

Effect of Lactate Accumulation during Exercise-induced Muscle Fatigue on the Sensorimotor Cortex

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Abstract. [Purpose] During exercise, skeletal muscle motor units are recruited based on afferent sensory input following peripheral metabolic by-product accumulation. The purpose of this study was to investigate whether lactate plays a role in conveying fatigue-related information to the brain. [Subjects] Eleven healthy adults participated in this study. [Methods] Subjects performed handgrip exercises at 10%, 30%, and 50% maximal voluntary contraction for 120 s. They were monitored for brachial artery blood pressure, respiratory quotient, muscle fatigue (integrated electromyogram, median power frequency), blood lactate levels, muscle blood flow, and brain activity. [Results] The handgrip exercise protocol caused significant muscle fatigue based on 28% and 37% reductions in median power frequency detected at 30% and 50% maximal voluntary contraction, respectively. Subjects exhibited intensity-dependent increases in blood pressure, respiratory quotient, muscle blood flow, and circulating lactate concentrations. Furthermore, brain activity increased at 30% and 50% maximal voluntary contraction. Multiple regression analysis identified muscle blood flow at 30% maximal voluntary contraction and lactate at 50% maximal voluntary contraction with standardized partial regression coefficients of -0.64 and 0.75 , respectively. [Conclusion] These data suggest that blood lactate concentration and muscle blood flow, which reflect muscle metabolism, may convey load intensity information to the brain during muscle fatigue.

Key words: Lactate, Fatigue, Brain blood flow

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INTRODUCTION

Muscle fatigue in human performance is defined as any exercise-induced decrease in maximal voluntary force or power produced by a muscle or muscle group¹). Muscle fatigue is a hindrance during exercise, as it causes dysfunction. More moderate-intensity exercise is recommended to enhance aerobic capacity²). Nevertheless, the beneficial effects of training could be obtained by exercising at a higher intensity and adapting this exercise stimulus. Thus, physical adaptation to fatigue is important for enhancement of aerobic capacity.

Currently, the fatigue mechanism is generally considered an integrated phenomenon, with a complex interaction between central and peripheral factors³). The most popular peripheral fatigue theory suggests that fatigue is caused by lactate accumulation^{4, 5}). Nevertheless, following discovery of the monocarboxylate transporter⁶), recent studies have suggested that lactate is an important fuel source during

high-intensity exercise⁷). There is strong evidence that factors including reduction in pH^{8, 9}) and blood flow¹⁰) do not affect exercise-induced fatigue and that loss of homeostasis does not occur at the end of exercise^{11, 12}). Thus, it remains difficult to determine exercise-induced fatigue by only evaluating peripheral fatigue.

Numerous studies have also examined central fatigue by monitoring brain activity during exercise^{13–18}). In the Central Governor Model¹⁹), it is hypothesized that using feed-forward control in response to afferent feedback from different physiological systems, the extent of skeletal muscle recruitment is controlled as part of a continuously altering pacing strategy, with the sensation of fatigue being the conscious interpretation of homeostasis^{19–21}). Moreover, this model proposes that peripheral metabolites have signaling properties that assist in determining the continuously reset pacing strategy and are not merely energy substrates or inert metabolic by-products²⁰). Thus, according to this model, the role of peripheral metabolites is to transmit the status of skeletal muscle to the brain.

Recent reports have described how lactate released from ischemic muscle may contribute to ischemic pain by acting on sensory neurons innervating muscles²²), while lactate was also shown to cause an increase in blood pressure through activation of groups III and IV afferent muscles (i.e., muscle metaboreflex)²³). Furthermore, lactate can af-

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fect motor cortex excitability²⁴) and attentional processes²⁵). Nevertheless, the role of lactate as a signal of fatigue to the brain during exercise compared with peripheral factors remains unclear.

