Influence of Cerebrovascular Arteriosclerosis on Cerebral Oxygenation During Exercise

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Background Although it is assumed that cerebral oxygenation during exercise is influenced by both cardiopulmonary function and cerebrovascular arteriosclerosis, the latter factor has not been fully clarified. In the present study the relationship between the degree of cerebrovascular arteriosclerosis and cerebral oxygenation during exercise was investigated.

Methods and Results A total of 109 patients (69 patients with coronary artery disease, 40 patients with hypertensive heart disease) (61.7±9.7 years) performed a symptom-limited exercise test with respiratory gas measurements (CPX). From the respiratory gas analysis, peak O2 uptake (VO2), the slope of the increase in VO2 to the increase in work rate (ΔVO2/ΔWR), and the slope of the increase in ventilation to the increase in CO2 output (VE/VCO2 slope) were calculated. Oxyhemoglobin (O2Hb) at the forehead was monitored using near-infrared spectroscopy. The brain ischemic score was counted based upon fluid-attenuated inversion recovery images of magnetic resonance imaging and expressed from 0 to 4. When compared with patients with a lower ischemic score (<2, n=67), those with a higher ischemic score (≥2, n=42) had a lower increase in brain O2Hb during exercise (-1.08±2.7 vs 0.77±4.1 μmol/L, p=0.011). Of brain ischemic score, left ventricular ejection fraction, peak VO2, ΔVO2/ΔWR, and the VE/VCO2 slope, ΔVO2/ΔWR was found to be the sole independent index determining cerebral O2Hb during exercise. The CPX parameters were also significantly related to the degree of cerebrovascular arteriosclerosis.

Conclusions Although cerebral oxygenation during exercise is mainly related to cardiopulmonary function, the degree of cerebrovascular arteriosclerosis partly influences cerebral oxygenation in patients with risk factors for atherosclerosis. (Circ J 2007; 71: 782–787)

Key Words: Brain; Cerebrovascular circulation; Exercise

In the resting condition, complex compensatory mechanisms are believed to adequately regulate blood flow to vital organs, especially to the brain. However, during exercise, the O2 demand by muscle cells increases tremendously compared with rest. To meet this sudden increase in O2 demand, a convergence of blood flow to the exercising muscles occurs, leading to relative hypoperfusion of other organs.

Recently, we evaluated the change in cerebral oxygenation during exercise in cardiac patients, by measuring cerebral oxyhemoglobin (O2Hb) with a near-infrared spectroscopy (NIRS) system. In that study, we found that the level of cerebral O2Hb during exercise was significantly related to the indexes of cardiopulmonary exercise testing (CPX), which reflect the increase in cardiac output (CO) during exercise. It was found that cerebral O2Hb even decreased during exercise in approximately half of the patients, especially in those with a lower left ventricular ejection fraction (LVEF). Those findings suggest that cerebral oxygenation during exercise is dependent, at least in part, on cardiac function during exercise.

Cerebral oxygenation must be influenced not only by cardiac function, but also by the degree of cerebrovascular arteriosclerosis. However, the contribution of the latter factor has not been fully clarified. Patients with cerebrovascular arteriosclerosis may not necessarily develop cerebral hypoperfusion at rest, but cerebral hypoperfusion may easily occur in these patients during high-intensity exercise.

In the present study, we hypothesized that the presence of cerebrovascular disease influences cerebral oxygenation during exercise. In order to test this hypothesis, we firstly selected patients with coronary artery disease (CAD) and those with high blood pressure (BP), because both diseases are significant risk factors for cerebrovascular arteriosclerosis. In these subjects, we investigated the relationship between the degree of cerebrovascular arteriosclerosis and cerebral O2Hb during maximal exercise. In addition, we evaluated whether the parameters of cardiopulmonary function during exercise have any association with the degree of cerebrovascular arteriosclerosis in these patients.

