Short communication

Detecting changes in human cerebral blood flow after acute exercise using arterial spin labeling: Implications for fMRI

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ABSTRACT

The use of arterial spin labeling to measure cerebral blood flow (CBF) after acute exercise has not been reported. The aims of this study were to examine: (1) the optimal inversion time to detect changes in CBF after acute exercise and (2) if acute exercise alters CBF in the motor cortex at rest or during finger-tapping. Subjects ($n = 5$) performed 30 min of moderate intensity exercise on an electronically braked cycle ergometer (perceived exertion 'somewhat hard'). Before and after exercise, relative CBF was measured using multiple inversion time (TI) pulsed arterial spin labeling (PASL). Two multiple TI runs were obtained at rest and during 4 Hz finger-tapping. Four inversion times (675, 975, 1275, and 1575 ms) were acquired per run, with 20 interleaved pairs of tag and control images per inversion time (320 s run). The results indicated that global CBF increased approximately 20% following exercise, with significant differences observed at an inversion time of 1575 ms ($p < .05$). Finger-tapping induced CBF in the motor cortex significantly increased from before to after exercise at TI = 1575 ms ($p < .01$). These findings suggest changes in human cerebral blood flow that result from acute moderate intensity exercise can be detected afterwards using PASL at 3T with an inversion time of 1575 ms. The effect of prior acute exercise to increase motor cortex CBF during the performance of a motor task suggests future use of indices of functional activation should account for exercise-induced changes in cardio-pulmonary physiology and CBF.

1. Introduction

The research regarding the effects of exercise on human brain function using magnetic resonance imaging (MRI) indicates physical exercise may promote enhanced functional activation during executive function tasks and enhance the structural integrity of both white matter and gray matter (Colcombe et al., 2006), and may enhance cerebral blood volume in the dentate gyrus (Pereira et al., 2007). This evidence is based on MRI scans obtained while at metabolic rest on a day that exercise is not performed. There is very little known, however, about the acute effects of exercise on MRI-based indices of human brain function. An understanding of how a single session of dynamic large-muscle exercise may alter brain function immediately following exercise is important to advance our understanding of the adaptations that occur to repeated bouts of exercise that may provide beneficial effects on brain function.

There has been recent interest in utilizing acute exercise to examine neural activation using functional MRI (fMRI) (Janse Van Rensburg et al., 2009). However, the large-scale effects of exercise on the cardio-pulmonary systems may influence the blood oxygen-level dependent (BOLD) signal independent of neuronal activation (Chang and Glover, 2009). Thus, it is important to understand how acute exercise affects cerebral blood flow (CBF), and the physiological markers known to influence CBF, due to the strong positive association between CBF and the BOLD signal (Chen et al., 2008).

Arterial spin labeling (ASL) is a reliable non-invasive method for quantifying CBF using MRI (Chen et al., 2008; Golay et al., 2004). The basis of contrast in ASL is the difference in magnetization derived from binary states of magnetically labeled and non-labeled arterial blood water destined to perfuse a region of interest. Because the difference in magnetization between the control and the tagged blood is affected by the inflow or inversion time (TI), which can vary based on the tissue type and age, multiple TI pulse sequences have been utilized along with a general kinetic model to quantify CBF using ASL (Buxton et al., 1998).

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Research regarding the effects of exercise on cerebral blood flow has been focused on estimating CBF *during* exercise (Ogoh and Ainslie, 2009). As Ogoh and colleagues have noted, the physiological factors that drive increased CBF during exercise are extremely complex. Using the Xe clearance (Thomas et al., 1989) and transcranial Doppler methods (Jorgensen et al., 1992), it has been shown that regional CBF increases during exercise, and now this effect is well-established (Ogoh and Ainslie, 2009).

