Dynamic cerebral autoregulation during and after handgrip exercise in humans

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Dynamic cerebral autoregulation during and after handgrip exercise in humans. J Appl Physiol 108: 1701–1705, 2010.—The purpose of the present study was to examine the effect of static exercise on dynamic cerebral autoregulation (CA). In nine healthy subjects at rest before, during, and after static handgrip exercise at 30% maximum voluntary contraction, the response to an acute drop in mean arterial blood pressure and middle cerebral artery mean blood velocity was examined. Acute hypotension was induced nonpharmacologically via rapid release of bilateral thigh occlusion cuffs. Subjects were instructed to avoid executing a Valsalva maneuver during handgrip. To quantify dynamic CA, the rate of regulation (RoR) was calculated from the change in cerebral vascular conductance index during the transient fall in blood pressure. There was no significant difference in RoR between rest (mean ± SE, 0.278 ± 0.052/s), exercise (0.333 ± 0.053/s), and recovery (0.305 ± 0.059/s) conditions (P = 0.747). In addition, there was no significant difference in the rate of absolute cerebral vasodilatory response to acute hypotension between three conditions (P = 0.737). This finding indicates that static exercise and related elevations in blood pressure do not alter dynamic CA.

METHODS

Subjects

Nine healthy individuals [5 men and 4 women; age 22 ± 3 yr, weight 59 ± 6 kg, and height 166 ± 6 cm (means ± SD)] volunteered for this study, which was approved by the Ethics Committee of the Japan Women’s College of Physical Education (no. 2009-3) and conformed to the standards set by the Declaration of Helsinki. All subjects were free of any known cardiovascular or respiratory diseases and were not taking any medications. Each subject received a verbal and written explanation of the study objectives, measurement techniques, and risks and benefits associated with the investigation. Before the actual experimental day, each subject was familiarized with the equipment and the study protocol. The subjects were requested to abstain from caffeinated beverages for 12 h and strenuous physical activity and alcohol intake for at least 24 h before testing.

Measurements

A standard three-lead electrocardiogram was used for heart rate monitoring. Middle cerebral artery blood velocity (MCA V) was measured by TCD ultrasonography (WAKI, Atys Medical, St Genislaual, France). The MCA V was monitored on the same side as the exercising hand to avoid metabolic influence associated with this form of exercise (14). A 2-MHz Doppler probe was placed over the temporal windows and fixed with an adjustable headband and adhesive ultrasonic gel. Beat-to-beat ABP was monitored with finger photoplethysmography (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands). Subjects breathed through a leak-free respiratory mask (4342S, Bird, Chiba, Japan) attached to a one-way non-rebreathing valve. End-tidal Pco2 (Petco2) was sampled from a non-rebreathing valve and measured by a gas analyzer (AE300S, Minato Ikagaku, Tokyo, Japan). All data were acquired continuously at 200 Hz using an analog-to-digital converter (Powerlab/16SP ML795; ADInstruments) interfaced with a computer and were subsequently analyzed using commercially available software (Chart version 5.5.5, ADInstruments).
Experimental Protocols

MVC test. After arrival at the laboratory, each subject performed three maximal static handgrip contractions of the dominant arm, during which time MVC was determined. After the MVC trials, the subjects rested for at least 30 min before commencement of the protocol.

Deflating thigh occlusion cuffs protocol. After they were instrumented, subjects were seated in a semi-recumbent position (~45°) in a reclining seat and rested quietly for ~10 min. This protocol started with a baseline period (1 min), followed by inflation of thigh cuffs (>220 mmHg) for 3 min, and then thigh cuffs were deflated. This protocol was performed twice at each condition (resting control, exercise, and recovery; 3 × 2, total of 6 trials) to assess the CBF response to a rapid and transient drop in ABP to identify dynamic CA (Fig. 1). An average value of two trials at each condition was used as an individual data. All trials were randomized and separated by a minimum of 30 min. Throughout the experimental protocol at each condition, subjects were instructed to adjust their respiratory rate according to the sound of a metronome (15 breaths/min).

Each protocol consisted of 1 min of resting baseline measures, followed by 3 min of cuff inflation and subsequent thigh-cuff release under each respective condition (either rest, handgrip, or post-handgrip) and 1 min of post-thigh-cuff release measures.

