Alterations in autonomic function and cerebral hemodynamics to orthostatic challenge following a mountain marathon

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1Department of Physiology and 2School of Physical Education, University of Otago, Dunedin, New Zealand; 3Department of Integrative Physiology, University of North Texas Health Science Center, Fort Texas, Texas; and 4Research Institute for Sport and Exercise Science, Liverpool John Moores University, Liverpool, United Kingdom

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Murrell C, Wilson L, Cotter JD, Lucas S, Ogoh S, George K, Ainslie PN. Alterations in autonomic function and cerebral hemodynamics to orthostatic challenge following a mountain marathon. J Appl Physiol 103: 88–96, 2007. First published March 22, 2007; doi:10.1152/japplphysiol.01396.2006.—We examined potential mechanisms (autonomic function, hypotension, and cerebral hypoperfusion) responsible for orthostatic intolerance following prolonged exercise. Autonomic function and cerebral hemodynamics were monitored in seven athletes pre-, post- (<4 h), and 48 h following a mountain marathon [42.2 km; cumulative gain ∼100 m; ∼15°C; completion time, 261 ± 27 (SD) min]. In each condition, middle cerebral artery blood velocity (MCAv), blood pressure (BP), heart rate (HR), and cardiac output (Modelflow) were measured continuously before and during a 6-min stand. Measurements of HR and BP variability and time-domain analysis were used as an index of sympathovagal balance and baroreflex sensitivity (BRS). Cerebral autoregulation was assessed using transfer-function gain and phase shift in BP and MCAv. Hypotension was evident following the marathon during supine rest and on standing despite increased sympathetic and reduced parasympathetic control, and elevations in HR and cardiac output. On standing, following the marathon, there was less elevation in normalized low-frequency HR variability (P < 0.05), indicating attenuated sympathetic activation. MCAv was maintained while supine but reduced during orthostasis postmarathon (−10.4 ± 9.8% prevs. −15.4 ± 9.9% postmarathon (%change from supine); P < 0.05); such reductions were related to an attenuation in BRS (r = 0.81; P < 0.05). Cerebral autoregulation was unchanged following the marathon. These findings indicate that following prolonged exercise, hypotension and postural reductions in autonomic function or baroreflex control, or both, rather than a compromise in cerebral autoregulation, may place the brain at risk of hyperperfusion. Such changes may be critical factors in collapse following prolonged exercise.

Subject and Methods

Subjects

Nine healthy individuals [5 men, 4 women; aged 32 ± 10 (mean ± SD) years; body mass 73.2 ± 3.9 kg; body mass index 22.8 ± 1.6 kg/m²; maximal oxygen consumption 56.8 ± 5.9 ml·kg⁻¹·min⁻¹] exercise may compromise cerebral autoregulation, although CBF will clearly be influenced by the extent of the postexercise reduction in BP. For example, low peripheral resistance from dilated muscle and skin are likely to be critical factors in postexercise collapse if the vasodilation and subsequent hypotension are enough to compromise CBF. Importantly, however, the potential extent by which a lowered peripheral resistance and hypotension may impact on cerebral perfusion has not been previously examined.

Alterations in autonomic function (i.e., increased sympathetic activity and reduced vagal activity) following prolonged exercise have been observed in athletes competing in events ranging from 4–100+ h (3, 5, 17, 23). Such changes in reflex autonomic mechanisms adjust the response of hemodynamic parameters to orthostasis, i.e., in response to a change from supine to an upright posture. Despite these findings, no studies to date have investigated the role of the autonomic nervous system combined with cardiovascular and cerebrovascular measures and their integrated function in the orthostatic intolerance (syncope) observed following prolonged exercise. Since orthostatic intolerance is fundamentally due to a compromise in cerebral perfusion, the aims of this investigation were to examine 1) changes in hemodynamic [BP, heart rate (HR), cardiac output (Q) and CBF velocity] and autonomic function during an orthostatic challenge both before and following a bout of prolonged exercise, and 2) whether the onset of orthostatic intolerance after prolonged exercise is due, in part, to a compromised dynamic cerebral autoregulation. On the basis of the aforementioned observations, we tested two original hypotheses: first, CBF velocity would be maintained while resting supine but would be reduced to a greater extent during an orthostatic challenge following prolonged exercise than in a control state; second, cerebral autoregulation would be maintained during supine recovery following prolonged exercise but impaired during an orthostatic challenge after prolonged exercise, thus contributing, in part, to the reduction in CBF velocity.