Few studies, however, have examined CBF immediately *after* exercise. In an early investigation (Kleinerman and Sokoloff, 1953), it was reported that CBF remained elevated and cerebral vascular resistance was decreased after moderate intensity exercise. However, the spatial resolution to localize increased CBF during or after exercise has been restricted and inferred in previous studies based on the blood supplied by major arteries. ASL achieves greater spatial resolution of CBF changes. The use of ASL to quantify changes in CBF immediately after exercise has not been reported, and the optimal TI to detect changes in CBF after exercise has not been established. Thus, the aims of this study were to compare recordings before versus after acute moderate intensity exercise to: (1) determine the optimal inversion time to detect changes in global CBF; (2) examine differences in CBF in the motor cortex at rest or during a finger-tapping task; and (3) describe the physiological effects of exercise measured during the MRI scan session.

2. Materials and methods

2.1. Participants

The IRB approved this research, and written informed consent was obtained from each participant. Participants were healthy physically active adults ($n = 5$; 3 women) with a mean ($\pm$SD) age of 24.8 (1.5 years), height of 172.7 (13.3 cm), weight of 71.9 (13.2 kg).

2.2. Procedures

Participants completed the informed consent form, a MRI safety screening form, a health history questionnaire, and the Godin Leisure-Time Exercise Questionnaire (Godin and Shephard, 1985). Resting and finger-tapping induced CBF were measured during two sessions using pulsed arterial spin labeling (PASL) on a 3.0 T GE MRI scanner (Milwaukee, WI) (Section 2.3). The first scan session occurred immediately before 30 min of exercise, and the second scan session began approximately 10 min after the exercise ended. The exercise was performed on a Lode Corival (Groningen, Nederland) electronically braked cycle ergometer located just outside the MRI scanner room. Participants were instructed to pedal at a subjective perception of effort corresponding to the verbal anchor 'somewhat hard' (rating of 13) on the Borg 6-20 Rating of Perceived Exertion (RPE) scale. Participants were provided standard instructions for making RPE and leg muscle pain ratings and were fitted with a heart rate monitor. After a 5-min warm-up, the participant adjusted the work rate on the cycle ergometer until it matched their own perception of effort as 'somewhat hard'. The participant was free to adjust the work rate whenever the intensity did not match a 'somewhat hard' perception of effort. An RPE rating of 13/'somewhat hard' has been shown to correspond to an intensity just below the ventilatory threshold and has been shown to be a valid method to prescribe an exercise intensity relative to individual maximal capacity (Dishman et al., 1994). Heart rate, RPE, and leg muscle pain were obtained every 5 min. After the 30 min of exercise, a 5-min cool down was provided and water ad libitum. The participant then entered the MRI scanner for the second MRI session.

2.3. Pulsed arterial spin labeling (PASL)

Imaging was performed on a 3T GE Signa MRI scanner using an 8-channel head coil. A custom, single-shot, lipid-suppressed, multi-slice 2D, gradient-echo, spiral-out sequence with a PICORE/QUIPSS II labeling scheme was used to acquire PASL images. Four contiguous, 6-mm dorsally located axial slices (1 mm gap) were collected at multiple inversion times (TI) (FOV = 24 cm², 3.75 mm² in-plane resolution, FA = 90°, TE = 3.2 ms, TR = 2000 ms, tag width = 600 ms, tag thickness = 10 cm, with a 1 cm gap between the tagging band and proximal slice). The placement of the four slices was guided based on 3D SPGR images collected prior to each of the pre- and post-exercise PASL runs. Four inversion times were acquired serially per run (675, 975, 1275, and 1575 ms), with 20 interleaved pairs of tag and control images per inversion time (run time 320 s). Two identical multiple TI runs were obtained at rest and then two runs were obtained during 4 Hz finger-tapping (total of 40 interleaved pairs at each TI). For the resting data, the 20 interleaved pairs of tag and control images corresponding to each inversion time were extracted from each of the two runs. For each inversion time, the images from the two runs were concatenated, yielding 40 interleaved pairs for each inversion time. Each run was corrected for head motion (AFNI 3dvolreg), and the mean difference between the tag and control images was computed at each TI using nearest neighbor subtraction. There were no statistically significant differences between the two runs, and so these were averaged for analysis.