Methods

Study Patients
We consecutively enrolled 69 patients with CAD and 47 patients with high BP into the study (age 61.7±9.7 years; male/female 88/21). CAD was diagnosed by the presence of significant coronary stenosis defined as ≥75% reduction in the coronary lumen size.
in the luminal diameter of coronary vessels or the presence of a myocardial infarction (MI)\textsuperscript{4} Among the 69 patients who were categorized as having CAD, 34 had a previous MI. In all, 3 subjects were in atrial fibrillation. Any patient who could not perform the exercise testing because of physical limitation was not included. Those with a cerebrovascular disease diagnosed based on clinical documentation were also excluded. Medications influencing hemodynamic variables included calcium-channel blockers prescribed in 62 cases, \(\beta\)-blockers in 36 cases, nitrates in 31 cases, angiotensin-receptor blockers in 27 cases, diuretics in 18 cases, angiotensin-converting enzyme inhibitors in 9 cases, and digitalis in 1 case. The institution’s human subjects committee approved the study protocol. The purposes and risks of the study were explained to the subjects, and informed consent was given by each.

**Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA)**

MRI and MRA were performed using a 1.5 T Magnetom Symphony Sonata (Siemens, Germany). Based upon fluid-attenuated inversion recovery (FLAIR) MRI images, a brain ischemic score from 0 to 4 was given as follows: 0 for no abnormal signals, 1 for several small abnormal signals, 2 for about 10 small abnormal signals, 3 for 10s of punctate or mucular abnormal signals, and 4 for many abnormal signals spread out to some extent (Fig 1). In 105 of the 109 patients, the degree of cerebral artery stenosis was evaluated using MRA and expressed from 1 to 3: score 1 was defined as no significant abnormality, score 2 was defined as a suspected abnormality, and score 3 was defined as an apparent abnormality.

**Exercise Testing**

An incremental symptom-limited maximal exercise test was performed using an upright, electromagnetically braked cycle ergometer (Corival 400; Lode; Groningen, Holland). After beginning with a 4-min warm-up at 20 W of 60 rpm, the exercise load was increased incrementally by 1 W every 6 s (10 W/min). ECG was monitored continuously during the test (System ML-6500; Fukuda Denshi Co Ltd, Tokyo, Japan). Cuff BP was measured at rest on the cycle ergometer and once every minute during the exercise test using an automatic indirect manometer (STBP-780; Nippon Colin Co Ltd, Komaki, Japan)\textsuperscript{5}.

**NIRS Monitoring**

Cerebral oxygenation was monitored using a commercially available NIRS system (NIRO-300, Hamamatsu Photonics KK, Hamamatsu, Japan). The methodology of this system has been described in detail in previous reports\textsuperscript{3,6–11} A probe holder containing an emission probe and detection probe was attached to the left side of the forehead with a distance of 5 cm between the probes. The NIRO-300 measures the changes in the concentration of \(\text{O}_2\text{Hb}\) using a modified Beer-Lambert law\textsuperscript{8,10} It expresses the changes as an absolute unit (\(\text{mmol/L}\)) by incorporating an optical path length, assuming that the initial value is “0”. For the brain, this path length is 30 cm when the distance between the emission probe and detection probe is set at 5 cm\textsuperscript{6,12} \(\text{O}_2\text{Hb}\) was measured every 2 s from 4 min before the start of exercise until the end of exercise.

\(\text{O}_2\text{Hb}\) at rest was determined as the average of the values obtained as the subjects rested on the ergometer over a 4-min period before the start of the exercise test. \(\text{O}_2\text{Hb}\) at peak exercise was defined as the average value obtained during

**Fig 1.** Brain ischemic score, based on fluid-attenuated inversion recovery (FLAIR) images from magnetic resonance imaging and quantified on a scale from 0 to 4.
the last 30 s of incremental exercise. The change in O2Hb during exercise (ΔO2Hb) was defined as the peak exercise value – resting value.