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volunteered for this study, which was approved by the University of Otago Human Ethics Committee. Subjects were informed of the experimental procedures and possible risks involved in the study before their written informed consent was obtained. Subjects were not taking any medications, all were nonsmokers, and none had any history of cardiovascular, cerebrovascular, or respiratory disease. All participants in the study were experienced runners [2–25 years regular running; 1–47 previous long-distance runs (i.e., half marathon to ultramarathon) completed].

**Experimental Protocol**

Subjects reported to the laboratory on five occasions. Two baseline tests (premarathon), each separated by at least 2 days and undertaken at the same time of day, were performed in the 2 wk leading up to the mountain marathon (42.2 km; 535–887 m above sea level; cumulative gain ~1,000 m), one test was performed within 4 h of marathon completion (postmarathon), and the fifth test was performed 2 days postmarathon (48 h postmarathon) at the same time of day as the baseline tests. Before each visit, participants were informed to abstain from alcohol and caffeine in the 12 h before testing and to avoid the consumption of a large meal 3–4 h prior. With the exception of the postmarathon visit, participants were also asked to avoid exercise in the 12 h before testing sessions. On arrival at the laboratory for these four visits, subjects voided their bladder and assumed the supine position. Following 15 min supine, a venous blood sample was procured, without stasis, for analysis of hematocrit and hemoglobin concentration to allow the estimation of changes in plasma volume (18). Posture-induced changes in blood volume occur rapidly, probably exponentially, and are virtually complete within this time period (22). Hydration status was also estimated in duplicate from urine specific gravity (Hand refractometer, Atago, Tokyo, Japan) and from changes in body mass. The refractory index is a ratio of the velocity of light in air to the velocity in urine (8); the change in velocity deviates (refracts) the path of light, the extent of which is read from a scale on the refractometer reference glass (8). The degree of refraction is proportional to the number and type of particles dissolved in the urine, providing valid indirect estimate of urine specific gravity (8). Maximal aerobic power was measured in a final visit, by using specific software; TNO; TPD Biomedical Instruments). This method provides a reliable estimate of changes in Q at rest and during exercise in healthy young humans (46); however, since the method has not been validated following prolonged exercise, we express the changes in Q both in absolute and as an index of relative change. All data were sampled continuously at 200 Hz using an analog-to-digital converter (Powerlab/16SP ML795; ADInstruments, Colorado Springs, CO) interfaced with a computer. Data were later analyzed using commercially available software (Chart version 5.4.2, ADInstruments). Total peripheral resistance (TPR) was calculated by mean arterial blood pressure (MAP)/Q. Cerebrovascular resistance (CVR) was calculated by MAP/MCAv. We also calculated cerebrovascular conductance (CVC; MCAv/MAP) to normalize for the prevailing blood pressure and as an index of static autoregulation.

**Cerebral orthostatic tolerance test.** Following at least 25 min supine rest, participants quickly (within ~3 s) assumed an upright free-standing posture where they remained standing for 6 min. To limit the effect of the skeletal muscle pump, subjects were instructed not to make any major muscle contractions at rest or during the stand. MCAv, BP, HR, SV, Q, and ECG were monitored continuously.

**Dynamic cerebral autoregulation.** Three-minute steady-state data segments while supine and upright were used for transfer function analysis to identify an index of dynamic cerebral autoregulation. The beat-to-beat data of MAP and MCAv were then linearly interpolated and resampled at 2 Hz for spectral analysis. The transfer gain and phase shift reflect the relative amplitude and time relationship between the changes in MAP and MCAv over a specified frequency range. From the temporal sequences, the frequency-domain transforms were computed with a fast Fourier transformation algorithm. The transfer function H(f) between the MAP and MCAv signals was calculated as:

\[ H(f) = \frac{S_{xy}(f)}{S_{xx}(f)} \]

where \( S_{xy}(f) \) is the autospectrum of input signal (MAP) and \( S_{xx}(f) \) is the cross-spectrum between the two signals. The transfer function magnitude \( |H(f)| \) and phase spectrum \( \Phi(f) \) were obtained from the real part \( H_R(f) \) and imaginary part \( H_I(f) \) of the complex transfer function:

\[ H(f) = \left\{ \frac{[H_R(f)]^2 + [H_I(f)]^2}{[H_R(f)]^2 + [H_I(f)]^2} \right\} \]

\[ \Phi(f) = \tan^{-1}\left[\frac{H_I(f)}{H_R(f)}\right] \]

The squared coherence function MSC(f) was estimated as:

\[ MSC(f) = \left[ \frac{S_{xy}(f)}{S_{xx}(f)} \right]^2 \]

where \( S_{xy}(f) \) is the autospectrum of changes in MCAv.

