Clinical Significance of Cerebral Oxygenation During Exercise in Patients With Coronary Artery Disease

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Background Recent investigations have demonstrated that cerebral oxyhemoglobin (O₂Hb) decreases during exercise in patients with left ventricular dysfunction, reflecting a cerebral hypoxia. We sought to establish a prognostic value of decreased cerebral O₂Hb during exercise in cardiac patients, and to compare it with those of indexes obtained from cardiopulmonary exercise testing (CPX).

Methods and Results A total of 344 consecutive patients with coronary artery disease were enrolled in the study. All the patients performed CPX, during which cerebral O₂Hb was continuously monitored using near-infrared spectroscopy. There were 13 cardiac deaths and 78 cardiovascular events during the prospective follow-up period of 1,231±538 days. The change of O₂Hb measured at the forehead from rest to peak exercise (Δ O₂Hb) was significantly lower in non-survivors than in survivors (-1.5 ± 3.3 vs 1.7 ± 3.2 μ mol/L, $p=0.0004$). By multivariate Cox proportional hazards analysis, Δ O₂Hb and left ventricular ejection fraction (LVEF) were found to be independent prognostic markers for cardiac deaths. The Δ O₂Hb, LVEF and peak oxygen uptake were found to be significant prognostic markers for cardiovascular events, mainly for heart failure worsening and sudden cardiac death.

Conclusion The present findings suggest that a decrease in cerebral O₂Hb during exercise predicts future cardiovascular events in patients with coronary artery disease. (Circ J 2008; 72: 1852–1858)

Key Words: Brain; Cerebral oxygenation; Exercise

In resting conditions, complex compensatory mechanisms are believed to adequately regulate blood flow to vital organs, especially to the brain. During exercise, however, the O₂ demand of exercising muscles surges to levels 10–15 times higher than that in the resting condition. The blood flow to the exercising muscles increases tremendously to meet this sudden surge in O₂ demand, thereby leading to a relative hypoperfusion of other organs. Our group recently studied cerebral oxygenation during exercise using near-infrared spectroscopy (NIRS) in patients with left ventricular dysfunction.¹ We found, as a result, that nearly half of the patients exhibited decreases in the cerebral oxyhemoglobin (O₂Hb) during exercise, and that the decrease was more prominent in patients with a lower left ventricular ejection fraction (LVEF).¹ In these patients, cerebral O₂Hb, a parameter that initially remained constant at lower work rates during incremental exercise, began to decrease at higher work rates.^{1,2} The decrease in cerebral O₂Hb presumably reflected a cerebral hypoxia during exercise resulting from impaired O₂ transport to the brain.

While risk stratification of chronic heart disease had been primarily based on resting hemodynamic measurements,

cardiopulmonary exercise testing (CPX) has now become indispensable in singling out those patients with a poor prognosis. Among the parameters obtained from CPX, the peak O₂ uptake ($\dot{V}O_2$) is considered a gold standard for identifying patients with a poor prognosis and selecting candidates for cardiac transplantation.³ The ratio of the increase in ventilation ($\dot{V}E$) to the increase in CO₂ output ($\dot{V}CO_2$) during exercise ($\dot{V}E/\dot{V}CO_2$ slope) and the ratio of the increase in $\dot{V}O_2$ to the increase in work rate ($\Delta\dot{V}O_2/\Delta WR$) are also independent prognostic markers in cardiac patients.⁴

In 1999, Lee et al reported that cerebral metabolism measured by magnetic resonance spectroscopy is abnormally deranged in patients with heart failure.⁵ They also found that this abnormality is an independent predictor of mortality in these patients.⁶ The cerebral metabolic abnormality is assumed to be due to overall and/or local disturbances of cerebral blood flow, that is, impaired cerebral oxygenation.⁵ The impaired cerebral oxygenation can be detected by the non-invasive measurement of cerebral O₂Hb using NIRS, and the detection might be more sensitive during exercise in which the O₂ demand by exercising muscles increases tremendously, rather than measurements taken at rest. If the cerebral metabolic abnormality resulting from decreased cerebral O₂ transport is related to prognosis, the decrease in cerebral O₂Hb during exercise must also influence the prognosis.

