Changes in regional cerebral blood flow distribution during postexercise hypotension in humans

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Williamson, J. W., R. McColl, and D. Mathews. Changes in regional cerebral blood flow distribution during postexercise hypotension in humans. J Appl Physiol 96: 719–724, 2004. First published October 10, 2003; 10.1152/japplphysiol.00911.2003.—This investigation compared patterns of regional cerebral blood flow (rCBF) during exercise recovery both with and without postexercise hypotension (PEH). Eight subjects were studied on 3 days with randomly assigned conditions: 1) after 30 min of rest; 2) after 30 min of moderate exercise (M-Ex) at 60–70% heart rate (HR) reserve during PEH; and 3) after 30 min of light exercise (L-Ex) at 20% HR reserve with no PEH. Data were collected for HR, mean blood pressure (MBP), and ratings of perceived exertion and relaxation, and rCBF was assessed by use of single-photon-emission computed tomography. With the use of ANOVA across conditions, there were differences (P < 0.05; mean ± SD) from rest during exercise recovery from M-Ex (HR = +12 ± 3 beats/min; MBP = −9 ± 2 mmHg), but not from L-Ex (HR = +2 ± 2 beats/min; MBP = −2 ± 2 mmHg). After M-Ex, there were decreases (P < 0.05) for the anterior cingulate (−6.7 ± 2%), right and left inferior thalami (−10 ± 3%), right inferior insula (−13 ± 3%), and left inferior anterior insula (−8 ± 3%), not observed after L-Ex. There were rCBF decreases for leg sensorimotor regions after both M-Ex (−15 ± 4%) and L-Ex (−12 ± 3%) and for the left superior anterior insula (−7 ± 3% and −6 ± 3%), respectively. Data show that there are rCBF reductions within specific regions of the insular cortex and anterior cingulate cortex coupled with a postexercise hypotensive response after M-Ex. Findings suggest that these cerebral cortical regions, previously implicated in cardiovascular regulation during exercise, may also be involved in PEH.

Brain mapping: single-photon-emission computed tomography; magnetic resonance imaging; autonomic nervous system

POSTEXERCISE HYPOTENSION (PEH) is a well-documented phenomenon that is largely dictated by both the duration and intensity of exercise (for review, see Ref. 9). The PEH response is important to understand as underlying mechanisms may be involved in the potential antihypertensive benefits of exercise. The PEH response is more pronounced in hypertensive individuals (11, 25) and spontaneously hypertensive rats (24). It is characterized by reductions in sympathetic nerve activity coupled with alterations in vascular vasoconstrictor responsiveness (10, 15). This results in a postexercise decrease in systemic vascular resistance that cannot be completely compensated for by increases in cardiac output (9, 10, 13). During PEH, there are alterations within the arterial baroreflex network such that it is reset to a lower operating point, which effectively reduces sympathetic outflow compared with preexercise levels (7, 10). The central neural mechanisms contributing to PEH appear to involve the modulation of barosensitive neurons within the brain stem involving the nucleus tractus solitarius (NTS) (4) and the rostral ventrolateral medulla (rVLM) (12). Neural activity in both the NTS and rVLM can be affected by descending signals from higher brain centers (3, 27). Regions of the higher brain with connectivity to midbrain regions of cardiovascular integration are involved in cardiovascular modulation during exercise (31, 32), and these same regions may play a role in the postexercise hypotensive response.

Human studies investigating the functional anatomy of central cardiovascular modulation, termed central command (for review, see Ref. 29), during exercise have identified a network of cortical structures including the insular cortex (5, 14, 19, 30–32) and anterior cingulate cortex (5, 14, 30–32) by examining changes in regional cerebral blood flow (rCBF). Changes in rCBF within the insular cortex and anterior cingulate cortex during exercise and during postexercise circulatory occlusion suggest that these structures participate in central command during exercise (30). Central command is further involved in a baroreflex resetting during exercise (6, 8, 20, 22), and the insular cortex has long been recognized for its role in modulation of autonomic function with neural connectivity to both the NTS and rVLM (3, 27). Cechetto and Saper (3) have used cobalt injection at the rVLM to block sympathetic responses evoked from stimulation of the posterior insular cortex. Taken together, these findings suggest that the central command-related changes within the insular cortex may be involved in the PEH response, yet this relationship has not been explored.