The squared coherence function reflects the fraction of output power that can be linearly related to the input power at each frequency. Mean value of transfer function gain, phase, and coherence function were calculated in the very-low-frequency (VLF; 0.02–0.07 Hz), low-frequency (LF; 0.07–0.20 Hz), and high-frequency (HF; 0.20–0.30 Hz) ranges to reflect different patterns of the dynamic pressure-flow relationship (54). We used the LF range of each variable for the spectral analysis to identify dynamic cardiovascular and CBF regulation because BP fluctuations in the LF (0.07–0.20 Hz) range are independent of the respiratory frequency and dampened by autoregulatory mechanisms (13). Thus we used the LF spectral power of the mean value of transfer gain, phase, and coherence function to identify dynamic cerebral autoregulation during both supine and standing conditions.

**HR variability and baroreflex sensitivity.** Power spectral analysis of the beat-to-beat variability of HR was obtained by the autoregressive method. Specific characteristics of the power spectrum of HR variability (HRV) were used as an index of sympathetic and parasympathetic control of the cardiovascular system (47a). Two frequency bands were considered: LF (0.05–0.15 Hz) and HF (0.15–0.30 Hz). Power of the R-wave to R-wave interval (RRi) spectra (LF-RRI and HF-RRI, respectively) were calculated from the integration of the autoregula. Spectral analysis of HRV quantifies the dynamic, frequency-dependent changes in HR, which reflect autonomic modulation of sinus node activity (2, 33). HF power of RRI variability appears to be modulated predominantly by respiration-induced changes in vagal activity, whereas LF power of RRI variability is modulated by both vagal and sympathetic activity (2, 33, 47a). HF and LF values at each specific frequency range were also normalized by dividing by the total spectral power (33) to minimize the effect of the changes in total power on the LF and HF components. This data acquisition and processing strategy conforms to consensus panel recommendations for the assessment of cardiovascular variability (47a). While supine, subjects were asked to control their respiratory frequency (controlled breathing) at a fixed rate of 12 breaths/min (0.2 Hz). After a 2-min adjustment period, 3 min of steady-state data were recorded for this controlled respiration data collection period. Following this period, subjects were instructed to breathe normally (normal
breathing) and, after a 2-min adjustment period, 3 min of uncontrolled respiration data were collected and used for analysis. Steady-state data from both the normal and controlled respiration protocol were used for spectral HRV and baroreflex sensitivity (BRS) analysis.

Time-domain analysis of spontaneous BRS data were obtained from the Finometer BP waveform using the cross-correlation method PRV X BRS (52). The systolic BP (SBP) and interbeat interval (IBI) time series were interpolated and resampled at 1 Hz. In 10-s windows, the correlation and regression slopes between SBP and IBI were computed. Delays of 0- to 5-s increments in IBI were computed, and the delay with the highest positive coefficient of correlation was selected; the optimal delay (tau) was stored. The slope between SBP and IBI was recorded as a BRS estimate if the correlation was significant at \( P = 0.01 \). In addition to the 3 min of steady-state data collection during controlled and normal breathing, HRV and BRS data were also averaged over the final 3 min of upright standing.