Resting control condition. Subjects rested throughout the protocol.

Exercise condition. At 1.5 min after cuff inflation, subjects initiated handgrip exercise at 30% of MVC and continued to grip until 30 s after cuff deflation.

Recovery condition. Subject began the handgrip exercise at the same time that cuffs were inflated. The exercise was carried out for 2 min, followed by 1 min of rest before cuff deflation. To avoid the acute phase of physiological response to termination of static exercise, dynamic CA was identified at 1 min after the exercise termination.

Data Analysis

Beat-to-beat mean arterial pressure (MAP) and MCA Vmean were obtained from each waveform. The cerebrovascular conductance index (CVCi) was calculated by dividing MCA Vmean by MAP and was used as an estimate of changes in cerebrovascular conductance. The derived CVCi during acute hypotension is not directly related to state-dependent cerebrovascular conductance because changes in the vascular compliance and resistance affect CBF during dynamic regulation.

Cardiovascular responses to thigh-cuff release. The responses of MAP and MCA Vmean to acute hypotension immediately following cuff release were identified. Control values of MAP and MCA Vmean were defined by calculating their averages during the 4 s immediately before thigh-cuff release. The MAP and MCA Vmean responses were calculated by subtracting the control value from nadir value at the time of 1–3.5 s from cuff release.

Dynamic CA. Control values of MAP, MCA Vmean, and CVCi were defined by calculating their means during the 4 s immediately before thigh-cuff release. Changes in MAP, MCA Vmean, and CVCi during cuff release were determined relative to their concomitant control values. At the time of 1.0–3.5 s from cuff release, the rate of change in CVCi is directly related to dynamic CA (1). The rate of regulation (RoR) is calculated as an index of dynamic CA:

$$RoR = (\Delta CVCi/\Delta T)/\Delta relative MAP$$

where \(\Delta CVCi/\Delta T\) is the slope of the linear regression between relative CVCi and time (T), and \(\Delta relative MAP\), the magnitude of the step, was calculated by subtracting control relative MAP from averaged relative MAP during the interval from 1.0 to 3.5 s (1).

In addition, the rate of absolute cerebral vasodilatory response (absolute RoR) was calculated by absolute changes in MAP, MCA Vmean, and CVCi during cuff release to identify the effect of static exercise-induced high MAP on dynamic CA:

$$Absolute RoR = (\Delta CVCi/\Delta T)/\Delta MAP$$

$$\Delta MAP$$ where \(\Delta CVCi/\Delta T\) is the slope of the linear regression between CVCi and time (T), and \(\Delta MAP\), the magnitude of the step, was calculated by subtracting control MAP from averaged MAP during the interval from 1.0 to 3.5 s (1).

Statistics

Statistical comparison of physiological variables and RoR were made utilizing a repeated-measures, one-way ANOVA. A Student-Newman-Keuls test was employed post hoc when interactions were significant. Statistical significance was set at P < 0.05, and results are presented as means ± SE. Analyses were conducted using SigmaStat (Jandel Scientific Software, SPSS, Chicago, IL).

RESULTS

The release of the thigh cuffs elicited an acute decrease in ABP at all conditions (Figs. 2 and 3). Changes in MAP were -27 ± 2 (-26 ± 1%), -27 ± 2 (-23 ± 1%), and -26 ± 2 (-24 ± 2%) mmHg from prestimulation values at rest, and during and after handgrip exercise, respectively. There was no significant difference in the thigh-cuff release-induced absolute (P = 0.794) or percent (P = 0.277) changes in MAP between conditions. As intended, these decreases in ABP were sufficient to evoke a transient decrease in MCA Vmean and marked cerebral autoregulatory response (1). A reflection of dynamic CA, changes in MCA Vmean were attenuated (-20 ± 2, -15 ± 1, and -18 ± 2% from prestimulation values at rest, and during and after handgrip exercise, respectively) relative to MAP.

