

This study used healthy volunteers as subjects. Patients with ischemic heart disease or other lifestyle disease (eg, diabetes mellitus, hypertension, dyslipidemia) may show different results, and warrant examination in future studies.
Conclusion

Strenuous exercise dynamically alters blood rheology, probably by changes in plasma volume and sympathetic nerve activity. Water supply should be taken into consideration to improve rheological status during exercise, particularly in patients with ischemic cardiovascular disease.

References