The purpose of this investigation was to determine whether there were significant rCBF alterations, suggestive of changes in neuronal activity, within the insular cortex during PEH. Prior studies of the insular cortex have shown that specific regions are activated by central command during exercise in an intensity-dependent manner (31). However, these same regions involved in central command were not responsive to blood pressure increases produced by postexercise circulatory occlusion (30). It was hypothesized that regions of the insular cortex previously implicated in central command would show rCBF reductions below preexercise (control) levels during PEH. The rCBF distributions were determined after light exercise (with no anticipated PEH) and moderate exercise (to elicit PEH) for several cerebral cortical regions by use of single-photon-emission computed tomography (SPECT) coregistered with mag-
nomic resonance images (MRI). Although this human study does not define the specific neural interactions between the insular cortex and brain stem nuclei, it does provide novel evidence concerning the potential involvement of higher brain centers in the PEH response, as well as the regulation of blood pressure.

**METHODS**

**Subjects.** Eight subjects volunteered to participate in this experiment. All participants provided written, informed consent before participating in this study, which was approved by the University of Texas Southwestern Medical Center Institutional Review Board and Radiation Safety Committee. The study group included four women and four men (aged 27 ± 4 yr). All study participants were healthy and normotensive (resting blood pressure <140/90 mmHg), and none reported any history of neurological or cardiovascular disease. None reported being on a regular exercise program, but all did perform some type of aerobic exercise (e.g., walking, stationary cycling) at least one day per week. All had abstained from exercise and caffeine for at least 12 h before testing, and none were taking any prescription medications at the time of the investigation. Each participant completed three tests, performed in a random order on separate days. They were familiarized with all procedures and measurements before any data collection. Poststudy examination of individual magnetic resonance images recorded from that specimen confirmed that all postexercise blood pressure values were within normal limits. All participants provided written, informed consent before study participation.

**Instrumentation.** After familiarization procedures were completed, a venipuncture was made and capped with an injectable site to assess the representative baseline blood pressure for comparison with postexercise blood pressure values. Eight subjects volunteered to participate in this experiment. After familiarization procedures were completed, a venipuncture was made and capped with an injectable site to assess the representative baseline blood pressure for comparison with postexercise blood pressure values. Each participant was unaware of the exact time of injection and reported no noticeable side effects. After minute 10 of postexercise recovery, with the tracer uptake completed and bound in brain tissue, subjects rested for an additional 20 min before SPECT was assessed. All subjects were taken to the SPECT camera room and scanning was completed within 50 min of injection for all subjects. Brain scanning procedures have been previously reported in detail (31).

**Image processing.** Each individual’s brain images were aligned in three dimensions by a computer using an automated volume-coregistration algorithm widely used for positron emission tomography coregistration (33). Once the SPECT scans for a given subject were coregistered, normalization of total radioactive count variability was obtained by rescaling each volume so that total counts were equal for all volumes. After SPECT-SPECT coregistration for each individual, SPECT-MRI coregistration was obtained by using an interactive coregistration algorithm (19) implemented on the workstation, after the SPECT voxel size was made to match the MRI voxel size. The absolute and percentage count differences for each pixel were obtained between scans. These differences were then displayed, for a selected slice within the volume, as a color overlay superimposed on the natural color images of the MRI.

Specific brain regions and structures were located by using the coregistered magnetic resonance scans as an anatomic reference. By using the computer, regions of interest (ROI) were drawn around these areas as seen on the MRI slice. This procedure was repeated on contiguous transaxial slices until the entire brain region or structure had been assessed across all slices. The number of 1.5-mm slices assessed varied by specific region and subject but was consistent across subjects.

On the basis of findings from prior human studies involving the insular cortex (5, 14, 23, 30) and the spatial resolution of the SPECT methodology, the relatively large insular regions were divided into smaller divisions for analysis. The right and left insular regions were subdivided into four equal quadrants on the basis of each individual’s anterior-posterior midline (rostral-caudal) through the insula and superior-inferior (dorsal-ventral) midline through the insula. Although nonstandard neuroanatomic descriptors are used, the terminology selected best identifies the specific regions assessed by using standard anatomical planes of reference for human study. Furthermore, these regions are of adequate size so as not to compromise the spatial resolution of the methodology.

