Effects of Supplemental O2 Inhalation on Cerebral Oxygenation During Exercise in Patients With Left Ventricular Dysfunction

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Background  It has been recently reported that cerebral oxyhemoglobin (O2Hb) decreases during exercise in nearly 50% of patients with dilated cardiomyopathy. The present study evaluated whether the inhalation of supplemental O2 diminishes the decrease in cerebral O2Hb during exercise.

Methods and Results  Ten patients with a left ventricular ejection fraction <50% and a clearly observable decrease in cerebral O2Hb during preliminary exercise testing underwent 2 additional symptom-limited incremental exercise tests: 1 while breathing room air (control) and the other while breathing 50% O2. In the latter test, the switch from room air to 50% O2 was performed, on average, at 43.0±14.2 W. Cerebral O2Hb was continuously monitored during exercise using near-infrared spectroscopy. In the control exercise test, cerebral O2Hb gradually decreased as the work rate increased in all the subjects. When the subjects breathed 50% O2, this decrease in cerebral O2Hb was diminished. The change in cerebral O2Hb from rest to peak exercise during the test under 50% O2 was significantly higher than that during the control test (t -0.23±1.89 vs –2.47±1.57 μmol/L, p=0.002). Similarly, the change in the cerebral tissue oxygenation index was significantly higher in the test under 50% O2 (0.45±4.46 vs –3.33±3.06%, p=0.023).

Conclusions  Impaired cerebral oxygenation during moderate to heavy intensity exercise in patients with left ventricular dysfunction can be offset by breathing supplemental O2. (Circ J 2007; 71: 1418–1423)

Key Words:  Brain; Cerebrovascular circulation; Exercise; Oxygen inhalation

Cerebral blood flow is believed to be regulated exclusively by complex compensatory mechanisms1,2 assumed to be adequate even during exercise, when the demand for blood flow in the muscles dramatically increases. However, this may not be the case in cardiac patients with left ventricular (LV) dysfunction3,4. Our group recently studied cerebral oxygenation during exercise in patients with dilated cardiomyopathy3 using near-infrared spectroscopy (NIRS) to continuously measure the change in cerebral oxyhemoglobin (O2Hb) during exercise. As a result, we found that nearly 50% of the patients exhibited decreases in cerebral O2Hb during exercise, and the rate was even higher among those with lower LV ejection fraction (LVEF). Cerebral O2Hb, a parameter that initially remained constant at lower work rates during incremental exercise, began to decrease at higher work rates.

Our recent findings strongly suggested that the decrease in cerebral O2Hb during exercise in patients with LV dysfunction reflected cerebral hypoxia resulting from impaired O2 transport to the brain.3,4 If this is the case, inhalation of high O2 during exercise may be beneficial by raising PaO2 and consequently improving cerebral tissue oxygenation. We tested this hypothesis by selecting patients with LV dysfunction who showed decreased cerebral O2Hb during incremental exercise and evaluating whether this exercise-induced decrease in cerebral O2Hb was attenuated when the patients inhaled supplemental O2.

Methods

Study Patients  We enrolled 10 consecutive patients with LV dysfunction (LVEF <50%) at the Cardiovascular Institute, who clearly demonstrated decreased cerebral O2Hb during preliminary incremental exercise testing, and who voluntarily consented to participate in the study (Table 1). The diagnoses included idiopathic dilated cardiomyopathy in 6 patients and ischemic cardiomyopathy in 4 patients. Ischemic cardiomyopathy was diagnosed by the presence of significant coronary stenosis defined as ≥75% reduction in the luminal diameter of the coronary vessels or the presence of myocardial infarction3. Patients with cerebrovascular disease diagnosed based on clinical documentation and those with documented lung disease were excluded from the study. All patients were confirmed to be free of significant stenosis in major cerebral arteries by brain magnetic resonance angiography (MRA). Medications influencing hemodynamic variables included diuretics prescribed in 9 cases, β-blockers in 8, digitalis in 3, angiotensin-converting enzyme inhibitors in 3, angiotensin-receptor blockers in 3, nitrates in 3, and calcium-channel blockers in 1. The protocol was approved by the Human

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Subjects Committee of the Cardiovascular Institute. The purposes and risks of the study were explained to the patients, and written informed consent was given by each.