The aim of the present study was to examine the impact of lactate on brain activation during exercise-induced fatigue. We defined fatigue-related information as stated below. First, blood lactate concentration increased and brain blood flow, as measured by near-infrared spectroscopy (NIRS), increased with an increase in fatigue-induced intensity. Second, multiple regression analysis shows that blood lactate levels are significant contributors to brain blood flow. Also, whether or not such information reaches the brain is that multiple regression analysis indicates that lactate levels are a significant contributor to brain blood flow. We hypothesized that lactate would produce the greatest impact on brain blood flow changes as measured by NIRS in comparison with respiratory, circulatory, and metabolic responses and muscle activity. Brain activity during exercise is measured by functional magnetic resonance imaging (fMRI) and NIRS^{16, 17}). One limitation of fMRI is its poor temporal resolution, while by contrast, NIRS has a relatively good temporal resolution of 0.1 s, enabling detailed assessment of temporal changes in cerebral blood volume²⁶). Thus, NIRS is particularly useful for assessing dynamic changes in cortical activity during exercise.

SUBJECTS AND METHODS

Subjects

Eleven healthy men (mean \pm SD: age 20 ± 1 years; height 170.9 ± 3.7 cm; body weight 61.0 ± 5.9 kg) participated in this study. No subjects had any history of cardiovascular-related disease or were taking any medication. All subjects were informed about the experimental procedures and the purpose of the study, and written informed consent was obtained. The experimental procedures were approved by the Ethics Committee of Seirei Christopher University (approval no. 09011).

Methods

Exercise tests involved different levels of sustained handgrip exercise [10%, 30%, and 50% maximal voluntary contraction (MVC)] using a Smedley-type Hand Dynamometer (SPR_651; Matsumiya Medical Co. Ltd., Tokyo, Japan) in the supine position. A previous study reported lactate-induced elevation of blood pressure in such sustained handgrip exercises²⁷). All subjects performed MVC three times using the left hand, and blood pressure was measured on the right arm. MVC values were averaged three times, and this value was used to calculate 10%, 30%, and 50% MVC. After MVC measurement, subjects rested for 5 min with the hand dynamometer gripped. After resting, they performed a sustained handgrip exercise at each intensity level (in random order) for 120 s, during which the intensity levels were maintained by verbal feedback. Measurements were separated by an interval of at least 15 min in consideration of muscle fatigue. During measurement, breathing of the subjects was regulated by an electronic metronome.

In addition, they were instructed to avoid intense exercise and alcoholic beverages on the day before exercise tests and to avoid food, drinks (except water), and smoking for up to 2 h prior to exercise tests. Measurement of brain blood flow was performed every other day to limit any pain caused by blood sampling. Fluctuations in brain capillary oxygen saturation during exercise were monitored using a 47-channel NIRS unit (ETG-7100; Hitachi Medical Corporation, Tokyo, Japan), which uses two different wavelengths of near-infrared light (695 and 830 nm) to detect oxygenated and deoxygenated hemoglobin concentrations (oxy-Hb and deoxy-Hb, respectively). Injectors and detectors were 3.0 cm apart, and the equipment was designed to measure points at a depth of 2–3 cm from the scalp (i.e., the surface of the cerebral cortex)^{28, 29}). The probes were positioned over both sensorimotor cortices enclosing Cz, according to the international electroencephalogram 10–20 system. Subjects were instructed not to move their head during exercise to avoid changes in brain blood flow responses. They also rested in the same position as when exercising. By definition, the NIRS system monitors brain activity in terms of oxy-Hb levels³⁰), and we also selected the oxy-Hb channels that reflected the somatosensory cortex and showed changes opposite to deoxy-Hb. The most stable average value for 30 s during the rest period was defined as the baseline, and the oxy-Hb value during exercise was defined as the average value measured during the final 30 s of exercise. The change in oxy-Hb during exercise was defined as the value obtained by subtracting the baseline from the exercise oxy-Hb.

Blood lactate concentration was determined using a Lactate Pro lactate analyzer (Arkray, Inc., Kyoto, Japan). Blood samples were collected immediately after both rest and exercise using a disposable lancet device (Naturalet; Arkray, Inc.). Subjects were given orientation training for this device before collection of blood and took blood from a fingertip under our instructions and monitoring.