**Statistical Analysis**

Because there were no statistical differences between men and women, data were combined for statistical analysis. To calculate the absolute and percent (\%) change from baseline and to limit any natural diurnal variability in the autonomic responses, data were averaged over the 3-min period of baseline immediately preceding any postural change and over the final 3 min of orthostasis. Data were also averaged in 30-s blocks over the 6-min stand. Data from the two premarathon tests were averaged to obtain one premarathon value. Effect size estimates for the major hemodynamic dependent variables were derived from these between-day tests. On the basis of a one-way ANOVA model, a study sample of six was adequate to detect meaningful physiological changes in the main hemodynamic variables, defined as any value outside the 68% limits of agreement (± 1 SD) for between-day repeated differences without intervention. All data were analyzed using the SPSS statistics software. A Shapiro-Wilk test was applied to each dependent variable to assess distribution normality. A three-factor ANOVA (condition, state, and time) were used to test significance between and within conditions for each dependent variable. Following a significant F-test, differences were identified using Tukey’s honestly significant difference (HSD) post hoc procedure. Significance for all two-tailed tests was established at an \( \alpha \) level of \( P < 0.05 \), and data are expressed as means ± SD.

**RESULTS**

**Subjects**

Postmarathon data from two participants were not obtained, and therefore all data analysis was performed on seven of nine subjects. The average time to complete the off-road marathon was 261 ± 27 min [range 203–290 min]. The weather was stable (+15°C; sunny and light winds) throughout the event, and self-reported fluid intake during the run was 0.9 liters. There was a small reduction in body mass following the marathon.

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transfer gain or phase during supine or standing, indicating that dynamic cerebral autoregulation was unaltered following the marathon (Fig. 3). Likewise, cerebrovascular conductance, an index of static autoregulation, was not changed at either point following the marathon.

Following the marathon, there was a reduced change in BRS, normalized LF, and normalized HF on standing when compared with premarathon and 48 h postmarathon (P < 0.05; Fig. 4). These changes in LF and HF were reflected in an elevated LF/HF ratio (Fig. 4). Following the marathon, there was a reduced change in MCAv, compared with premarathon and 48 h postmarathon (P < 0.05). These changes in LF and HF were related to the steady-state reduction in MCAv (r = 0.81; P < 0.05), whereas no relationship was present between these variables during the premarathon or 48 h postmarathon.

**DISCUSSION**

This is the first study to provide a comprehensive examination of the potential integrative mechanisms responsible for a lowered orthostatic tolerance following an exhaustive bout of prolonged exercise. The major novel findings of this study were that following prolonged exercise (a mountain marathon), hypotension and postural reductions in autonomic function and/or baroreflex control, rather than a compromise in cerebral autoregulation, may place the brain at greater risk of hypoperfusion. Such changes may be critical events underlying collapse following prolonged exhaustive exercise events.

**Hemodynamic Alterations While Supine**

Despite increased sympathetic and reduced parasympathetic control (assessed from the HRV analysis), and elevations in HR and Q, hypotension was evident following the marathon during supine rest. Consistent with reports from animal studies that have demonstrated that resetting of the arterial baroreflex mediates the postexercise reductions in arterial blood pressure (9) and that BRS was also lowered. Previous work has shown that, even at rest, vagal blockade results in a decrease in BRS operating point (31). Since the elevated HR (and hypotension) following the marathon would have resulted from vagal withdrawal, it seems plausible that the cardiac-baroreflex function curve may move to a threshold from the centering point, potentially underlying the observed decrease in baroreflex sensitivity following the marathon. Another possibility is that