Respiratory Gas Analysis

The O2 uptake (VO2), CO2 output (VCO2), and minute ventilation (VE) were measured throughout the test using an Aeromonit AE-300S (Minato Medical Science, Osaka, Japan). Prior to calculating the parameters from respiratory gas analyses, a 5-point moving average of the breath-by-breath data was obtained. Peak VO2 was defined as the average value obtained during the last 15 s of incremental exercise. The slope of the increase in VO2 to the increase in the work rate (ΔVO2/ΔWR) was calculated from the data recorded between 30 s after the start of incremental exercise to 30 s before the end of the exercise by least squares linear regression. The slope of the increase in ventilation to the increase in CO2 output (VE/VCO2 slope) was calculated from the start of incremental exercise to the respiratory compensation point by least squares linear regression, as previously described.2,15

Statistical Analysis

Data are presented as the mean±SD. The unpaired t-test was used to compare variables between subjects with a lower ischemic score in the brain (<2, n=67) and those with a higher ischemic score (≥2, n=42). A stepwise multivariate regression model was used to select an independent predictor of cerebral O2Hb during exercise. Linear regression analysis was used to correlate the measured variables. A p-value of less than 0.05 was considered statistically significant for all comparisons.

Results

The LVEF measured by echocardiography was 61.4±14.5%, on average. The brain ischemic score calculated from FLAIR-MRI was, on average, 1.4±1.1; 26 patients with a score of 0, 41 with a score of 1, 25 with a score of 2, and 6 with a score of 3. The degree of cerebral artery stenosis on MRA was, on average, 1.4±0.7; 41 patients with a score of 0, 25 with a score of 1, 15 with a score of 2, and 2 with a score of 3. Heart rate was 73.8±14.0 beats/min at rest and increased to 137.6±22.2 beats/min at peak exercise. Systolic and diastolic BPs also increased from 132.1±21.5 mmHg to 200.9±36.2 mmHg, and from 78.9±13.9 mmHg to 112.7±35.6 mmHg, respectively. The maximal work rate attained during incremental exercise was 112.7±35.6 W.

In Table 1, the degree of cerebral artery stenosis on MRA is shown for the 2 groups of patients with a lower or higher ischemic score (<2 vs ≥2). Patients with a higher ischemic score had a significantly higher degree of cerebral artery stenosis (1.6±0.7 vs 1.3±0.5, p=0.014). The ΔO2Hb at the forehead during exercise (Fig 2) was –1.08±2.7 μmol/L in patients with a higher ischemic score, which was significantly lower than those with a lower ischemic score (0.77±4.1 μmol/L, p=0.011). The O2Hb during exercise even decreased in 29 of 42 patients with a higher ischemic score. There was a weak, but significant negative correlation between ΔO2Hb during exercise and the brain ischemic score (r=–0.20, p<0.05), showing lower or even negative values for ΔO2Hb in patients with a higher brain ischemic score.

By stepwise multivariate regression analysis, including the brain ischemic score, LVEF, peak VO2, ΔVO2/ΔWR, and the VE/VCO2 slope, ΔVO2/ΔWR was found to be the sole independent index determining cerebral O2Hb during exercise in all patients. The ischemic score from the FLAIR-MRI images was found to be an insignificant variable determining cerebral ΔO2Hb. Similarly, in the patients with a lower ischemic score (<2), ΔVO2/ΔWR was found to be the sole independent index determining cerebral O2Hb during exercise by this analysis. In the patients with a higher ischemic score (≥2), VE/VCO2 slope was the sole independent index determining cerebral O2Hb.