Electromyogram (EMG) measurements were recorded by telemetry (TeleMyo 2400; Noraxon USA Inc., Scottsdale, AZ, USA) at a sampling rate of 1500 Hz. The surface EMG signal was recorded from the left extensor carpi radialis longus muscle during MVC measurement, rest, and exercise. This muscle was identified by palpating the skin while the subject extended their wrist. Bipolar electrodes (Blue Sensor M-00-S; Ambu, Medicotest, Ølstykke, Denmark) were attached at a 30-mm center-to-center distance after dermal treatment by abrasion and alcohol at the intended electrode site. EMG signals were uploaded to a computer via an analog digital converter card. They were analyzed using MyoResearch software (EM-123; Noraxon USA Inc.). To characterize EMG amplitude, the signals received during MVC and sustained exercise were rectified and integrated (iEMG). iEMG during sustained exercise of 91–120 s was then normalized based on the MVC value (%iEMG). To examine the status of muscle fatigue, the median power frequency (MdPF) was calculated using fast Fourier transform, and the average values over 3 s at commencement of exercise (resting value) and for a stable 3-s period within the 5 s before the end of exercise (exercise

Table 1. Impact of muscle fatigue on physiological and clinical parameters (N = 11)

		Mean blood pressure (mmHg)	Respiratory quotient	%integrated electromyogram (%)	Median power frequency (Hz)	Deoxy-Hb in the muscle blood flow (%)	Blood lactate concentration (mmol/L)	Oxy-Hb in the brain blood flow (mmol*mm)
10%	Rest	83.0 ± 7.14	0.88 ± 0.111	-	86.6 ± 21.85	-	1.5 ± 0.27	-
MVC	Exercise	95.0 ± 12.14*	0.92 ± 0.165	19.1 ± 7.12	77.6 ± 23.96	11.6 ± 9.54	1.5 ± 0.35	0.004 ± 0.1000
30%	Rest	82.4 ± 5.88	0.84 ± 0.100	-	93.5 ± 28.47	-	1.3 ± 0.29	-
MVC	Exercise	109.7 ± 11.59*	1.06 ± 0.207*	42.7 ± 16.15#	59.4 ± 19.29*	20.5 ± 14.55	1.5 ± 0.30*	0.284 ± 0.3527
50%	Rest	85.2 ± 9.64	0.84 ± 0.121	-	83.0 ± 24.44	-	1.2 ± 0.19	-
MVC	Exercise	120.5 ± 19.07*#	1.39 ± 0.503*#	72.4 ± 14.90§#	52.2 ± 22.25*#	31.2 ± 36.26#	1.8 ± 0.24*	0.872 ± 0.5731#§

Values are expressed as the mean ± SD. The median power frequency values at rest were obtained at initiation of movement. The values of the oxy-Hb in the brain blood flow, %integrated electromyogram, and deoxy-Hb in the muscle blood flow are presented relative to the rest values. MVC, maximal voluntary contraction. *p < 0.05 compared with rest. #p < 0.05 compared with 10% MVC. §p < 0.05 compared with 30% MVC.

value) were recorded.

Muscle blood flow during rest and exercise was determined using a near-infrared continuous-wave spectroscopic (NIRcws) monitor (Omegamonitor; BOM-L1 TRW, Omegawave, Tokyo, Japan). The wavelengths of emission light were 780, 810, and 830 nm. A probe fitting a dedicated holder for shade was attached to the area of greatest diameter on the left forearm muscle with surgical tape and an elastic bandage. The NIRcws signals were stored on a personal computer. To examine muscle metabolism, the average deoxy-Hb value registered during exercise at 91–120 s was calculated as the rate of increase from rest using the individual difference in light reduction and the influence of subcutaneous fat by scattering and absorption, with Hb and myoglobin excluded.

A breath-by-breath gas analyzer (AE-300; Minato Medical Science, Osaka, Japan) was used to measure the respiratory exchange ratio during rest and exercise. The respiratory data were averaged for 30 s before rest and at the end of the exercise period.