2.4. Finger-tapping

The order of the resting and finger-tapping runs was the same during the pre- and post-exercise scan sessions. Finger-tapping at 4 Hz was cued by a visual metronome that consisted of an alternating checkerboard. Participants pressed a button with their right index finger in synchrony with the alternating checkerboard. Button presses were recorded to verify tapping rate. Four participants were right handed and one participant was left-handed. Tapping performance did not differ for the left-handed participant.

2.5. Physiological monitoring

Pulse oxymetry, heart rate, end-tidal CO_2, and respiratory rate were recorded continuously (Mellenia). Blood pressure was measured in the scanner immediately before and after each run.

2.6. Data analysis

To determine the optimal TI to detect increased CBF after exercise, the resting CBF from the entire acquired volume was analyzed using a 2 (pre- vs. post-exercise) by 4 (TI) repeated measures ANOVA. Mauchly's test of sphericity was not significant ($p > .05$) for the TI factor. Post hoc comparisons were conducted using the Tukey LSD. The comparison of resting and finger-tapping induced CBF in the left primary motor cortex region of interest was analyzed using a priori paired samples *t*-tests between the pre- and post-exercise rest and tapping conditions at TI = 1575 ms. The motor cortex ROI was drawn along the dorsal part of the precentral gyrus/central sulcus. Depending on the slice prescription, one or two slices were used to construct the ROI. The final ROI was overlaid onto the 3D SPGR images for visual verification of appropriateness. Based on our directional hypothesis that motor cortex CBF would increase after exercise, we used an one-tailed alpha of $p < .05$ to determine statistical significance.

Table 1
Physiological data collected before and 10 min after 30 min of moderate intensity cycle ergometer exercise during the measurement of cerebral blood flow (CBF) using arterial spin labeling (ASL) perfusion imaging at 3.0 T during rest and during 4 Hz finger-tapping. Data are presented as mean (±SD).

	Pre-exercise		Post-exercise		Exer. effect		Task effect		Int.	
	Resting	Tapping	Resting	Tapping	p-Value	η^2_p	p-Value	η^2_p	p-Value	η^2_p
Heart rate (beats min^{-1})	55.2 (11.8)[a]	58.2 (10.3)[a]	61.5 (9.1)	61.5 (8.4)	0.110	0.512	0.206	0.363	0.002	0.993
SpO$_2$ (%)	98.4 (0.3)	98.0 (1.0)	97.7 (1.3)	97.3 (1.5)	0.292	0.269	0.396	0.184	0.860	0.009
Respiration rate (min^{-1})	15.8 (2.3)[a,b]	17.0 (2.4)[a]	17.2 (2.9)	17.3 (2.2)[b]	0.103	0.527	0.059	0.630	0.129	0.477
ETCO$_2$ (mmHg)	44.9 (3.3)[a,b,c]	43.4 (2.6)[a,b,c]	42.3 (3.1)[b]	42.2 (3.3)[c]	0.012	0.824	0.002	0.921	0.111	0.511

	Pre-exercise		Post-exercise		Exer. effect		Time effect		Int.	
	Pre-scan	Post-scan	Pre-scan	Post-scan	p-Value	η^2_p	p-Value	η^2_p	p-Value	η^2_p
SBP (mmHg)	119.4 (12.4)	115.6 (10.5)[a]	123.8 (10.5)[a,b]	113.2 (13.8)[b]	0.408	0.175	0.053	0.649	0.076	0.587
DBP (mmHg)	65.4 (7.3)	65.4 (3.6)	66.8 (5.8)	67.8 (3.6)	0.700	0.041	0.771	0.024	0.131	0.474
MAP (mmHg)	84.7 (6.5)	82.1 (5.6)	85.8 (5.1)	82.9 (7.0)	0.447	0.150	0.225	0.339	0.883	0.006

Note: η^2_p, partial eta-squared; SpO$_2$, saturation of peripheral oxygen; ETCO$_2$, end-tidal partial pressure of carbon dioxide; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure. Within each variable, values with a common superscript character indicate significant differences between the values, $p < .05$ (two-tailed).