In the present study, we sought to establish a prognostic value of decreased cerebral O₂Hb during exercise in cardiac patients. We selected patients with coronary artery disease, and compared the prognostic power of cerebral O₂Hb during exercise with those of established respiratory gas indexes obtained from CPX, as cerebral oxygenation depends on cardiopulmonary function during exercise.^{2,7}

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Methods

Study Patients

We prospectively evaluated 344 consecutive patients with stable coronary artery disease (65.0 ± 9.4 years). These patients performed CPX at the Cardiovascular Institute between February 2001 and August 2003. Coronary artery disease had been diagnosed by the presence of significant coronary stenosis defined as a $\geq 75\%$ reduction in the luminal diameter of coronary vessels or the presence of myocardial infarction diagnosed according to the World Health Organization criteria.⁸ Among these patients, 201 had previous myocardial infarction. Critical coronary stenosis considered inappropriate for performing CPX had been treated by percutaneous coronary intervention and/or coronary artery bypass graft surgery prior to CPX according to current therapeutic guidelines. Patients with orthopedic difficulty in pedaling a cycle ergometer and those with cerebrovascular disease diagnosed based on clinical documentation were excluded from the study. The protocol was approved by the Human Subjects Committee of the Cardiovascular Institute. Its purposes and risks were explained to each patient, and informed consent was obtained from all of them.

Follow-up

After the CPX, patients were prospectively followed up at the outpatient clinic of the Cardiovascular Institute. The primary endpoint was defined as cardiac death. Causes of cardiac death were categorized into acute myocardial infarction, progressive heart failure and sudden cardiac death. Sudden cardiac death was diagnosed according to published criteria.⁹ The secondary endpoint was defined as a composite of a worsening of angina pectoris requiring hospitalization, new acute myocardial infarction, a worsening of heart failure requiring hospitalization and cardiac death: only the first event in each patient was included in this analysis.

Exercise Testing

An incremental symptom-limited exercise test was performed using an upright, electromagnetically braked cycle ergometer (Corival 400, Lode, Holland). Exercise began with a 4-min warm-up at 0 W or 20 W at 60 rpm, with the load then being increased incrementally by 1 W every 6 s (10 W/min). The electrocardiogram 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 cycle ergometer and then every minute during exercise testing with an automatic indirect manometer (STBP-780; Nippon Colin Co Ltd, Aichi, Japan). Through a rubber mask attached to the subject's face, breath-by-breath $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ were measured during the test using an AE-300S Respiromonitor (Minato Medical Science, Osaka, Japan), as previously described.¹⁰

Respiratory Gas Analysis

Prior to the calculation of the parameters from respiratory gas analyses, a 5-point moving average of the breath-by-breath data was performed. The peak $\dot{V}O_2$ was defined as the average values obtained during the last 15 s of incremental exercise. The $\dot{V}E/\dot{V}CO_2$ slope was calculated from the start of incremental exercise to the respiratory compensation point by a least-squares linear regression.⁴ The respiratory compensation point was determined through the following criteria: (1) the ratio of $\dot{V}E$ to $\dot{V}CO_2$ starts to increase after a period of decrease or stasis; and (2) the PETCO₂ starts to

decrease after a period of stasis. When the respiratory compensation point could not be clearly identified, the $\dot{V}E/\dot{V}CO_2$ slope was calculated from the data recorded between the start of incremental exercise and the end of the exercise. The ratio of the increase in $\dot{V}O_2$ to the increase in work rate ($\Delta\dot{V}O_2/\Delta WR$) was calculated by a least-squares linear regression from the data recorded between 30 s after the start of incremental exercise and 30 s before the end of exercise.⁴