**Exercise Testing**

The subjects performed 2 exercise tests in randomized order on different days: 1 while breathing room air (control) and the other while breathing 50% O2. All patients were clinically stable, and the medications were not altered during the study period. Both tests were performed to the symptom-limited maximum using an upright, electromagnetically braked cycle ergometer (Corival 400; Lode, Groningen, the Netherlands). After a 4-min warm-up at 20 W (60rpm), the exercise load was increased incrementally by 1 W every 6 s (10 W/min). The subjects breathed through a face mask attached to a Hans-Rudolph 2-way valve. In the test with 50% O2, the subjects commenced with normal air and were switched to 50% O2 without notification when they reached the work rate at which cerebral O2Hb had begun to decrease in the preliminary exercise test.

The ECG was monitored continuously during the exercise tests using a System ML-6500 (Fukuda Denshi Co Ltd, Tokyo, Japan). Cuff blood pressure was measured at rest on the left side of the forehead with a distance of 5 cm between the probes. The methodology of this system has been described in previous reports.14-18 NIRS attached at the forehead measures brain tissue oxygenation at a depth of approximately 1 cm from the brain surface.15,16 The NIRO-300 measures the concentration changes of O2Hb and deoxyhemoglobin (HHb) using the modified Beer-Lambert law.16,18 It expresses the magnitude of the changes in O2Hb and HHb as an absolute unit (nmol/L) by incorporating an optical pathlength, assuming that the initial value is “0”. For the brain, this pathlength is 30 cm when the distance between the emission probe and detection probe is set at 5 cm.14,19 The NIRO-300 also measures a tissue oxygenation index [TOI; ie, O2Hb/(O2Hb+HHb)×100%], using a method based on photon diffusion theory.16,20 O2Hb, HHb, and TOI were measured every 2 s from 4 min before the start of exercise until the end of exercise.

Variables of NIRS at rest were determined as the averages of values obtained as the subjects sat on the ergometer for 4 min before the start of the exercise test. Each variable during incremental exercise was calculated every 5 W as a 30-s average. Each variable at peak exercise was defined as the average value obtained during the last 30 s of incremental exercise. The change in each variable during exercise was defined as the peak exercise value—resting value.

**Statistical Analysis**

Data are presented as the mean±SD. The paired t-test was used to compare variables between the control test and test under 50% O2. A p-value of less than 0.05 was considered statistically significant for all comparisons.

**Results**

Table 1 shows the hemodynamic and respiratory gas variables in the subjects. LVEF was 33.1±10.5% and LV diastolic and systolic dimensions were 61.8±13.4 mm and 52.2±14.0 mm, respectively. In the control exercise test,
peak VO₂, AT, and the maximal work rate were 16.2±4.2 ml·min⁻¹·kg⁻¹, 10.8±2.6 ml·min⁻¹·kg⁻¹, and 83.4±21.7 W, respectively. The peak VO₂ corresponded to 58.3±15.9% of the predicted peak VO₂, based on a normal Japanese population. The ΔVO₂/ΔWR, which reflects the increase in cardiac output during exercise and is approximately 10 ml·min⁻¹·W⁻¹ in healthy subjects, was 8.3±2.0 ml·min⁻¹·W⁻¹. The VE/VO₂ slope, which reflects heart failure severity and ranges from approximately 24 to 34 in healthy subjects, was 41.7±9.6.

Although there was no significant difference in the maximal heart rate between the control test and the test under 50% O₂ breathing, systolic blood pressure at peak exercise was significantly higher in the latter test (Table 2). Although the end-tidal PCO₂ did not significantly differ between the 2 tests in the resting condition, it was significantly higher in the test under 50% O₂ at peak exercise.

Fig 1 shows the NIRS variables during exercise for a representative subject (patient 8 in Table 1). This subject taking the control test exhibited decreases in oxyhemoglobin (O₂Hb) and tissue oxygenation index (TOI) noted during the control exercise test were attenuated by inhaling 50% O₂. HHb, deoxyhemoglobin.
average changes in \text{O}_2\text{Hb}, TOI, and HHb during exercise in 10 subjects. \text{O}_2\text{Hb} at the forehead gradually decreased with the increasing work rate in the control exercise test. In the test under 50% O\textsubscript{2}, the switch from room air to 50% O\textsubscript{2} was performed, on average, at 43.0±14.2 W (20–70 W, Table 1). The inhalation of 50% O\textsubscript{2} eliminated the decrease in \text{O}_2\text{Hb} at the forehead.