3. Results

3.1. Manipulation checks

The mean (±SD) power output during the 30 min of exercise was 98.0 (14.3 W) at a heart rate of 124.5 (6.6 bpm). This exercise intensity corresponded to a mean (±SD) rating of perceived exertion of 13.0 (0.2), which is associated with the verbal anchor 'somewhat hard' on the Borg 6-20 RPE scale. The mean (±SD) subjective ratings during the exercise were as follows: pain (0–10 scale), 0.5 (0.3) (associated with the verbal anchor 'just noticeable'); pleasantness (1–9 scale), 7.3 (0.7); arousal (1–9 scale), 4.6 (1.0). These data confirm the manipulation of a moderate intensity exercise session. The mean (±SD) finger-tapping rates pre- and post- exercise were 3.4 (0.6 Hz) and 3.6 (0.9 Hz), respectively, which did not differ ($p > .2$).

3.2. Resting CBF

Fig. 1a shows the effect of exercise on resting CBF as a function of inversion time. There was a significant interaction between Exercise and TI [$F(3,12) = 3.941$, $p = .036$, $\eta^2_p = .496$]. The main effect of exercise was significant [$F(1,4) = 7.646$, $p = .026$, $\eta^2_p = .657$], indicating that CBF increased globally from before to after exercise. Note also the expected linear effect of inversion time on the ASL measured change in magnetization (ΔM) [$F(3,12) = 40.701$, $p = .001$, $\eta^2_p = .911$]. Separate analyses at each TI revealed the change in CBF from before to after exercise was significant only at an inversion time of 1575 ms ($p < .05$). This represents an approximately 20% increase in CBF following exercise.

3.3. Motor cortex CBF

Based on the results from the first aim of the study, where significant effects of exercise on CBF were detected at TI = 1575 ms, we conducted a priori contrasts of the effects of exercise and finger-tapping in the motor cortex ROI at a TI of 1575 ms. As expected, CBF was greater during finger-tapping compared to rest both before and after exercise ($p = .025$). However, as shown in Fig. 1b, there were significant increases in finger-tapping induced CBF in the motor cortex from before to after exercise at TI = 1575 ms [$t(4) = 5.949$, $p = .002$]. At rest, the change in CBF from before to after exercise was not significant in the motor cortex ROI [$t(4) = 1.940$, $p = .062$].

3.4. Physiological monitoring

Table 1 shows the mean (±SD) data for heart rate (HR), saturation for peripheral blood oxygen (SpO$_2$), respiration rate, partial pressure of end-tidal carbon dioxide (ETCO$_2$), and blood pressure (BP) during the scanning sessions. Heart rate was greater during the finger-tapping task compared to rest before exercise, but not after exercise. The same pattern of results was observed for respiration rate and ETCO$_2$, however the interaction was not significant. ETCO$_2$ significantly decreased after exercise, and also significantly decreased during finger-tapping before exercise, but not after exer-
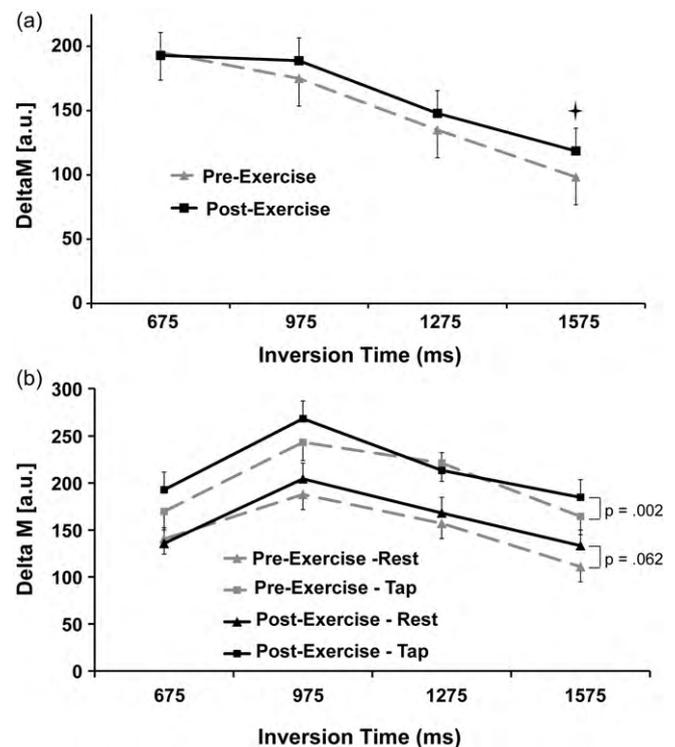