NIRS Monitoring

Cerebral oxygenation was monitored using a commercially available NIRS system (NIRO-300; Hamamatsu Photonics KK, Hamamatsu, Japan). A probe holder containing both 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 methodology of this system has been described in detail in previous reports.^{11–15} NIRS attached to the forehead measures the concentration changes of O₂Hb at a depth of approximately 1 cm from the brain surface using a modified Beer-Lambert law.^{12,13,15} It expresses the magnitude of the change in O₂Hb as an absolute unit ($\mu\text{mol/L}$) 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.^{11,16} O₂Hb was measured every 2 s from 4 min before the start of exercise until the end of exercise. O₂Hb at rest was determined as the average of the value obtained as the subjects sat on the ergometer over a 4-min period before the start of the exercise test. O₂Hb at peak exercise was defined as the average value obtained during the last 30 s of incremental exercise.^{1,2} The change in O₂Hb during exercise ($\Delta\text{O}_2\text{Hb}$) was defined as the peak exercise value—the resting value.

Statistical Analysis

Data are presented as the mean $\pm$ SD. Intergroup differences for variables were compared using the unpaired t-test or chi-squared analysis, where appropriate. A Cox proportional hazards model was used to measure the impact of $\Delta\text{O}_2\text{Hb}$ and cardiopulmonary variables on event-free survival time. The $\Delta\text{O}_2\text{Hb}$ and cardiopulmonary variables were entered into a Cox proportional hazards model as continuous variables rather than as categorical variables. We divided the subjects into 2 groups: patients with a $\Delta\text{O}_2\text{Hb}$ during exercise of $\geq 0 \mu\text{mol/L}$ ($n=252$) and those with a $\Delta\text{O}_2\text{Hb}$ during exercise of $< 0 \mu\text{mol/L}$ ($n=92$), and then compared the cardiovascular events between these 2 groups. We also compared the patient characteristics between survivors and non-survivors and between patients with cardiovascular events and those without events. Differences in event-free survival between the patients with a $\Delta\text{O}_2\text{Hb}$ of $\geq 0 \mu\text{mol/L}$ and those with a $\Delta\text{O}_2\text{Hb}$ of $< 0 \mu\text{mol/L}$ were detected by the Kaplan–Meier method and compared using the logrank test. For all comparisons, $p < 0.05$ was considered statistically significant.

Results

During the follow-up period of $1,231 \pm 538$ days, no patients underwent cardiac transplantation. By the end of the study, 13 cardiac deaths had occurred (Table 1). Of these, 7 patients died of progressive heart failure, 4 had a sudden cardiac death and 2 died of acute myocardial infarction. During the follow-up period, 78 cardiovascular events occurred (Table 1). Of these, 43 patients were hospitalized due to unstable angina, 30 were hospitalized due to a worsening of

Table 1 Comparisons of the Cardiovascular Events Between Patients With $\Delta\text{O}_2\text{Hb} \geq 0$ and Those With $\Delta\text{O}_2\text{Hb} < 0$

	All patients (n=344)	Patients with $\Delta\text{O}_2\text{Hb} \geq 0$ (n=252)	Patients with $\Delta\text{O}_2\text{Hb} < 0$ (n=92)	p value
Primary endpoint	13 (3.8)	4 (1.6)	9 (9.8)	0.001
Death due to worsening of heart failure	7 (2.0)	3 (1.2)	4 (4.3)	NS
Sudden cardiac death	4 (1.2)	0 (0)	4 (4.3)	0.005
Death due to acute MI	2 (0.6)	1 (0.4)	1 (1.1)	NS
Secondary endpoint	78 (22.7)	46 (18.3)	32 (34.8)	0.002
Hospitalization due to worsening of angina pectoris	43 (12.5)	31 (12.3)	12 (13.0)	NS
Hospitalization due to worsening of heart failure	30 (8.7)	15 (6.0)	15 (16.3)	0.005
Acute MI	2 (0.6)	0 (0)	2 (2.2)	NS
Sudden cardiac death	3 (0.9)	0 (0)	3 (3.3)	0.019

Data are no. (%) of patients.

$\Delta\text{O}_2\text{Hb}$, change of oxyhemoglobin (O_2Hb) measured at the forehead from rest to peak exercise; NS, not significant; MI, myocardial infarction.