Blood pressure of the right brachial artery was measured using a mercury manometer (Yamasu Model No. 620; Yamasu Co., Ltd., Japan) by a physical therapist. Measurements were performed at the 4–5 min stage during rest periods and at 91–120 s during the exercise periods. Mean blood pressure (MAP) data were calculated as $MAP = \text{diastolic blood pressure} + 0.33 \times (\text{systolic blood pressure} - \text{diastolic blood pressure})$.

To manage risk, heart rate was measured using bedside monitor (BMS2401; Nihon Kohden, Tokyo, Japan).

All data are expressed as means ± SD. A two-way (intensity × time) repeated-measures ANOVA was used to determine the interaction and main effects of MdPF data, and ANOVA was used to identify the fatigue point. When ANOVA revealed significant interaction or main effects, a Tukey–Kramer test was performed for post hoc analyses to assess differences. A paired t-test was performed to compare rest and exercise periods at each intensity, and either ANOVA or the Welch test was used to compare intensities. When ANOVA or the Welch test revealed significant interaction or main effects, a Tukey–Kramer or Games–Howell test was performed for post hoc analyses to assess differences. Multiple regression analysis was used to determine

the contributions of peripheral factors to the respiratory, circulatory, and metabolic responses to brain blood flow (somatosensory cortex). To assess multicollinearity, multiple regression analysis was preliminarily assessed for the presence of the coefficient of correlation ($r \neq 1$) in the correlation coefficient matrix among independent variables. A variance inflation factor of >10 was considered to have no multicollinearity. The stepwise procedure was used to select the independent variable, the utility of which as determined by the stepwise procedure was $p < 0.05$ for multiple regression analysis in the ANOVA table and partial regression coefficient. The goodness of fit of the multiple regression analysis was confirmed by the coefficient of determination. The Durbin–Watson ratio and Shapiro–Wilk test were applied to analyze residual error, which was calculated by subtracting exercise from rest, although deoxy-Hb values were based on the change ratio. Statistical analysis was performed using SPSS 16.0 J for Windows (SPSS Japan Inc., Tokyo, Japan). For all analyses, the significance level α was set at $p < 0.05$.

RESULTS

Heart rate in this study was 59.4 ± 7.21 bpm at rest, 66.1 ± 7.73 bpm at 10% MVC, 74.6 ± 8.85 bpm at 30% MVC, and 96.4 ± 13.56 bpm at 50% MVC, suggesting that handgrip exercise was safely performed. Static handgrip induced significant changes in all physiological and clinical parameters measured in this study, but with variable sensitivity and response to increasing MVC (Table 1). With respect to physiological parameters, mean blood pressure was significantly elevated at all intensity levels, and linearly increased with MVC. Respiratory quotient was less sensitive to handgrip exercise, as 30% MVC was required to detect significant increases. Furthermore, the values were significantly higher at 50% MVC than at 30% MVC. Accordingly, this protocol was sufficient to raise the mean blood pressure and respiratory quotient to maximum values of 144% and 158%, respectively.

The extensor carpi radialis longus experienced significant fatigue during handgrip exercise (Table 1). The amplitude of muscle contraction increased by threefold and fourfold when exercise intensity was increased to 30% and 50%

Table 2. Impact of exercise intensity on power frequency (N = 11)

	Rest	30 s	60 s	90 s	120 s
10% MVC	86.6 ± 21.85	85.6 ± 24.35	84.4 ± 25.33	79.6 ± 23.23	77.6 ± 23.96
30% MVC	93.5 ± 28.47	83.8 ± 22.19	74.5 ± 24.22	69.4 ± 27.31	59.4 ± 19.29*
50% MVC	83.0 ± 24.44	68.6 ± 19.32	60.9 ± 19.94	54.9 ± 26.46*	52.2 ± 22.25**

Values are expressed as the mean ± SD. The median power frequency is presented in hertz. MVC, maximal voluntary contraction. * $p < 0.05$ compared with rest. # $p < 0.05$ compared with 10% MVC.