Figs 3 and 4 show the comparison of cardiopulmonary indexes between patients with a higher brain ischemic score and those with a lower ischemic score. The former had a significantly lower LVEF than the latter (57.3±17.4 vs 63.8±11.8%, p=0.025). The CPX parameters were also significantly related to the degree of cerebrovascular atherosclerosis. Patients with a higher brain ischemic score had a significantly lower peak VO2 (19.0±5.3 vs 24.0±5.9 ml·min⁻¹·kg⁻¹, p<0.0001), a lower slope of ΔVO2/ΔWR (9.6±2.1 vs 10.8±1.6 ml·min⁻¹·W⁻¹, p=0.0008), and a higher VE/VCO2 slope (33.2±6.8 vs 29.1±4.8, p=0.0004).

Table 1 Score of Cerebral Artery Stenosis

<table>
<thead>
<tr>
<th>Score of cerebral artery stenosis</th>
<th>FLAIR score</th>
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<tr>
<td></td>
<td>&lt;2 (n=63)</td>
</tr>
<tr>
<td>1</td>
<td>n=46</td>
</tr>
<tr>
<td>2</td>
<td>n=15</td>
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<td>3</td>
<td>n=2</td>
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The score of cerebral artery stenosis on magnetic resonance angiography in patients with a lower ischemic score (<2) and those with a higher ischemic score (≥2). The ischemic score was based fluid-attenuated inversion recovery (FLAIR) images from magnetic resonance imaging.
Until recently, information on cerebral circulation has been difficult to obtain, especially during exercise. Although transcranial Doppler ultrasound is used to evaluate cerebral hemodynamics, the measurement of cerebral blood flow velocity with this technique inaccurately reflects the actual blood flow during dynamic exercise. The recent development of NIRS has expanded the diagnostic potential for tissue oxygenation.6–10,19,20

Previously, we reported that cerebral oxygenation during exercise, as reflected in $O_2Hb$ measured by NIRS attached to the forehead, is dependent on both the cardiovascular and pulmonary systems.3,11 Quite recently, we compared the decreased level of $O_2Hb$ at the forehead during exercise in patients with left ventricular dysfunction with that in subjects who had experienced reduced consciousness caused by a sudden drop in BP induced by a parasympathetic reflex or sustained ventricular tachycardia.21 We found that the decreases in these indexes during exercise in some patients were comparable to those in subjects who experienced reduced consciousness, which suggests that the indexes of cerebral oxygenation may drop to levels low enough to affect the level of consciousness during maximal exercise in patients with severe left ventricular dysfunction.

In the present study, we found that cerebral $O_2Hb$ during exercise is also partly related to the degree of cerebrovascular arteriosclerosis. We found that the indexes of CPX, which reflect the increase in CO during exercise and the severity of cardiovascular disease, are related to the degree of cerebrovascular arteriosclerosis in our subjects. Patients with advanced cerebral arteriosclerosis had a decreased exercise capacity in addition to a lower LVEF.

**Indexes of CPX Testing**

Peak $\dot{V}O_2$ is normally determined by maximum CO during exercise, and correlates well with the degree of hemodynamic abnormality in patients with cardiovascular disease. The $\dot{V}E/\dot{V}CO_2$ slope, which ranges from approximately 24–34 in normal subjects becomes steeper with the severity of heart failure. The slope of $\Delta\dot{V}O_2/\Delta WR$ reflects the rate of increase in CO during incremental exercise. $\Delta\dot{V}O_2/\Delta WR$ is
approximately 10 ml·min\(^{-1}\)·W\(^{-1}\) in healthy subjects\(^{30}\) and is known to fall to progressively lower levels in heart disease patients as the disease worsens\(^{30–32}\). In the present study, patients with a higher brain ischemic score were found to have a lower LVEF, peak VO\(_2\), and ΔVO\(_2\)/ΔWR and a higher VE/VCO\(_2\) slope, implying that the degree of cerebrovascular disease has an association with the severity of cardiac disease, which can be attributed to the fact that both diseases have the same pathological origin (ie, vascular atherosclerosis). In addition, the presence of cerebrovascular disease may cause a decrease in the performance of activities of daily living, and subsequently the decreased exercise capacity reflected in peak VO\(_2\).