The RoR, as an index of dynamic CA, was calculated from the change in CVCi from 1 to 3.5 s after cuff release for each subject (Fig. 2). There was no significant difference in RoR between rest (0.278 ± 0.052/s), exercise (0.333 ± 0.053/s), and recovery (0.305 ± 0.059/s) conditions (P = 0.747; Fig. 4). In addition, there was no significant difference in absolute RoR between the three conditions (0.141 ± 0.028, 0.168 ± 0.024, 0.166 ± 0.036 cm-mmHg-1·s-2 at rest, and during and after exercise, respectively; P = 0.737). There was also no signifi-
DISCUSSION

The aim of this study was to examine the hypothesis that static exercise alters dynamic CBF regulation to transient acute hypotension. In contrast, despite exercise-induced increases in MAP and MCA $V_{\text{mean}}$, the RoR to a transient fall in ABP was not different between resting conditions, exercise or post-static exercise. These data indicate that dynamic CA remains intact during and after static exercise at 30% MVC.

The maintenance of cerebral perfusion via dynamic CA is critical to avoid cerebral ischemia or hemorrhage (7, 15, 16, 31). Intense resistance exercise, in particular static exercise, may lead to risk of syncope (6) or cerebral bleeding (9); however, the physiological mechanisms responsible are not clear but presumably reside within the brain. Dynamic CA is an obvious candidate since it is integrally involved in CBF maintenance (17, 18), and its impairment could not maintain an adequate cerebral perfusion pressure. For example, impaired dynamic CA likely contributes to the reduced orthostatic tolerance after bed rest (35). Moreover, impairment of CA predisposes the brain to secondary damage in patients with subarachnoid hemorrhage or ischemic stroke (7).

Previous studies (28) demonstrated that MCA $V_{\text{mean}}$ increased during static handgrip exercise at 30% MVC. The increased MCA $V_{\text{mean}}$ was likely caused by changes in perfu-
sion pressure during handgrip exercise. These findings suggest that dynamic CA is attenuated during mild static exercise. Nevertheless, the results of the present study were inconsistent with our hypothesis. There was no significant difference in RoR between rest, exercise, and recovery conditions (P = 0.747; Fig. 4), suggesting that dynamic CA remains intact during and following static exercise. In addition, absolute RoR was unchanged by static exercise (P = 0.737), indicating that static exercise-induced high MAP does not modify dynamic CA. Dynamic CA prevents further changes in MCA Vmean during transient hyper- and hypotension (21). In the present study, there was no significant difference in this response of MCA Vmean between rest, exercise, and recovery (Figs. 2 and 3). These findings strongly suggest that static exercise does not alter the vasodilatory ability of cerebral resistance vessels to restore CBF against a rapid hypotension.

The autonomic neural control of cerebral circulation is an important component of dynamic CA (21, 34). Removal of autonomic neural activity by ganglion blockade decreased phase shift and increased transfer function gain between MCA Vmean and MAP oscillations, indicating that a lack of autonomic neural activity impairs dynamic CA (34). Also, Ogoh et al. (21) reported an impaired dynamic CA with an oral dose of the alpha-1 adrenergic receptor antagonist Prazosin. If the relationship between dynamic CA and sympathetic nerve activity is linear, then the above studies suggest that increased sympathetic nerve activity might augment dynamic CA; however, in the present study, static handgrip exercise did not affect dynamic CA, evidencing a non-linear relationship between dynamic CA and sympathetic nerve activity. In addition, respiration strongly interacts with dynamic CBF regulation (2, 5, 19, 24, 25, 32, 33). Under a background of hypocapnia, dynamic CA is enhanced (1); thus it would seem reasonable to expect that high-intensity exercise may augment dynamic CA because of hyperventilation-induced hypocapnia. Interestingly, this is not the case. Ogoh et al. (22) found that dynamic CA was reduced during exhaustive exercise despite hypocapnia. This suggests the possibility that the effect of CO2 on dynamic CBF regulation was modified by intense physical effort of exhaustive exercise. However, in the present study, a subject’s respiration was controlled, and there was no significant difference in PETCO2 between rest, exercise, and recovery conditions (Table 1), minimizing any effect of respiration (i.e., Valsalva maneuver) or PETCO2.