### Table 1. Steady-state cardiovascular and cerebrovascular measures during supine and standing

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Stand</th>
<th>Supine</th>
<th>Stand</th>
<th>48 h Postmarathon</th>
<th>Stand</th>
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<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
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<tr>
<td>HR, beats/min</td>
<td>57 ± 11</td>
<td>69 ± 12‡</td>
<td>77 ± 6*‡</td>
<td>98 ± 12*‡</td>
<td>58 ± 11</td>
<td>70 ± 12‡</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>80 ± 9</td>
<td>75 ± 14</td>
<td>74 ± 5*‡</td>
<td>64 ± 10*‡</td>
<td>80 ± 26</td>
<td>73 ± 7</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>116 ± 13</td>
<td>107 ± 19</td>
<td>104 ± 8*‡</td>
<td>89 ± 18*‡</td>
<td>115 ± 58</td>
<td>106 ± 10‡</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>63 ± 7</td>
<td>59 ± 12</td>
<td>58 ± 7</td>
<td>51 ± 7*‡</td>
<td>62 ± 7</td>
<td>58 ± 6</td>
</tr>
<tr>
<td>SV, ml</td>
<td>104 ± 17</td>
<td>80 ± 20‡</td>
<td>87 ± 26</td>
<td>65 ± 23*‡</td>
<td>102 ± 15</td>
<td>86 ± 15‡</td>
</tr>
<tr>
<td>Q, l/min</td>
<td>5.9 ± 1.4</td>
<td>5.4 ± 1.4</td>
<td>6.6 ± 2.0*‡</td>
<td>6.2 ± 2.0*‡</td>
<td>5.8 ± 1.2</td>
<td>6.0 ± 1.3*‡</td>
</tr>
<tr>
<td>TPR, mmHg·1⁻¹·min</td>
<td>14.2 ± 2.9</td>
<td>14.3 ± 3.3</td>
<td>12.0 ± 3.5*‡</td>
<td>10.9 ± 2.5*‡</td>
<td>14.1 ± 2.8</td>
<td>12.8 ± 2.7‡</td>
</tr>
<tr>
<td><strong>Cerebrovascular</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MCAv, cm/s</td>
<td>64.0 ± 10.8</td>
<td>57.2 ± 10.2‡</td>
<td>63.1 ± 12.5</td>
<td>53.5 ± 12.7*‡</td>
<td>66.8 ± 15.6</td>
<td>60.5 ± 10.6‡</td>
</tr>
<tr>
<td>SMCAv, cm/s</td>
<td>104.1 ± 18.9</td>
<td>92.3 ± 15.9‡</td>
<td>100.0 ± 16.8</td>
<td>87.2 ± 20.8*‡</td>
<td>104.8 ± 27.7</td>
<td>97.4 ± 20.8‡</td>
</tr>
<tr>
<td>DMCAv, cm/s</td>
<td>43.9 ± 7.5</td>
<td>39.6 ± 8.3‡</td>
<td>44.7 ± 11.0</td>
<td>36.7 ± 9.8‡</td>
<td>46.0 ± 10.3</td>
<td>42.0 ± 6.7‡</td>
</tr>
<tr>
<td>CVR, mmHg·cm⁻¹·s</td>
<td>1.27 ± 0.17</td>
<td>1.32 ± 0.28‡</td>
<td>1.21 ± 0.28</td>
<td>1.24 ± 0.28‡</td>
<td>1.25 ± 0.30</td>
<td>1.25 ± 0.23</td>
</tr>
<tr>
<td>CVC, cm·s⁻¹·mmHg⁻¹</td>
<td>0.80 ± 0.15</td>
<td>0.76 ± 0.19</td>
<td>0.85 ± 0.20</td>
<td>0.84 ± 0.17</td>
<td>0.84 ± 0.11</td>
<td>0.83 ± 0.13</td>
</tr>
</tbody>
</table>

Values are means ± SD based on 7 subjects. Supine data were averaged over the 3 min immediately before the stand. Standing data were averaged over the last 3 min of a 6-min stand. HR, heart rate; MAP, mean arterial blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; SV, stroke volume; Q, cardiac output; TPR, total peripheral resistance; MCAv, middle cerebral artery blood flow velocity; SMCAv, systolic MCAv; DMCAv, diastolic MCAv; CVR, cerebrovascular resistance; CVC, cerebrovascular conductance. *Different from premarathon (P < 0.05); †different from respective supine (P < 0.05); ‡different compared with 48 h postmarathon (P < 0.05); §different compared with premarathon (P < 0.05).

### Table 2. Steady-state HRV and BRS measures during controlled breathing and normal breathing while supine and while standing (normal breathing)