Table 2 Clinical Characteristics of the Subjects

	All patients (n=344)	Survivors (n=331)	Non-survivors (n=13)	p value
Age (years)	65.0 $\pm$ 9.4	64.8 $\pm$ 9.3	68.5 $\pm$ 10.6	NS
M/F, no.	306/38	294/37	12/1	NS
Diagnosis				
Old MI	201 (58.4)	191 (57.7)	10 (76.9)	NS
Coronary artery disease without MI	143 (41.6)	140 (42.3)	3 (23.1)	NS
Medication				
Nitrates	242 (70.3)	232 (70.1)	10 (76.9)	NS
Calcium-channel blockers	194 (56.4)	192 (58.0)	2 (15.4)	0.003
β -blockers	146 (42.4)	139 (42.0)	7 (53.8)	NS
Angiotensin receptor blockers	73 (21.2)	69 (20.8)	4 (30.8)	NS
ACEIs	61 (17.7)	59 (17.8)	2 (15.4)	NS
Diuretics	51 (14.8)	43 (13.0)	8 (61.5)	<0.0001
Digitalis	10 (2.9)	7 (2.1)	3 (23.1)	0.004
LVEF (%)	59.4 $\pm$ 15.1	60.6 $\pm$ 14.0	29.8 $\pm$ 13.1	<0.0001
Heart rate at rest	75.3 $\pm$ 13.5	75.1 $\pm$ 13.4	79.7 $\pm$ 13.6	NS
SBP at rest	124.9 $\pm$ 19.2	125.2 $\pm$ 19.0	117.8 $\pm$ 23.0	NS
Heart rate at peak exercise	123.8 $\pm$ 20.0	124.3 $\pm$ 20.0	112.1 $\pm$ 16.5	0.03
SBP at peak exercise	188.4 $\pm$ 32.9	190.0 $\pm$ 32.1	147.9 $\pm$ 26.8	<0.0001
$\Delta\text{O}_2\text{Hb}$ ($\mu\text{mol/L}$)	1.6 $\pm$ 3.3	1.7 $\pm$ 3.2	-1.5 $\pm$ 3.3	0.0004
Peak $\dot{V}\text{O}_2$ ($\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$)	17.9 $\pm$ 4.9	18.1 $\pm$ 4.9	12.8 $\pm$ 2.9	0.0001
$\Delta\dot{V}\text{O}_2/\Delta\text{WR}$ ($\text{ml} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$)	9.3 $\pm$ 2.1	9.4 $\pm$ 2.1	6.8 $\pm$ 1.5	<0.0001
$\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope	33.0 $\pm$ 7.3	32.6 $\pm$ 7.0	41.9 $\pm$ 7.7	<0.0001

Data are mean $\pm$ SD or no. (%) of patients unless otherwise indicated.

ACEI, angiotensin-converting enzyme inhibitor; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; $\dot{V}\text{O}_2$, peak O_2 uptake; ΔWR , work rate; $\dot{V}\text{E}$, ventilation; $\dot{V}\text{CO}_2$, increase in CO_2 output. Other abbreviations see in Table 1.

heart failure, 2 had new acute myocardial infarction and 3 had a sudden cardiac death (only the first event was counted in this analysis). As compared to patients with a $\Delta\text{O}_2\text{Hb}$ of ≥ 0 , those with a $\Delta\text{O}_2\text{Hb}$ of < 0 had higher rates of sudden cardiac death and hospitalization due to worsening of heart failure.

Primary Endpoint

Table 2 shows a comparison of clinical characteristics between survivors and non-survivors. There was no significant difference between the 2 groups regarding the presence of myocardial infarction, while the uses of calcium-channel blockers, diuretics and digitalis were different between the groups. The LVEF was 29.8 $\pm$ 13.1% in non-survivors, which was lower than that of survivors (60.6 $\pm$ 14.0%, $p < 0.0001$). Both heart rate and systolic blood pressure at peak exercise were significantly lower in non-survivors than in survivors. The change of O_2Hb at the forehead from rest to peak exercise ($\Delta\text{O}_2\text{Hb}$) was significantly lower in non-survivors than

in survivors (-1.5 $\pm$ 3.3 vs 1.7 $\pm$ 3.2 $\mu\text{mol/L}$, $p = 0.0004$). Non-survivors achieved lower peak $\dot{V}\text{O}_2$, lower $\Delta\dot{V}\text{O}_2/\Delta\text{WR}$ and a higher $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope than survivors.