Fig. 1. Cerebral blood flow (CBF) measured by pulsed arterial spin labeling before and after 30 min of moderate intensity cycling exercise. (a) Mean relative CBF as a function of inversion time (TI) in all voxels within the four dorsally located slices obtained at rest before (dashed line) and after (solid line) exercise. (b) Mean relative CBF as a function of TI in a left primary motor cortex region of interest at rest (♦) and during 4 Hz finger-tapping (■) before (dashed lines) and after (solid lines) exercise.

cise. Systolic blood pressure was significantly greater immediately after exercise (before the post-exercise scan session), and significantly decreased over time during the post-exercise scan session. There were no significant effects of exercise or finger-tapping on SpO_2, diastolic blood pressure or mean arterial pressure.

4. Discussion

Using PASL at 3T, we found that the optimal TI to detect changes in CBF after exercise was 1575 ms, and that global CBF was elevated by 20% up to 30 min after the cessation of 30 min of moderate intensity upright pedaling exercise. As 1575 was the upper limit of our multiple TI pulse sequence, it is possible that a longer TI may be more sensitive to the effects of acute exercise. However, due to the T1 of blood at 3T, any increases in sensitivity at much longer inversion times will be hampered by decay of the label. It is worth emphasizing that ASL is completely non-invasive (requires no injections) and that "tagged blood" refers to magnetically labeled water as opposed to radioactively labeled water. Position emission tomography (PET) can also be used to quantify CBF but requires exposing participants to exogenous radiotracers. Thus, ASL derived measures of CBF can be obtained repeatedly over time with minimal risk.

While the effects of exercise on motor cortex CBF differed between the resting state and during finger-tapping, it seems unlikely given the small sample size that the effects of exercise on CBF may interact with task related changes in CBF. It is likely that both exercise and finger-tapping independently increased motor cortex CBF. The effect of prior performance of acute exercise to increased motor cortex CBF during the subsequent performance of a motor task suggests that exercise may promote increased perfusion in task-activated brain regions. Whether or not this increased perfusion reflects increased neuronal activation at rest or during the performance of a task is yet to be determined.

Given the known effects of carbon dioxide as a strong stimulus for cerebral vasodilation, which results in increased CBF, it is important to consider the physiological effects of acute exercise, especially potential changes the CO_2 content of blood. Increased CBF results in removal of deoxyhemoglobin from tissue, which results in an increase in T2* (the BOLD contrast). Variability in $PETCO_2$ has been reported to predict a significant proportion of variance in the BOLD signal time series (Chang and Glover, 2009). Increases in blood pressure are known to increase the BOLD signal, and these effects may accentuate task-related BOLD activation (Wang et al., 2006). While low-frequency variation (<0.1 Hz) in respiration and the cardiac cycle may affect the BOLD signal, these effects are most pronounced during rest-state connectivity analyses (Birn et al., 2006). In the current study, several physiological changes occurred as a result of finger-tapping and the performance of moderate intensity exercise. Considering the effect of finger-tapping, prior to the bout of exercise we observed a significant increase in heart rate and respiration rate, and decreased $ETCO_2$. One plausible interpretation of this pattern is that the task-related increase in respiration resulted in reduced partial pressure for CO_2. In order to maintain CBF, heart rate increased. Notably, over the course of the entire scan session SBP decreased a small but significant amount (~4 mmHg before exercise and ~10 mmHg after exercise). While we did not measure peripheral or cerebral vascular resistance, one might speculate that in order to maintain and increase CBF during finger-tapping, vascular resistance (at least in the left primary motor cortex) decreased.