<table>
<thead>
<tr>
<th></th>
<th>Controlled Breathing</th>
<th>Normal Breathing</th>
<th>Stand</th>
<th>Controlled Breathing</th>
<th>Normal Breathing</th>
<th>Stand</th>
<th>Controlled Breathing</th>
<th>Normal Breathing</th>
<th>Stand</th>
<th>Controlled Breathing</th>
<th>Normal Breathing</th>
<th>Stand</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LF, ms⁻²</strong></td>
<td>472 ± 130‡</td>
<td>645 ± 43†</td>
<td>1.128 ± 511</td>
<td>460 ± 474</td>
<td>483 ± 338</td>
<td>668 ± 824*</td>
<td>722 ± 550</td>
<td>978 ± 515</td>
<td>742 ± 402</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LF, nu</strong></td>
<td>39 ± 15‡</td>
<td>48 ± 21‡</td>
<td>77 ± 13</td>
<td>72 ± 12*‡</td>
<td>82 ± 9*‡</td>
<td>92 ± 3*‡</td>
<td>45 ± 24‡</td>
<td>58 ± 17‡</td>
<td>73 ± 15</td>
<td></td>
<td></td>
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<tr>
<td><strong>HF, ms⁻²</strong></td>
<td>934 ± 787‡</td>
<td>747 ± 594‡</td>
<td>341 ± 222</td>
<td>215 ± 324*‡</td>
<td>95 ± 99*‡</td>
<td>50 ± 64*‡</td>
<td>800 ± 515‡</td>
<td>734 ± 597‡</td>
<td>233 ± 173</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>HF, nu</strong></td>
<td>58 ± 15‡</td>
<td>45 ± 22‡</td>
<td>23 ± 12</td>
<td>25 ± 12*‡</td>
<td>15 ± 9*‡</td>
<td>6 ± 2*‡</td>
<td>53 ± 23‡</td>
<td>38 ± 16</td>
<td>23 ± 13</td>
<td></td>
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<tr>
<td><strong>LF/HF</strong></td>
<td>0.96 ± 0.99‡</td>
<td>1.98 ± 2.19‡</td>
<td>5.86 ± 3.80</td>
<td>3.52 ± 1.87*‡</td>
<td>8.01 ± 5.02*‡</td>
<td>18.13 ± 7.35*‡</td>
<td>1.24 ± 1.07‡</td>
<td>2.25 ± 1.21‡</td>
<td>4.56 ± 3.11</td>
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<tr>
<td><strong>BRS, ms/mmHg</strong></td>
<td>14.3 ± 5.7‡</td>
<td>14.9 ± 5.4‡</td>
<td>3.2 ± 1.7</td>
<td>7.1 ± 5.4*‡</td>
<td>6.2 ± 3.9*‡</td>
<td>3.4 ± 2.1‡</td>
<td>14.9 ±7.3*</td>
<td>13.3 ± 6.0*</td>
<td>7.9 ± 3.9</td>
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</tbody>
</table>

Values are means ± SD based on 7 subjects. Controlled breathing at a rate of 12 breaths/min. LF (ms⁻²), low frequency; LF (nu), low-frequency normalized units; HF (ms⁻²), high frequency; HF (nu), high-frequency normalized units; LF/HF, low-frequency/high-frequency ratio; HRV, heart rate variability; BRS, baroreflex sensitivity. *Different from premarathon (P < 0.05); †different from 48 h postmarathon (P < 0.05); ‡different from stand (P < 0.05).
central command is reduced following the marathon, and thus the baroreflex function curve may move toward baseline (29). Further research in this area, combining assessment of full cardiac and vasomotor baroreflex, is needed to examine these possibilities.

Hemodynamic Alterations on Postural Challenge

The initial circulatory responses induced by standing are consistent with earlier observations of an immediate rise in Q (~25% above control) followed by a decrease during steady-state stand (~25% below control) (21, 45). The trend for a decrease in stroke volume (~21 ± 7% (premarathon; P = 0.06); ~27 ± 10% (postmarathon; P = 0.05); ~13 ± 20% (48 h postmarathon; P = 0.09]) indicates that these initial changes in Q are determined prominently by elevations in HR. Another possibility is that the lowered SV and transient loss of Q responses postexercise could be related to changes in central venous pressure or volume. In otherwise healthy humans, SV and Q are mainly determined by venous return, whereas the arterial response is mainly manifest as TPR. During an orthostatic challenge, in patients with vasovagal syncope, some studies indicate that the fall in BP could be related to an impairment of venous return due to inadequate venoconstrictive response (20, 26, 48), whereas other studies indicate that the fall in BP could be secondary to inadequate arterial vasocostriction during orthostatic or physical stress (43, 49). It is also possible that the potential reductions in SV might be related not only to reduced venous return but also to a reduction in myocardial contractility. Impairments in left ventricular function have been observed following Ironman triathlons and a multiday adventure race (3, 14, 17); however, evidence of impairment following marathon distance events is conflicting (28, 38, 51). In the present study, it would seem unlikely that alterations in left ventricular function may account for the different initial responses of Q to orthostatic stress postmarathon since Q is submaximal during recovery and any impair-