The insular quadrants served as ROIs for analysis and were termed anterior superior (rostral dorsal), anterior inferior (rostral ventral), posterior superior (caudal dorsal), posterior inferior (caudal ventral), for the right and left sides. Similarly, ROIs were formed from the two halves of the thalamus divided into two equal superior (dorsal) and inferior (ventral) regions. Other regions and structures analyzed, with corresponding Brodmann’s areas (BA) approximated when applicable, included leg sensorimotor regions (BA 1–4), anterior cingulate

**rCBF assessment.** To determine the rCBF distributions during each testing condition, 20 mCi of freshly reconstituted technetium-99m ECD (Neurolite, DuPont Pharma, Billerica, MA) was injected intravenously. This retained brain blood flow tracer is a photon emitter with a physical half-life of 6 h. Increases in rCBF to a particular region of the brain are related to increases in neuronal activity, subsequently leading to an increase in the amount of radioactivity recorded from that specific region (26). The retained brain blood flow tracer uptake is rapid and is basically completed within 2 min of injection. Thus the reported rCBF distributions represent a 2-min window of time. Although rCBF can last for hours, the time frame for injection at 8–10 min postexercise was selected to correspond with reported times for peak changes in postexercise blood pressure between 5 and 15 min (17, 18). During this time, participants were asked to remain quiet with their eyes closed. A technician administered the blood flow tracer and flushed the catheter with normal saline. Participants were unaware of the exact time of injection and reported no noticeable side effects. After minute 10 of postexercise recovery, with the tracer uptake completed and bound in brain tissue, subjects rested for an additional 20 min before SPECT was assessed. All subjects were taken to the SPECT camera room and scanning was completed within 50 min of injection for all subjects. Brain scanning procedures have been previously reported in detail (31).
cortex (BA 24 and 32), cerebellar vermis, a white matter region encompassing the anterior corpus callosum, and a gray matter region (BA 44 and 45) involved in speech (not expected to be affected by exercise).

The total number of radioactive SPECT counts within each ROI was then compared between conditions, for each subject, as absolute counts and as a percent change from the resting condition. The SPECT data were corrected by using white matter rCBF from the resting condition to negate the possibility that differences in global cerebral blood flow between conditions accounted for any observed rCBF changes. During the processing and rCBF data assessment, data were coded such that the researchers performing these analyses were blinded with regards to the subject identity and order of experimental conditions.

Statistical analysis. A univariate analysis was used to assess normality. The data were normally distributed, and a repeated-measures ANOVA was used to compare differences in dependent variables across the resting period and the two postexercise recovery periods during the time frame when rCBF was assessed (using raw counts for each ROI). A Bonferroni correction was used to account for multiple comparisons. If significance was detected, a Tukey’s post hoc analysis was performed to determine specific differences for pairwise comparisons. A Pearson correlation was used to assess the relationship between changes in mean blood pressure and changes in rCBF for both right and left insular regions. The alpha level was set at $P < 0.05$ for all analyses.

RESULTS

Data for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), HR, RPE, and a pre- and postexercise RPR are reported across conditions (control, light exercise, moderate exercise) for pretest, testing, and posttesting time frames. Data for these dependent variables are presented in Table 1. For the resting control condition, SBP, DBP, MBP, HR, and RPR were all reduced from initial values ($P < 0.05$) for the last measurement when rCBF was assessed. Thus the values recorded after 30 min of supine rest (+8 min) were used as the “baseline” data for comparison between conditions.

For the light exercise, SBP, HR, and RPE were elevated from preexercise values. For the postexercise responses, there were no differences from the baseline control values, with the exception of RPR. For the moderate exercise, SBP, MBP, HR, and RPE were higher ($P < 0.05$) than preexercise values. During postexercise recovery, SBP, DBP, MBP, and RPR were reduced ($P < 0.05$), whereas HR was elevated.

Postexercise rCBF responses. The rCBF changes are presented in Table 2. Statistical analyses were performed on raw counts, and percent changes are reported to allow for comparison with other studies. The leg sensorimotor region showed decreases ($P < 0.05$) from control after both light ($−11.6 \pm 3%$) and moderate exercise ($−14.6 \pm 4%$). Likewise, the left superior anterior insula showed similar decreases after light ($−6.5 \pm 3%$) and moderate ($−7.3 \pm 3%$).

The following regions of the brain showed a decrease in rCBF from control after moderate exercise only and were significantly different from the light exercise recovery: anterior cingulate cortex ($−6.7 \pm 2\%$), right inferior thalamus ($−10.4 \pm 3\%$), left inferior thalamus ($−11.2 \pm 3\%$), right inferior anterior insula ($−8.4 \pm 3\%$), right inferior posterior insula ($−12.9 \pm 3\%$), and left inferior anterior insula ($−7.8 \pm 3\%$). These data are represented as rCBF changes for specific anatomic locations within the brain (Fig. 1).