The effects of exercise on physiological responses indicated that $ETCO_2$ was reduced after exercise. In addition, unlike prior to the exercise session, $ETCO_2$ did not change during finger-tapping after the exercise session. This same pattern of results was also observed

for respiratory rate and heart rate. We did not measure expired respiratory gases during or after exercise, nor did we determine the blood lactic acid response during or after exercise. Nevertheless, a moderate intensity exercise session at an RPE of 13 has been associated with a relative exercise intensity that is just below the ventilatory threshold (when CO_2 production begins to outpace O_2 consumption) in normally physically active healthy young adults (Dishman et al., 1994). It is plausible that the increased respiration during exercise, which facilitates the removal of accumulated CO_2 from the venous circulation, resulted in reduced $ETCO_2$ after exercise. There was a small but significant increase in SBP from the end of the pre-exercise scan to the beginning of the post-exercise scan session. As participants entered the scanner within a few minutes after the exercise session (during which SBP readings in the range of 160–180 mmHg would be expected), this change may reflect a state of recovery. As noted above, SBP continued to decrease to the pre-exercise level over the course of the post-exercise scan session. Given the relative stability of heart rate and respiration during the post-exercise scan session (during both rest and finger-tapping), coupled with decreased $ETCO_2$ and a dynamic hypotensive response, the interpretation of greater finger-tapping induced CBF after exercise compared to before exercise is difficult. There were small (~0.5%) and statistically non-significant decreases on SpO_2 after exercise (although the size of the effect was large). A reduced oxygen content of blood could increase CBF as well. Assuming all other factors are equal, the lack of a decrease in $ETCO_2$ during finger-tapping could explain the greater relative increase in CBF after exercise. The more parsimonious interpretation is that exercise had similar effects on resting and finger-tapping induced increases in CBF.

The effects of exercise on resting and finger-tapping induced CBF, and the effects of exercise on $ETCO_2$, underscore the importance of taking these variables into consideration in the context of fMRI after acute exercise. One limitation of this study is the small number of subjects. While some of the effects of exercise, finger-tapping, and the interactions between exercise and finger-tapping, on CBF and physiological responses did not reach statistical significance, in some cases the effect sizes were very large. Thus, it is possible that we have committed a Type II error by accepting the null hypothesis in these cases. With a greater number of subjects, these large effects are likely to be statistically significant. This underscores our recommendation that CBF and physiological measures need to be carefully considered during fMRI immediately after a session of exercise. One recent study reported fMRI results regarding the effects of acute exercise in response to smoking-related pictures compared to neutral pictures in regular smokers (Janse Van Rensburg et al., 2009). While subjective ratings of cigarette craving were reduced after exercise, the effects of exercise on the fMRI responses to smoking-related and neutral pictures were not different. Thus, there may have been a global effect of exercise on CBF that was related to physiological changes after exercise that were unrelated to neural activation in response to smoking cues. Unfortunately, physiological data were not acquired during the scans to account for these effects on the BOLD signal.

4.1. Conclusion

An effective inversion time to detect changes in CBF after exercise using PASL is 1575 ms. Thirty minutes of moderate intensity upright pedaling exercise in healthy young adults results in a global 20% increase in CBF at a TI of 1575 ms, and these effects were measured up to 30 min after the cessation of the exercise. Exercise also resulted in a reduction in $ETCO_2$, and there was evidence of recovery in SBP after exercise, that may contribute to CBF effects at rest and during a finger-tapping task. The large-scale cardio-pulmonary effects of acute exercise may introduce variance into the fMRI signal

related to CBF. Caution is warranted before making interpretations that acute exercise may alter neural activation. Future studies, in the context of both acute and chronic exercise, should measure and account for the variance in physiological effects that may co-vary with the BOLD signal

Acknowledgment

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