Table 3 shows the univariate and multivariate Cox proportional hazards analyses of the association between the cardiopulmonary indexes including $\Delta\text{O}_2\text{Hb}$ and cardiac deaths. By the univariate analysis, LVEF, heart rate and systolic blood pressure at peak exercise, $\Delta\text{O}_2\text{Hb}$, peak $\dot{V}\text{O}_2$, $\Delta\dot{V}\text{O}_2/\Delta\text{WR}$ and the $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope were all found to be significant indexes for survival. When these significant indexes including use of medications were entered all together, only LVEF and $\Delta\text{O}_2\text{Hb}$ were found to be independent predictors for cardiac death. Fig 1 shows the Kaplan–Meier survival in each group of subjects divided on the basis of $\Delta\text{O}_2\text{Hb}$ at the forehead during exercise. The Kaplan–Meier survival curves demonstrated a significantly lower survival rate in patients with a $\Delta\text{O}_2\text{Hb}$ of $< 0 \mu\text{mol/L}$ than in those with a $\Delta\text{O}_2\text{Hb}$ of $\geq 0 \mu\text{mol/L}$ ($p = 0.0005$).

Table 3 Predictors for Cardiac Death

	Univariate analysis				Multivariate analysis			
	X ₂	p value	HR	95% CI	X ₂	p value	HR	95% CI
Age	2.08	0.1491	1.050	0.983–1.122	—	—	—	—
LVEF	29.73	<0.0001	0.889	0.852–0.927	11.18	0.0008	0.903	0.851–0.959
Heart rate at peak exercise	5.07	0.0243	0.969	0.943–0.996	1.50	0.2210	0.968	0.919–1.020
SBP at peak exercise	19.70	<0.0001	0.957	0.938–0.976	0.95	0.3310	0.984	0.954–1.016
ΔO_2Hb	15.98	<0.0001	0.793	0.707–0.888	3.92	0.0476	0.793	0.631–0.998
Peak $\dot{V}O_2$	16.57	<0.0001	0.761	0.667–0.868	0.01	0.9211	0.985	0.728–1.332
$\Delta \dot{V}O_2/\Delta WR$	25.61	<0.0001	0.615	0.509–0.742	0.01	0.9379	0.976	0.533–1.787
$\dot{V}E/\dot{V}CO_2$ slope	22.20	<0.0001	1.096	1.055–1.139	1.75	0.1859	1.069	0.968–1.180
Use of calcium-channel blockers	6.99	0.0082	0.131	0.029–0.591	1.88	0.1708	0.271	0.042–1.756
Use of diuretics	18.15	<0.0001	11.509	3.739–35.424	2.94	0.0865	0.154	0.018–1.307
Use of digitalis	12.82	0.0003	10.599	2.911–38.595	1.31	0.2521	3.104	0.447–21.572

All variables were entered to a Cox proportional hazards model as continuous variables except for use of medications.

Age was not entered into the multivariate analysis because of no significance in the univariate analysis.

HR, hazard ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.

Fig 1. Kaplan–Meier survival curves for patients stratified into 2 groups on the basis of the change in oxyhemoglobin (ΔO_2Hb) during exercise (ΔO_2Hb): patients with a ΔO_2Hb of $\geq 0 \mu\text{mol/L}$ ($n=252$) and those with a ΔO_2Hb of $< 0 \mu\text{mol/L}$ ($n=92$). The survival rate in patients with a ΔO_2Hb of $< 0 \mu\text{mol/L}$ was significantly lower than that in those with a ΔO_2Hb of $\geq 0 \mu\text{mol/L}$ ($p=0.0005$).