There was a correlation between changes in blood pressure from baseline control after exercise (both exercise conditions) and changes in rCBF for right ($r = 0.86; P < 0.001$) and left insular ($r = 0.68; P < 0.05$) regions (Fig. 2).

DISCUSSION

The primary goal of this investigation was to compare patterns of rCBF within the insular cortex during exercise recovery both with and without PEH by using two different intensities of exercise. The main finding was that there were regions of the insular cortex with reduced rCBF (or having decreased activation from baseline) after exercise, but only after the moderate exercise when PEH was present. The insular cortex regions showing decreased rCBF are consistent with those previously reported to be involved in the central modulation of autonomic function (central command) during exer-

Table 1. Data for dependent variables

<table>
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<tr>
<th>Phase</th>
<th>Condition</th>
<th>Variable</th>
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<tr>
<td></td>
<td></td>
<td>SBP, mmHg</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>Pre-rest control</td>
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</tr>
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<td>Resting control  (at 30 min)</td>
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<td>3</td>
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</tr>
<tr>
<td>2</td>
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<tr>
<td>3</td>
<td>Post-Ex recovery  (8 min)</td>
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<tr>
<td>Moderate Exercise</td>
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<tr>
<td>3</td>
<td>Post-Ex recovery  (8 min)</td>
<td>112±5*†</td>
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Values are means ± SD across conditions for nonexercise rest (control), light exercise (Ex) (20% maximal heart rate (HR max)) with no postexercise hypotension, and moderate exercise (60–70% HR max) with postexercise hypotension (PEH). Variables reported include systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), heart rate (HR), rating of perceived exertion (RPE), and rating of perceived relaxation (RPR). *Significance ($P < 0.05$) from resting values across conditions by phase of the condition (i.e., 1, 2, or 3); †significance ($P < 0.05$) between exercise conditions by phase.
Exercise elicits an intensity-dependent activation of the insular cortex and anterior cingulate cortex (30, 31); however, few studies have examined postexercise rCBF responses. It has been reported that there were no significant changes in rCBF after 3 min of static handgrip exercise that did not result in PEH (30). Using a different approach, Zanette et al. (34)  

![Fig. 1. Differences in brain activation from rest for light and moderate exercise recovery. Coregistered single-photon-emission computed tomography (SPECT) and MRI data representing a transaxial slice from 1 subject are shown. The coronal and sagittal MRI figures (middle) show lines of orientation for the transaxial slice. The top and bottom of the transaxial figures correspond to an anterior and posterior orientation, respectively. Changes in regional cerebral blood flow (rCBF) distribution from SPECT data were mapped on the MRI by using an arbitrary color scale with a positive range from 5 to 25% (from green through yellow to red) and negative range from −5 to −25% (from purple through dark blue to light blue). The black lines denote the specific regions of interest (ROI) assessed (in this brain slice) and encompass the right and left insular cortices for inferior anterior (ICia) and inferior posterior (ICip) regions, right and left inferior thalamic regions (THi), and anterior cingulate cortex (AC). The image shows the significant decreases in activation for both anterior cingulate and insular regions for this subject during the period of recovery after moderate exercise with postexercise hypotension. These regions were not deactivated (reduced rCBF) during recovery from light exercise with no postexercise hypotension.  

<table>
<thead>
<tr>
<th>Condition</th>
<th>%Change from rest</th>
<th>%Change from PEH</th>
<th>%Change from no PEH</th>
<th>Condition</th>
<th>%Change from rest</th>
<th>%Change from PEH</th>
<th>%Change from no PEH</th>
</tr>
</thead>
<tbody>
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<td>No PEH</td>
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<td></td>
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<tr>
<td>PEH</td>
<td></td>
<td></td>
<td></td>
<td>Moderate</td>
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Table 2. Regional cerebral blood flow responses
examined a depression of cortical excitability after exercise. They found that motor-evoked potentials to transcranial magnetic stimulation were depressed for motor regions after repetitive hand movements. Furthermore, the depression was categorized into three distinct phases: a rapid decrease phase within first 5 min, a maximal depression phase from minutes 5 to 15, and a slow recovery phase lasting for ~35 min. This pattern of cortical depression, with peak responses occurring around 10–15 min, does tend to track the typical magnitude of change during the recovery of postexercise blood pressure (in normotensive subjects) (17).