Fig. 1. Representative recordings from one subject before the marathon (premarathon; left) and 90 min following the marathon (postmarathon; right) 1 min before and during the first 2 min of standing. Hypotension and lowered middle cerebral artery blood flow velocity (MCAv) on standing is clearly evident immediately (~90 min) following the marathon. The typical transient elevation in cardiac output (Q) is apparent on the first 15-20 s of standing followed by a sustained decrease from supine values. Such a transient elevation in Q following the marathon is abolished. There is also a notable reduction in stroke volume (SV), which was apparent in 6 of 7 participants (supine; 104 ± 17 (premarathon) vs. 87 ± 26 ml (postmarathon); P = 0.06; stand; 80 ± 20 (premarathon) vs. 65 ± 23 ml (postmarathon) P = 0.07; see Table 1). HR, heart rate (beats/min); BP, blood pressure.

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In left ventricular function could be accommodated by an increase in HR. From the present data set, although we cannot differentiate the venous contribution from that of the arterial system, it seems conceivable that both systems may be affected by the marked reduction in sympathetic activation when moving to the upright posture (Fig. 4).

The mechanisms of syncope following exercise are currently unknown, but most probably involve a complex mixture of interrelated factors (i.e., endocrine, physical, interactions between preload and afterload, etc.) that can affect Q and ultimately cerebral perfusion. It has been shown that at rest and during exercise, alterations in Q can affect MCAv independently of cerebral autoregulation (30). Therefore, since dynamic and static cerebral autoregulation were well maintained following the prolonged exercise, the apparent initial attenuation in Q following prolonged exercise may lead to a compromise in cerebral perfusion. After this initial decrease on orthostasis, however, Q was maintained while standing postmarathon despite reductions in MCAv; therefore, downregulation of vasomotor baroreflex function (9) may explain, in part, the compromise in MCAv. Such changes are entirely consistent with the finding that the carotid baroreflex function ceases during vasovagal syncope (32, 39) and of an attenuated transduction of sympathetic activity into vascular resistance following dynamic exercise (19).

In addition to a decrease in BRS at rest, there was less of a decrease on postural change following the marathon. Previous reports have highlighted a lowered (11), unchanged (44), or enhanced BRS (10) following exercise. Differences in the intensity and duration of the exercise and the methodological assessment of BRS may explain the discrepancy between our findings with those of more acute exercise. It is important to recognize that, in the present study, using only BRS we have only one point of the baroreflex stimulus-response curve, and although maximal gain may not have changed, we cannot quantify this from the BRS measurements, which are an index of the operating point gain (31). Interestingly, recent evidence indicates that the arterial baroreflex regulation of BP via reflex control of the systemic vasculature becomes more involved in maintaining cerebral perfusion during exercise (31). Furthermore, in well-controlled animal studies, it has been shown that the removal of arterial baroreflex activity reduces cerebral vasodilation associated with breakthrough of autoregulation (47). Cerebrovascular conductance was calculated as an addi-

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Fig. 2. Absolute (left) and relative (right) postural changes in mean arterial blood pressure (MAP; A), MCAv (B), HR (C), Q (D), and total peripheral resistance (TPR; E). *Difference (P < 0.05), postmarathon compared with premarathon; †difference (P < 0.05), postmarathon compared with 48 h postmarathon. Values are means ± SD based on 7 subjects; each data point is an average of the preceding 30 s.
tional assessment of static autoregulation and, importantly, as
a means to minimize the effects of BP on the cerebrovascular
responses to the postural change. This calculated conductance
was unchanged across all conditions, indicating that the pr-
esyncopal related symptoms and reduction in MCAv were not
mediated by a reduction in BP per se. In the present study, the
correlation between the smaller reduction in BRS on standing
after the marathon with the steady-state reduction in MCAv
indicates a physiological significant role of the involvement of
arterial baroreflex in the regulation of cerebral perfusion during
postural change.