MVC, respectively. However, the subjects exhibited a 37% decrease in median power frequency at both 30% and 50% MVC intensity. This measure of muscle fatigue was supported by the linear and significant decrease in blood oxygenation level detected with increasing exercise intensity. Deoxy-Hb levels were threefold higher during 50% MVC handgrip exercise compared with 10% MVC handgrip exercise, suggesting a significant decrease in peripheral blood flow. Finally, blood lactate concentrations increased significantly by 15% and 50% above baseline under 30% and 50% MVC, respectively. Taken together, these data show that subjects experienced considerable muscle fatigue during static handgrip exercises.

The most remarkable response to handgrip exercise was recorded in the brain, where the levels of oxy-Hb increased by 68-fold and 207-fold when the intensity was raised from 10% to 30% MVC and from 30% to 50% MVC, respectively. This indirect measure of cerebral blood flow highlights the tremendous impact of a simple handgrip on the brain.

Median power frequency, a decline in which indicates muscle fatigue³¹, was measured at rest and at different time points during the 120-s handgrip sessions at each exercise intensity. Table 2 shows that the median power frequency remained stable during 10% MVC exercise, while values gradually decreased over time at 30% MVC and became statistically significant at the 120-s time point ($p < 0.05$). The highest exercise intensity caused a similar decline, which was significant at both the 90-s and 120-s time points, for a maximal decrease of 37%. Taken together, these data suggest that 30% and 50% MVC caused muscle fatigue.

The independent variables departed from normality and did not exhibit a frequency bias. Thus, we did not convert the independent variables to dummy variables. Furthermore, the correlation matrix of the independent variables did not exist at $r > 0.9$ or < -0.9 . Thus, all data were used as independent variables. Multiple regression analysis of 10% MVC did not identify any variables. Multiple regression analysis of 30% MVC data indicated that deoxy-Hb in the muscle blood flow was a significant contributor to blood flow in the somatosensory cortex, with a standardized partial regression coefficient of -0.636 , r^2 of 0.40, and a Durbin-Watson ratio of 2.818; the Shapiro-Wilk test of residual error was $p < 0.05$. At 50% MVC, blood lactate concentrations were significant contributors to blood flow in the somatosensory cortex, and the standardized partial regression coefficients of these relationships were 0.750. The r^2 was 0.562, the Durbin-Watson ratio was 2.027, and the Shapiro-Wilk test of residual error was $p < 0.05$. These data suggest that lactate accumulation during muscle fatigue may contribute to reduced blood flow to the brain.

DISCUSSION

The development of high-intensity training programs addressing muscle fatigue remains challenging due to the current poor understanding of the complex interactions between peripheral and central factors. The aim of our study was to determine whether circulating factors accumulating during exercise-induced muscle fatigue could stimulate activity in areas of the brain controlling muscle contraction. Our study established a selective and powerful positive relationship between circulating lactate and brain activity in the sensorimotor cortices.

Median power frequency in this study remained stable under 10% MVC but decreased by 37% under 30% and 50% MVC (Table 1). In addition, the median power frequency under 50% MVC decreased earlier than that under 30% MVC and by more than that under 10% MVC (Table 2). Based on the decline in median power frequency during muscle fatigue³¹, our results show that the greatest degree of muscle fatigue developed at 50% MVC. Muscle fatigue during a continuous submaximal isometric contraction performed at middle to high intensity ($>30\%$ MVC) can largely be explained by excitation-contraction coupling failure attributed to a change in Ca^+ metabolism³². The Ca^+ concentration has been demonstrated to control both muscle contraction and the rate of glycogenolysis³³. Also, muscle work is supported by glucose supply from glycogen, its concentration representing one step in pathways requiring a high rate of energy delivery or power³³. Thus, muscle fatigue occurs during sustained handgrip exercise when the Ca^+ concentration changes and glycogenolysis is enhanced. In this study, deoxy-Hb levels decreased with increasing exercise intensity, and blood lactate concentrations increased at 30% and 50% MVC, suggesting that these maximal voluntary contraction levels limited muscle blood flow and enhanced glycolysis, resulting in muscle fatigue in terms of muscle metabolism. In addition, brain blood flow increased by 68-fold at 30% MVC and 207-fold at 50% MVC compared with 10% MVC. A previous study reported that cerebral artery blood flow velocity is elevated by muscle ischemia¹⁴, and output of brain activity increased to reinforce muscle contraction during submaximal fatigue muscle contraction¹⁷. Thus, at 30% MVC, brain blood flow increased as a result of increased motor unit recruitment because muscle fatigue was induced. At 50% MVC, muscle ischemia affects the increase in brain blood flow because of decreased muscle blood flow. In this study, static handgrip exercise altered the physiological and clinical parameters, causing muscle fatigue.