Table 4 Clinical Characteristics of the Subjects

	Event (–) ($n=266$)	Event (+) ($n=78$)	p value
Age (years)	64.4±9.3	66.8±9.5	<0.05
M/F, no.	235/31	71/7	NS
Diagnosis			
Old MI	148 (55.6)	53 (67.9)	NS
Coronary artery disease without MI	118 (44.4)	25 (32.1)	NS
Medication			
Nitrates	184 (69.2)	58 (74.4)	NS
Calcium-channel blockers	158 (59.4)	36 (46.2)	NS
β -blockers	110 (41.4)	36 (46.2)	NS
Angiotensin receptor blockers	51 (19.2)	22 (28.2)	NS
ACEIs	46 (17.3)	15 (19.2)	NS
Diuretics	31 (11.7)	20 (25.6)	0.004
Digitalis	3 (1.1)	7 (9.0)	0.002
LVEF (%)	61.5±13.2	52.5±18.9	<0.0001
Heart rate at rest	75.3±13.6	75.3±13.0	NS
SBP at rest	124.6±19.3	125.8±18.8	NS
Heart rate at peak exercise	125.4±20.2	118.5±18.2	0.007
SBP at peak exercise	192.3±31.4	175.3±34.5	<0.0001
ΔO_2Hb ($\mu\text{mol/L}$)	1.9±3.3	0.5±2.9	0.0009
Peak $\dot{V}O_2$ ($\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$)	18.6±4.7	15.4±4.6	<0.0001
$\Delta \dot{V}O_2/\Delta WR$ ($\text{ml} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$)	9.6±2.1	8.4±1.9	<0.0001
$\dot{V}E/\dot{V}CO_2$ slope	32.3±6.9	35.2±7.9	0.002

Data are mean ± SD or no. (%) of patients unless otherwise indicated.

Abbreviations see in Tables 1,2.

Table 5 Predictors for Cardiovascular Events

	Univariate analysis				Multivariate analysis			
	X ₂	p value	HR	95%CI	X ₂	p value	HR	95%CI
Age	4.72	0.0298	1.029	1.003–1.055	0.22	0.6383	1.007	0.979–1.034
LVEF	33.16	<0.0001	0.961	0.947–0.974	8.87	0.0029	0.975	0.959–0.991
Heart rate at peak exercise	9.23	0.0024	0.983	0.972–0.994	0.03	0.8692	1.001	0.987–1.015
SBP at peak exercise	23.18	<0.0001	0.983	0.976–0.990	1.10	0.2940	0.995	0.987–1.004
ΔO_2Hb	14.00	0.0002	0.894	0.843–0.948	3.93	0.0474	0.920	0.848–0.999
Peak $\dot{V}O_2$	34.75	<0.0001	0.858	0.816–0.903	3.90	0.0483	0.923	0.852–0.999
$\Delta\dot{V}O_2/\Delta WR$	29.61	<0.0001	0.765	0.695–0.842	0.24	0.6268	0.960	0.813–1.133
$\dot{V}E/\dot{V}CO_2$ slope	17.70	<0.0001	1.049	1.026–1.072	0.02	0.8945	0.998	0.963–1.034
Use of diuretics	18.03	<0.0001	3.055	1.824–5.116	0.28	0.5942	0.822	0.399–1.692
Use of digitalis	12.47	0.0004	4.060	1.865–8.839	1.16	0.2823	1.611	0.675–3.841

All variables were entered to a Cox proportional hazards model as continuous variables except for use of medications.

Abbreviations see in Tables 1–3.

Fig 2. Kaplan–Meier event-free survival curves for patients stratified into 2 groups on the basis of the change in oxyhemoglobin (O_2Hb) during exercise (ΔO_2Hb): patients with a ΔO_2Hb of $\geq 0 \mu\text{mol/L}$ ($n=252$) and those with a ΔO_2Hb of $< 0 \mu\text{mol/L}$ ($n=92$). The event-free survival rate in patients with a ΔO_2Hb of $< 0 \mu\text{mol/L}$ was significantly lower than that in those with a ΔO_2Hb of $\geq 0 \mu\text{mol/L}$ ($p=0.0016$).