Although Zanette et al. (34) did not report blood pressure responses, they did show that there might be specific task-related regions of brain demonstrating decreased excitability after exercise. The present study found significant decreases in leg sensorimotor regions after both intensities of walking exercise, yet there were other rCBF changes only occurring during PEH (Table 2). Furthermore, the rCBF for Broca’s area (BA 44 and 45) was not altered after exercise, as would be expected for this gray matter involved in speech and language. This suggests that there were unique changes resulting from moderate-intensity exercise capable of eliciting PEH, as opposed to a generic whole brain response to the exercise itself (independent of type or intensity).

The moderate exercise was sufficient to produce significant postexercise decreases in blood pressure consistent with prior findings in normotensive subjects (17, 18). During PEH, there were significant decreases to regions of the insular cortex previously reported to be involved in central command during exercise (30). Both the left inferior anterior insular and the right inferior posterior insular regions showed significant decreases in rCBF after the moderate-intensity exercise. There were significant correlations for both the right and left insular regions with changes in mean blood pressure (Fig. 2). This association was stronger for the right insular cortex, consistent with prior findings (31). The anterior cingulate cortex and inferior right and left thalamus also had reductions in rCBF below baseline levels after moderate exercise. The design of this study does not allow one to establish causal relationships, but the regions affected are identical to those showing increased activation during exercise when blood pressure is elevated.

**Limitations.** The cerebral cortical regions identified in this study may not be inclusive of all brain regions involved in postexercise rCBF changes because the regions were preselected on the basis of prior data showing their involvement in cardiovascular regulation during exercise. Additionally, the spatial limitations of the SPECT technique (~10 mm) do not allow us to assess, with confidence, smaller regions that may also play an important role in cardiovascular regulation, such as specific nuclei of the thalamus or other subcortical structures. The rCBF distributions reported reflect the changes from the baseline or control condition but do not define the specific type of neural activity (i.e., excitatory or inhibitory) associated with the rCBF changes.

The rCBF changes were intentionally assessed during a time period when the PEH response was near its reported peak response (17, 18) and should not be extrapolated beyond this time point. Although correlations between changes in mean blood pressure and rCBF distribution for insular regions across conditions were significant, further study is warranted to establish causation. Changes in Pco₂ that can affect global cerebral blood flow were not directly measured. However, assessment of white matter blood flow, which is reflective of global cerebral blood flow, was not significantly different from baseline conditions, nor did it differ between the two exercise conditions during recovery.

The control or sham condition involving 30 min of supine rest was used to ensure that baseline blood pressure was representative of a true resting state. Table 1 shows that the 30 min of supine rest lowered MBP by 5 mmHg (from the initial measurement). The rCBF used for comparison with exercise conditions was assessed after the supine rest during the time when blood pressure was lower. This approach served to minimize the observed PEH responses but was deemed to provide a more appropriate baseline for comparison. However, by using a supine resting control the potential for differences in acute fluid volume shifts between supine rest and the transition from upright exercise conditions was increased. All rCBF measurements were assessed in the supine position after at least 8 min. The cerebral blood flow is relatively constant across a range of mean arterial pressures from 50 to 140 mmHg (16) and responds quickly (within 3–5 s) to step changes in blood pressure (28). Thus, given the slight variations in global cerebral blood flow across a wide range of blood pressures, the rapid response of cerebral blood flow to pressure changes, and the finding that white matter flow and gray matter rCBF for Broca’s speech area were similar across conditions suggests that the supine control posture did not significantly influence the findings of the study. Although the room temperature was held constant at 68°F, it is possible that there were differences in core temperature during the recovery periods that may have affected rCBF responses.

In conclusion, data show that there are rCBF reductions within specific regions of the insular cortex and anterior cingulate cortex coupled with a postexercise hypotensive response.
after moderate-intensity dynamic exercise. These initial findings of rCBF changes after exercise appear novel in their identification of specific cerebral cortical regions demonstrating a postexercise deactivation (rCBF below baseline values). These regions of the insular cortex found to have reduced rCBF during PEH also have neural connections to brain stem regions of cardiovascular integration (3, 27). Although these findings cannot define specific mechanisms of interaction between cerebral cortical regions and the brain stem nuclei involved in PEH (4, 12), they do provide evidence that higher brain regions with the capacity for modulation of autonomic function are altered after moderate-intensity exercise. Thus the same cerebral cortical regions activated by central command during exercise that act to modulate cardiovascular responses are also deactivated after moderate-intensity aerobic exercise and may play a significant role in the postexercise hypotensive response.

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