At 30% MVC, we found that muscle fatigue occurred at

120 s and that muscle blood flow was a significant contributor to brain blood flow. Although r^2 was 0.40, which is lower than the value generally considered ideal (0.5) for multiple regression analysis, the aim of our study was simply to examine the degree of effect on the dependent variable. Deoxy-Hb levels were twofold higher under 30% MVC handgrip exercise than under 10% MVC handgrip exercise, suggesting a decrease in peripheral blood flow. Also, blood lactate concentration and respiratory quotient increased significantly, by 15% and 26% above baseline, respectively, at 30% MVC. Because reduced blood flow does not affect exercise-induced fatigue¹⁰, our findings show that alteration of muscle metabolism by reduced blood flow could have a role in conveying fatigue information to the brain.

Exercise at 50% MVC also caused muscle fatigue and exhibited the highest elevations in blood lactate concentration, blood pressure and respiratory exchange ratio. Furthermore, blood lactate levels were significant contributors to brain blood flow ($r^2 = 0.56$). In addition, the standard partial regression coefficients for blood lactate, which indicate the degree of effect of the dependent variable, were 0.75, suggesting that lactate level affected brain blood flow. This may be related to the fact that blood lactate concentration during exercise exhibited the greatest increase at this intensity. Lactate was reported to play a role in the sensation of pain²² and metaboreflex²³ via groups III and IV muscle afferents. At 50% MVC, we observed an elevation in blood lactate concentration and evidence of metaboreflex. It was also reported that muscle pain is associated with reduced performance³⁴, while groups III and IV muscle afferents contribute to ventilator and cardiovascular responses to rhythmic exercise³⁵. Furthermore, elevated blood lactate was shown to increase motor cortex excitability²⁴. As the somatosensory cortex is modulated by the premotor cortex during voluntary movements³⁶, activation of the somatosensory cortex in the present study may have resulted from lactate accumulation. Thus, lactate is likely the most important peripheral factor measured in our study. Taken together, physical adaptation to the lactate-related fatigue mechanism during exercise may be important for enhancing aerobic capacity.

There are certain limitations in this study. The NIRS technique assessed the surface of the cortex immediately beneath the probe, had a relatively low spatial resolution, and may have simultaneously measured both brain activation and skin blood flow of the scalp. Furthermore, because skin blood flow can be affected by sudor during exercise, we selected a static exercise (sustained handgrip exercise) to exclude these effects. Use of a sustained handgrip exercise may not be directly comparable with other types of exercise such as walking and pedaling. Future studies are required to examine in more detail the fatigue mechanism by which lactate accumulation conveys fatigue-related information to the brain during other forms of exercise. Finally, as the intent to exercise was reported to influence cerebral metabolism¹³, this may have contributed to the brain blood flow changes observed in our study.

In conclusion, we found that blood lactate concentration reflects muscle metabolism, rather than respiratory and cir-

culatory responses, and that muscle activity might convey fatigue-related information to the brain during load intensity when muscle fatigue occurs. Furthermore, with increasing load intensity, lactate may be increasingly important in this process. This signaling system may be important for enhancement of aerobic capacity achieved by physical adaptation to fatigue to increase muscle metabolism.

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