Secondary Endpoint

Table 4 shows a comparison of clinical characteristics between patients with cardiovascular events and those without events. There was no significant difference between the 2 groups regarding the presence of myocardial infarction. The mean age of the patients with cardiac events was 66.8 ± 9.5 years at the time of the exercise testing, which was significantly higher than that of the patients without events (64.4 ± 9.3 years, $p < 0.05$). As compared to patients without cardiac events, those with events had significantly lower LVEF and lower heart rate and systolic blood pressure at peak exercise. The patients with events also had significantly lower ΔO_2Hb during exercise, lower peak $\dot{V}O_2$, lower $\Delta\dot{V}O_2/\Delta WR$, and a higher $\dot{V}E/\dot{V}CO_2$ slope (Table 4).

Table 5 shows univariate and multivariate Cox proportional hazards analyses of the association between cardiopulmonary indexes including ΔO_2Hb and cardiovascular events. In the univariate analysis, age, LVEF, both heart rate and systolic blood pressure at peak exercise, ΔO_2Hb at the forehead, peak $\dot{V}O_2$, $\Delta\dot{V}O_2/\Delta WR$ and the $\dot{V}E/\dot{V}CO_2$ slope were all found as significant prognostic indexes for event-free survival. In the multivariate analysis, only the LVEF, ΔO_2Hb at the forehead and peak $\dot{V}O_2$ were found as independent prognostic indexes. As shown in Fig 2, the Kaplan–Meier survival curves demonstrate a significantly lower event-free survival rate in patients with a ΔO_2Hb of $< 0 \mu\text{mol/L}$ than in those with a ΔO_2Hb of $\geq 0 \mu\text{mol/L}$ ($p=$

0.0016).

Discussion

During exercise, the sudden surge in O_2 demand by muscle cells generates a tremendous increase in blood flow to the exercising muscle. The increased distribution of blood flow to the exercising muscle results in a relative hypoperfusion in other organs. As a consequence, cerebral circulation becomes insufficient during exercise, especially in cardiac patients whose cardiac output fails to increase normally. In our previous study, we found that cerebral oxygenation during exercise was strongly related to the indexes of CPX in cardiac patients.¹ We also found that cerebral O_2Hb actually decreased during exercise in a considerable number of patients with dilated cardiomyopathy, indicating the presence of their cerebral hypoperfusion.¹ In the present study, we extended our scope, and newly discovered that the decrease in cerebral O_2Hb during exercise predicts future cardiovascular events in patients with coronary artery disease.

Mechanisms Determining Cerebral Oxygenation During Exercise

Cerebral oxygenation is determined by O_2 supply and O_2 demand. Although not measured in the present study, cerebral blood flow is most important for O_2 supply and is determined by perfusion pressure and cerebral vessel resistance.

Cerebral perfusion pressure is equal to the difference between arterial pressure and venous (right atrial) pressure. While 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. In cardiac patients with left ventricular dysfunction, the level of venous pressure would be particularly increased during exercise, which might then decrease the level of cerebral perfusion pressure.

Even in the resting condition, patients with left ventricular dysfunction are known to have reduced cerebral blood flow as compared to normal subjects, which has been shown to be normalized by cardiac transplantation.¹⁷ On the transition from rest to moderate exercise, global cerebral blood flow increases by 20–30% in both animals and humans.¹⁸ During maximal exercise, however, a recent investigation by González-Alonso et al indicated that blood flow to the brain decreases even in healthy subjects.¹⁸ They suggested the impaired increase in cardiac output, reduction in cerebral perfusion pressure, and local factors relating to the vasoconstrictor and/or vasodilator activities in the brain as possible mechanisms underlying this phenomenon.¹⁸ Thus, cerebral blood flow during maximal exercise would be more easily decreased in cardiac patients, such as those with coronary artery disease, because of their insufficient increase in cardiac output during exercise. Although not measured in the present study, another possible determinant of cerebral oxygenation is the level of PaCO₂ during exercise. Cerebral blood flow is known to positively correlate with PaCO₂; a decrease in PaCO₂ leads to cerebral hypoperfusion and a rise in PaCO₂ increases cerebral blood flow.

Study Limitations

From the results of the previous investigations,^{1,2,7,19} we assumed that the decrease in O₂Hb during exercise would be an abnormal phenomenon. Thus, we used the Δ O₂Hb level of “0” as a cut-off point for the Kaplan–Meier method without using a receiver operating characteristics (ROC) curve analysis.