**Rationale of Measuring Tissue Oxygenation by NIRS**

NIRS uses non-damaging doses of near-infrared radiation in the wavelength range from 700 to 1,000 nm\(^{20}\) in which hemoglobin displays O\(_2\)-dependent absorption characteristics. Thus, hemoglobin can be noninvasively detected by NIRS\(^{20}\). NIRS is now being used as a noninvasive tool for monitoring cell metabolism, cerebral hemodynamics, and O\(_2\) transport to tissues\(^{3,20}\). When NIRS is attached to the forehead, the emitted laser light passes through the skull and is dispersed through the brain tissue. It measures brain tissue oxygenation locally, at a depth of approximately 1 cm from the brain surface just under the attachment area. Previous reports have already confirmed the reproducibility of cerebral O\(_2\)Hb measurements during exercise with this technique. In 2004, we compared ΔO\(_2\)Hb at the forehead between 2 incremental symptom-limited exercise tests in 12 patients with stable chronic heart disease and there was good reproducibility in the measurements\(^{3}\).

**Factors Controlling Cerebral Oxygenation During Exercise**

The results of our previous investigations indicated that cerebral oxygenation is mainly dependent on cardiopulmonary function during exercise\(^{5,11}\). In the present study, ΔVO\(_2\)/ΔWR, which reflects the increase in CO during exercise, was found to be the sole independent index determining cerebral O\(_2\)Hb during exercise. The present findings confirm our previous studies and further indicate that cerebral oxygenation during exercise is partly related to the degree of cerebrovascular disease.

**Study Limitations**

In the present study, we found that the increase in cerebral O\(_2\)Hb during exercise was significantly lower in patients with a higher brain ischemic score than in those with a lower ischemic score. However, we cannot exclude the possibility that the lower increase, or even a decrease in cerebral O\(_2\)Hb during exercise, in patients with a higher brain ischemic score is not the result of cerebral arteriosclerosis, but from coincidental cardiovascular disease. Patients with cerebral arteriosclerosis often have cardiovascular disease, and the degree of cerebral arteriosclerosis would be related to the severity of that cardiovascular disease. Thus, because of coincidental cardiovascular disease, patients with advanced cerebral arteriosclerosis might have an impaired increase in CO during exercise, thereby causing cerebral hyperperfusion.

In addition to cardiopulmonary function, systolic BP also plays an important role in regulating cerebral oxygenation via the control of cerebral blood flow. Another partial determinant of cerebral oxygenation is the level of PaCO\(_2\). A falling PaCO\(_2\), for example, leads to decreases in cerebral blood flow. We assume that the decrease in cerebral O\(_2\)Hb during exercise in patients with left ventricular dysfunction reflects a cerebral hypoxemia caused by an impaired O\(_2\) transport to the brain. However, the wide variation of cerebral O\(_2\)Hb, including the apparent increase in O\(_2\)Hb in some subjects (Fig 2), might be partly attributed to the changes in systolic BP and PaCO\(_2\) during exercise.

The relatively weak correlation between cerebral O\(_2\)Hb during exercise and the degree of cerebrovascular arteriosclerosis might be caused by locality of the measurement of cerebral O\(_2\)Hb (ie, the left frontal lobe). In the present study, we selected subjects who could easily perform a bicycle exercise, excluding those with clinically manifest cerebrovascular disease. In order to confirm our present findings on the relationship between cerebral oxygenation during exercise and the brain ischemic score, a future study of subjects with more advanced cerebrovascular disease is necessary. It has to be determined in the future study if the measurement of cerebral O\(_2\)Hb during exercise can be used to predict the degree of cerebrovascular disease.

**Conclusions**

Although cerebral oxygenation during exercise is mainly related to cardiopulmonary function, the degree of cerebrovascular arteriosclerosis partly influences cerebral oxygenation in patients with risk factors of atherosclerosis.

**References**