Fig 3A shows the change in \text{O}_2\text{Hb} at the forehead from rest to peak exercise (\(\Delta\text{O}_2\text{Hb}\)) in all subjects. The \(\Delta\text{O}_2\text{Hb}\) during the test under 50% O\textsubscript{2} was significantly higher than that during the control test (–0.23±1.89 vs –2.47±1.57 \text{mmol/L}, \(p=0.002\)). Similarly, the change in TOI at the forehead from rest to peak exercise (\(\Delta\text{TOI}\)) was significantly higher in the test under 50% O\textsubscript{2} (0.45±4.46 vs –3.33±3.06\%, \(p=0.023\), Fig 3B). On the other hand, there was no statistical difference between the 2 tests in the change in HHb (Fig 3C).

Discussion
A body at rest can usually maintain an adequate blood flow to the main organs, even with moderate LV dysfunction. During exercise, however, the sudden surge in the demand for O\textsubscript{2} by the muscle cells generates a tremendous increase in the blood flow to the muscles. Given that the blood flow to each organ is determined by cardiac output, increased distribution of blood flow to the muscle cells may result in relative hypoperfusion in other organs. As a consequence, cerebral circulation might become insufficient during exercise, especially in cardiac patients whose cardiac output fails to increase normally. In support of this hypothesis, we found in our previous study that the cerebral oxygenation during exercise in cardiac patients was strongly related to cardiopulmonary variables that reflect...
cardiac function during exercise. We also found that cerebral O$_2$Hb actually decreased during exercise in 43% of patients with dilated cardiomyopathy, indicating cerebral hypoperfusion in these patients.

We recently compared the decreased levels of O$_2$Hb and TOI at the forehead during exercise in patients with LV dysfunction with those in subjects who had experienced reduced consciousness because of a sudden drop in blood pressure induced by a parasympathetic reflex or sustained ventricular tachycardia. 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 LV dysfunction.

Based on these findings, we hypothesized that breathing high O$_2$ would raise the PaO$_2$ and subsequently improve cerebral oxygenation in patients with LV dysfunction. As expected, in the present study we found that breathing 50% O$_2$ diminished the decrease in cerebral O$_2$Hb in patients with reduced LVEF who had clearly demonstrated it during moderate to high intensity exercise while breathing room air.

**Mechanisms Determining Cerebral Oxygenation During Exercise**

In the present study, higher ∆O$_2$Hb and ∆TOI during exercise under 50% O$_2$ indicated an improvement in cerebral oxygenation, which probably resulted from increased PaO$_2$ and subsequent improvement in O$_2$ diffusion to the brain tissue. Cerebral oxygenation is determined by oxygen supply and oxygen demand. The decrease in O$_2$Hb and TOI at the forehead was therefore expected during maximal exercise in cardiac patients with LV dysfunction, because the decrease in O$_2$Hb was most important for oxygen supply. In the resting condition, patients with heart failure have reduced cerebral blood flow compared with normal subjects, and this has been shown to be normalized by cardiac transplantation. On the transition from rest to moderate exercise, global cerebral blood flow increases by 20–30% in both animals and humans. However, during maximal exercise, the recent investigation by González-Alonso et al indicated that blood flow to the brain declines, even in healthy subjects. They suggested impaired increase in cerebral output, reduction in cerebral perfusion pressure, and local factors relating to vasoconstrictor and/or vasodilator activities in the brain as possible mechanisms underlying this phenomenon. Thus, cerebral blood flow during maximal exercise would be more easily decreased in patients with LV dysfunction because of their insufficient increase in cardiac output. Probably because of the reduction in cerebral blood flow, cerebral O$_2$Hb decreased in the control exercise test of the present study.