The possibility of contamination from extracranial tissues has to be considered when we evaluate cerebral oxygenation using NIRS attached to the forehead. In our previous investigations performed with the same methodology, pulse oximetric saturation was also measured at the earlobe near the NIRS probes during exercise.^{1,2} There was no decrease in pulse oximetric saturation during exercise in spite of the apparent decrease in O₂Hb at the forehead. Thus, we assume that the influence of extracranial factors was minimal for the present findings. Our previous report has already confirmed the good reproducibility of cerebral O₂Hb measurements during exercise by this technique.²

In the present study, we selected only the patients with coronary artery disease. However, the prognostic value of decreased cerebral O₂Hb during exercise would be applicable to patients with any type of left ventricular dysfunction if the cardiac output response to exercise is impaired. Although patients with cerebrovascular disease having a clinical manifestation were excluded in the present study, the decrease in cerebral O₂Hb during exercise in patients with a poor prognosis might have partly stemmed from concomitant stenosis in small cerebral arteries.⁷

Clinical Implications

Quite recently, we compared the decreased level of cerebral O₂Hb during exercise in cardiac patients with those in

subjects who had experienced reduced consciousness due to a sudden drop in blood pressure induced by a parasympathetic reflex or sustained ventricular tachycardia.¹⁹ We found that the decreases in cerebral O₂Hb during exercise in some patients were comparable to those in subjects who experienced reduced consciousness. This finding suggests that the index of cerebral oxygenation might drop to levels low enough during maximal exercise to affect the level of consciousness in some cardiac patients, especially those with severe left ventricular dysfunction.¹⁹

While factors determining cerebral oxygenation are complex, the regulation of cerebral oxygenation is critically important in humans even during exercise. This regulation must depend largely on cardiac function and additionally on the cerebral vessel resistance. Both of these factors would be diseased in patients with coronary artery disease, as it is one of the manifestations resulting from systemic arteriosclerosis. The decrease in cerebral O₂Hb during exercise in our patients must reflect the disturbance of auto regulation of cerebral oxygenation. In the present study, the patients with a Δ O₂Hb of <0 had significantly higher rates of sudden cardiac death and hospitalization due to worsening of heart failure, as compared to those with a Δ O₂Hb of $\geq$ 0. However, there was no significant difference in the event rate of hospitalization due to worsening of angina pectoris or of acute myocardial infarction between the 2 groups. Our findings suggest that the patients with the disturbance of cerebral oxygenation, which is related to the underlying coronary artery disease, were prone to have future cardiovascular events, especially worsening of heart failure.

Cerebral O₂Hb during exercise reflects cerebral oxygenation, which is determined by cardiac function and cerebral vessel resistance. The decrease in cerebral O₂Hb in cardiac patients would imply impaired cardiac response to exercise, that is, the insufficient heart's pumping reserve. The heart's pumping reserve during exercise does not necessarily correlate with resting cardiac function. By these reasons, Δ O₂Hb during exercise in our subjects predicted the future events related to heart failure independently from resting LVEF.

Patients with decreased cerebral O₂Hb during exercise would be exposed to a chronic impairment of cerebral oxygenation during daily life, which might lead to cognitive dysfunction and decreases in quality of life and activities of daily living. In the future, a consideration of the specific treatments that might improve cerebral oxygenation might become important in patients with decreased cerebral O₂Hb during exercise. In patients with severely decreased LVEF, such as the candidates for cardiac transplantation, the parameters obtained from CPX are known to be superior to resting cardiac function for predicting future prognosis.³ In the present study, however, resting LVEF was confirmed to be a strong prognostic index in patients with coronary artery disease with a wide range of LVEF.

Conclusions

The decrease in cerebral O₂Hb during exercise was found to strongly predict future cardiovascular events in patients with coronary artery disease. The prognostic power of cerebral O₂Hb during exercise for future cardiovascular events was independent of the indexes obtained from CPX, and even stronger than these indexes for cardiac mortality.

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