Hypohydration

Recent research suggests that hypohydration incurred during
exercise may compromise orthostatic tolerance (7). Following
heat stress-induced hypohydration, MCAv was attenuated on
standing when compared with euhydration (7). There were no
significant differences in hydration status of participants post-
marathon (when compared with premarathon), suggesting that

the reduction in MCAv and orthostatic tolerance observed
postmarathon was not due to this mechanism. The drop in body
mass was by an extent that would be expected because of
depletion of fat and glycogen and its associated bound intra-
cellular water (1). Although plasma volume change, body mass
change, and urine specific gravity were used as indexes of
hydration, it is recognized that direct measurement of hydra-
tion is difficult and that caution should be used in the use of
urine specific gravity in the manner used here. Furthermore, it
is important to note that although hydration measures were
unchanged, this does not necessarily indicate that there were no
body fluid changes, as compartment shifts or alterations in
central venous pressure or blood volume may have ensued,
especially during the postural challenge. Even so, it seems

Fig. 3. Group-averaged LF (0.07–0.02 Hz) transfer function phase (A), gain
(B), and coherence (C) between MAP and MCAv during supine (left) and
steady-state stand (right) before the marathon, following the marathon, and
48 h following the marathon. Values are means ± SD based on 7 subjects.
There were no differences at any time point.

Fig. 4. Postural changes (supine minus stand) in steady-state HR variability
(B–D) and baroreflex sensitivity (BRS; A) before the marathon (Pre), following
the marathon (Post), and 48 h following the marathon (48 h Post). LF (nu),
low-frequency normalized units; HF (nu), high-frequency normalized units;
LF/HF, low-frequency/high-frequency ratio. *Different from premarathon
(P < 0.05); †different from 48 h postmarathon (P < 0.05). Values are means ± SD
based on 7 subjects.
unlikely that a lack of blood volume per se could account for the observed hemodynamic responses.

**Time Course of Recovery**

Alterations in both hemodynamic and autonomic variables observed within 4 h of completing the marathon had returned to baseline levels by 48 h following the marathon. Bernardi et al. (5) found persistent alterations in sympathovagal balance 24 h following a 46-km run. Likewise, Hautala et al. (23) observed greater sympathetic predominance 24 h after a 75-km cross-country skiing race (average race time: 4 h, 30 min), which had returned to prerace levels 48 h following. Our data are consistent with these previous findings and the related time course of recovery.

Methodological considerations of our study should be noted. First, we were unable to measure end-tidal CO₂. Although end-tidal CO₂ is known to decline when subjects assume an upright posture and has been reported to account for ~50% of the reduction in mean CBF (25), previous studies indicate that end-tidal CO₂ at syncope does not contribute substantially to the decline in CBF (40, 42). Second, the practical value of BRS from spontaneous BP and HR variability analysis as an insight into autonomic function has been the issue of recent discussions in the literature (27, 34, 35). These reports indicate that the use of the variability methods, valid from a theoretical point of view, requires more clinical application for validation. In relation to the present methodological techniques, however, it has been reported that spontaneous and pharmacologically determined BRS are complementary (36) and that the BRS methods may contribute to examination of the baroreflex circulatory control in greater detail (53). Third, similar to other related studies (12, 17), we chose to use the stand test because of its practical and physiological generalizability to the realistic problems that occur following prolonged exercise (i.e., the inability to maintain an upright posture). Although it is unclear how the integrated hemodynamic changes during postural change may translate to those induced during a more severe orthostatic stress test (e.g., lower body negative pressure; tilt), both active standing and passive head-up tilt have been reported to provoke comparable changes in spontaneous baroreflex and related hemodynamic variables (4). It is unknown if this relationship may change following prolonged exercise. Furthermore, while we ensured that there were no major muscle contractions at rest or during the stand, it is acknowledged that some leg muscles are required to maintain posture and that it is not possible to remove this action during a stand. Finally, we used Doppler ultrasound to measure flow velocity, rather than blood flow, in the MCA. Nevertheless, research indicates that MCAv is a reliable index of CBF (16, 41). The use of CVR index as a measure of cerebrovascular resistance has been discussed and used extensively (15, 31, 42). True cerebrovascular resistance depends on the pressure gradient across the vascular bed and its related flow. This pressure gradient was unknown as venous and intracranial pressure could not be measured in our healthy subjects. However, our subjects remained relatively motionless during supine rest and upright stand, where the venous influences on resistance and flow should be fairly constant.

In conclusion, findings from the present study indicate that following prolonged exercise, hypotension and postural reductions in autonomic function and/or baroreflex control, rather than a compromise in cerebral autoregulation, may place the brain at greater risk of hypoperfusion. Such changes may be critical factors in collapse following prolonged exercise.