Cerebral blood flow is determined by cerebral vessel resistance and perfusion pressure. Cerebral perfusion pressure is equal to the difference between arterial pressure and venous (right atrial) pressure. In cardiac patients with LV dysfunction, the level of venous pressure would be increased, especially during exercise, which might have decreased the level of cerebral perfusion pressure. Although the influence of O$_2$ inhalation on venous pressure during exercise is not well understood in cardiac patients, O$_2$ inhalation might have decreased it, thereby increasing cerebral perfusion pressure in some of the present patients, especially those with ischemic cardiomyopathy.

Although blood pressure maintenance is partly related to cardiac function, an attenuated increase in blood pressure during exercise impairs cerebral oxygenation, irrespective of the presence of cardiac disease. The higher systolic blood pressure at peak exercise in the test under 50% O$_2$ in the present study, which might be partly caused by hyperoxic vasoconstriction or by increased myocardial contractility in some patients with ischemic cardiomyopathy, might have been instrumental in improving the cerebral oxygenation.

Another possible determinant of cerebral oxygenation might be the level of PaCO$_2$ during exercise. Cerebral blood flow is known to positively correlate with PaCO$_2$: a decrease in PaCO$_2$ leads to cerebral hypoperfusion and a rise in PaCO$_2$ increases cerebral blood flow. Usually a 1-mmHg increase in PaCO$_2$ results in several percent increase in cerebral blood flow. In the present study, breathing 50% O$_2$ was found to raise end-tidal PCO$_2$ at peak exercise by 3 mmHg on average, a noninvasive parameter reflecting PaCO$_2$. This probably resulted from inhibition of the carotid body contribution to ventilatory drive and the increase in end-tidal PCO$_2$ must have been related to the improved cerebral oxygenation in the test under 50% O$_2$.

**Study Limitations**

It is known that inhalation of high O$_2$ concentration causes constriction of the cerebral vessels, which may nullify the favorable effects of a high PaO$_2$ on cerebral oxygenation. Thus, we selected 50% O$_2$ because this concentration seemed high enough to raise the PaO$_2$. There was no significant difference in the peak work rate between the control test and the test under 50% O$_2$. This finding is reasonable, given that acute increases in O$_2$ transport to the exercising muscles do not always improve exercise capacity in cardiac patients. Although we excluded patients with cerebrovascular disease from the present study, the decrease in O$_2$Hb during the control exercise might have at least partly stemmed from stenoses in small cerebral arteries that the brain MRA failed to detect.

In the present study, pulse oximetric saturation measured at the left earlobe near the NIRS probes did not decrease during the control exercise tests (Table 2), despite an apparent decrease in O$_2$Hb at the forehead. As in the case of the scalp and skull, the earlobe is perfused by an external carotid artery. If the decrease in O$_2$Hb at the forehead was caused by the change of extracranial circulation, pulse oximetric saturation had to decrease. We believe that the influence of extracranial information was negligible for the observed findings in O$_2$Hb in the present study. Exercise is known to activate certain brain areas, including the frontal cortex, thereby increasing oxygen demand and the levels of lactate and Hb in certain brain regions. These factors might have partly influenced our findings obtained from the NIRS during exercise.

**Clinical Implications**

Previous reports and our present findings suggest that patients with heart failure might have cerebral hypoperfusion during daily life. In a recent investigation using proton magnetic resonance spectroscopy to evaluate the cerebral metabolism of heart failure patients, Lee et al discovered abnormalities in patients with advanced heart failure. They speculated that this abnormality was chiefly attributable to cerebral hypoperfusion. Chronic impairment in cerebral oxygenation might lead to cognitive dysfunction and influence the activity, quality of life, and mortality of these patients.
Treatments that improve cardiac output during exercise might be capable of normalizing cerebral oxygenation in patients with decreased cerebral O$_2$Hb. Exercise training has recently been recommended in patients with chronic heart failure. Now that it is known that supplemental O$_2$ has recently been recommended in patients with chronic heart failure patients enrolled in exercise training, we may bestow favorable effects in patients with chronic obstructive pulmonary disease during exercise training, we may have to also consider supplemental O$_2$ in some chronic heart failure patients enrolled in exercise training.

Conclusions
Our present findings suggest that impaired cerebral oxygenation during moderate to heavy intensity exercise in patients with LV dysfunction can be offset by breathing supplemental O$_2$.

References