The findings of the present study also indicate that static exercise-induced increase in MCA Vmean is not a result of impaired dynamic CA. Similarly, previous studies demonstrated that cerebral perfusion during dynamic exercise is independent of ABP (10, 12, 22, 26). For example, during postexercise muscle ischemia, increased MCA Vmean returns to resting values despite a sustained increase in ABP (12, 26). Other studies reported that CBF decreases toward baseline values during heavy exercise intensity despite further increases in ABP (10, 22). Therefore, dynamic CBF regulation may be altered by other physiological changes induced by physical effort (e.g., central command, cardiac output, etc.). An increase in cardiac output augments CBF velocity at rest and during exercise (17, 18, 20). Indeed, although cardiac output was not measured in the present study, cardiac output was increased to ∼40% by 2 min of static elbow-flexion exercise at 30% MVC (28). In addition, previous reports (14, 28) suggest that the influence of central command (cerebral neural activity) contributes to CBF regulation during static exercise. However, further studies are needed to explore these relations in more detail.

### Technological Considerations

The TCD-determined blood flow velocity in the large basal cerebral arteries [i.e., middle cerebral artery (MCA)] is widely used as an index of CBF and can identify a transient change in CBF. A potential limitation of estimating CBF using TCD ultrasonography is that changes in the diameter of the isolated vessels could modulate CBF independently of flow. However, the MCA diameter appears to remain relatively constant in humans during moderate variations in blood pressure and CO2 and also during orthostatic stress (8, 26, 29, 30). In addition, the changes in MCA Vmean during submaximal dynamic exercise appear to be similar to the changes in global CBF determined by other exercise valid techniques [e.g., internal carotid artery blood flow (10) and 133Xe clearance technique (11, 12)]. Despite some limitations compared with other CBF measurement methods, TCD ultrasonography remains a simple and easily taken technique that can be repeated over time. Furthermore, it is non-invasive, does not require sedation, and can be performed during any condition, including sleep. Thus, TCD ultrasonography could be a useful tool for monitoring CBF during dynamic exercise

### Table 1. Hemodynamic values at rest and during and immediately after a static handgrip exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
<th>Recovery</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>99 ± 4</td>
<td>115 ± 5*</td>
<td>109 ± 4*</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>73 ± 4</td>
<td>88 ± 5*</td>
<td>78 ± 5*</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>MCA Vmean, cm/s⁻¹</td>
<td>51 ± 4</td>
<td>60 ± 4*</td>
<td>58 ± 4*</td>
<td>P = 0.006</td>
</tr>
<tr>
<td>CVCl, (cm·s⁻¹·mmHg⁻¹)</td>
<td>0.514 ± 0.027</td>
<td>0.526 ± 0.032</td>
<td>0.533 ± 0.028</td>
<td>P = 0.610</td>
</tr>
<tr>
<td>PETCO₂, Torr</td>
<td>40 ± 2</td>
<td>39 ± 2</td>
<td>41 ± 1</td>
<td>P = 0.711</td>
</tr>
</tbody>
</table>

Value are means ± SE. MAP, mean arterial pressure; HR, heart rate; MCA Vmean, middle cerebral artery mean blood velocity; CVCl, cerebral vascular conductance index; PETCO₂, end-tidal partial pressure of carbon dioxide. *Significant difference from rest (P < 0.05). †Significant difference from exercise (P < 0.05).
ment techniques, the use of TCD has many benefits in the measurement of CBF during exercise. TCD possesses the temporal resolution and utility such that a non-invasive and beat-to-beat measurement of changes in MCA blood flow velocity during exercise can be quantified. When combined with beat-to-beat blood pressure TCD measure, MCA V can be used to quantify static and/or dynamic CA. Another potential limitation is that exercise involving large muscles, i.e., leg exercise, may alter dynamic CA. The cuff release technique can obviously not be used during leg exercise. In addition, another technique (i.e., transfer function analysis) could not be used to identify dynamic CA, because it is difficult during static exercise to keep steady-state cardiovascular hemodynamics for a couple of minutes. Thus it may be impossible to identify dynamic CA during exhaustive heavy static exercise, such as weight-lifting.

In summary, this study tested the hypothesis that static exercise alters dynamic CA. Counter to our initial hypothesis, such as weight-lifting.

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