Acta Cardiol Sin 2020;36:667–674
Original Article
doi: 10.6515/ACS.202011_36(6).20200519C

Others

Cerebral Oxygenation during Exercise in Patients with Cardiopulmonary Diseases: A Prospective Observational Study

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Background: The relationship between exercise and cerebral oxygenation has gained increasing attention. However, few studies have investigated the correlation between exercise and cerebral oxygenation in patients with cardiopulmonary diseases.

Objectives: To investigate the correlation between exercise and cerebral oxygenation in patients with cardiopulmonary diseases.

Methods: Thirty eligible patients with cardiopulmonary diseases underwent incremental cardiopulmonary exercising test (CPET) and near-infrared spectroscopy with both right and left sensors placed at the mid forehead to detect oxygen saturation of cerebral tissue (STO2). Parameters of cerebral oxygenation and exercise intensity were collected and analyzed.

Results: The average age of the patients was 51.17 ± 10.21 years and included 23 males and 7 females. The average maximal STO2 of the left and right brain during CPET were 51.850 ± 1.57% and 51.755 ± 1.90%, respectively. Meanwhile, mean oxygen consumption (VO2) while reaching maximal STO2 was 4.42 ± 1.05 metabolic equivalents (METs) over the left brain and 4.34 ± 1.17 METs over the right brain. The exercise intensity upon reaching maximal STO2 was 84.91 ± 11.70% over the left brain and 83.16 ± 14.64% over the right brain. Peak VO2 was significantly correlated to VO2 upon reaching maximal STO2 over the left and right brain ($R = 0.805$, $p < 0.001$ and $R = 0.739$, $p < 0.001$, respectively). Age was significantly negatively correlated to VO2 upon maximal STO2 over the left and right brain ($R = -0.378$, $p = 0.039$ and $R = -0.513$, $p = 0.004$, respectively).

Conclusions: Cerebral oxygenation increases with higher exercise intensity, and it reaches a maximal STO2 between respiratory compensation point and peak exercise. The higher the peak VO2, the better the VO2 upon reaching maximal STO2.

Key Words: Cardiopulmonary diseases • Cerebral oxygenation • Exercise

INTRODUCTION

The relationship between exercise and cerebral oxygenation has gained increasing attention. Incremental exercise has been shown to increase oxygenated/deoxygenated hemoglobin and blood volume in the prefrontal cortex of healthy adults.[1] A previous study investigated cerebral oxygenation in cardiac patients,[2] and implicated that cerebral oxygenation is a prognostic factor in heart failure.[3] However, few studies have investigated this correlation and physiological changes during exercise in pa-

Received: January 7, 2020 Accepted: May 19, 2020
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tients with cardiopulmonary diseases. Thus, we aimed to investigate cerebral oxygenation during exercise in patients with cardiopulmonary diseases in this study.

METHODS

We enrolled 91 patients with different cardiopulmonary diseases and excluded those patients with maximal oxygen saturation of cerebral tissue (STO2) during the warm-up or recovery phase while performing an incremental cardiopulmonary exercising test (CPET), since these patients were not doing incremental exercise during either warm-up or recovery phase and thus their cerebral oxygenation, oxygen consumption, metabolic equivalent and exercise intensity could not be compared with those who had maximal STO2 during the incremental exercising phase. Thirty eligible patients with various main cardiopulmonary diagnoses were finally recruited (Table 1). Near-infrared spectroscopy (NIRS) with both right and left sensors wrapped in a circular headband was placed at the mid forehead of the patients to detect hemoglobin under the headband to reflect oxygen saturation of cerebral tissue during CPET (Figures 1, 2). Measurements included STO2 obtained during peak exercise (pSTO2), STO2 obtained at anaerobic threshold (atSTO2), STO2 obtained at respiratory compensatory point (rcpSTO2), maximal STO2 during exercise (maxSTO2), STO2 while resting (restSTO2), metabolic equivalents (METs) obtained while reaching maximal STO2 (maxSTO2_METs), maximal STO2 divided by resting STO2 (max/restSTO2), duration before reaching maxSTO2 (maxSTO2_time), METs upon RCP (rcp_METs), METs upon peak exercise (peak_METs) and duration before reaching peak exercise (peak_time). Resting STO2 was acquired before starting CPET. These measurements were recorded both in the left and right hemisphere. The CPET protocol was a 3-minute warm-up, including 1-minute at 0 watts and 2-minute at 10 watts, and resistance training of adding on 15 watts per minute with 70 rad/minute until the patient wished to stop the test. A 3-minute recovery phase with continuous 10 watts was then performed. After data collection, SPSS software was utilized for statistical analysis. The study design was approved by the Institutional Review Board of Chi Mei Medical Center (10602-007).

RESULTS

The average age of the eligible patients was 51.17 ± 10.21 years, including 23 males and 7 females. The average maximal STO2 of the left and right brain during CPET was 51.85 ± 1.57% and 51.75 ± 1.90%, respec-

Figure 1. *A near-infrared spectroscopy (NIRS) with both right and left sensors wrapped in circular headband.*

Table 1. Main diagnosis of participants

Disease	Numbers	Percentages
Chronic obstructive pulmonary disease	1	3.3%
Paroxysmal supraventricular tachycardia	1	3.3%
Lung cancer	1	3.3%
Acute myocardial infarction status post percutaneous coronary intervention	16	53.5%
Acute myocardial infarction status post coronary artery bypass graft	3	10%
Chronic heart failure	6	20%
Stroke	1	3.3%
Myocarditis	1	3.3%

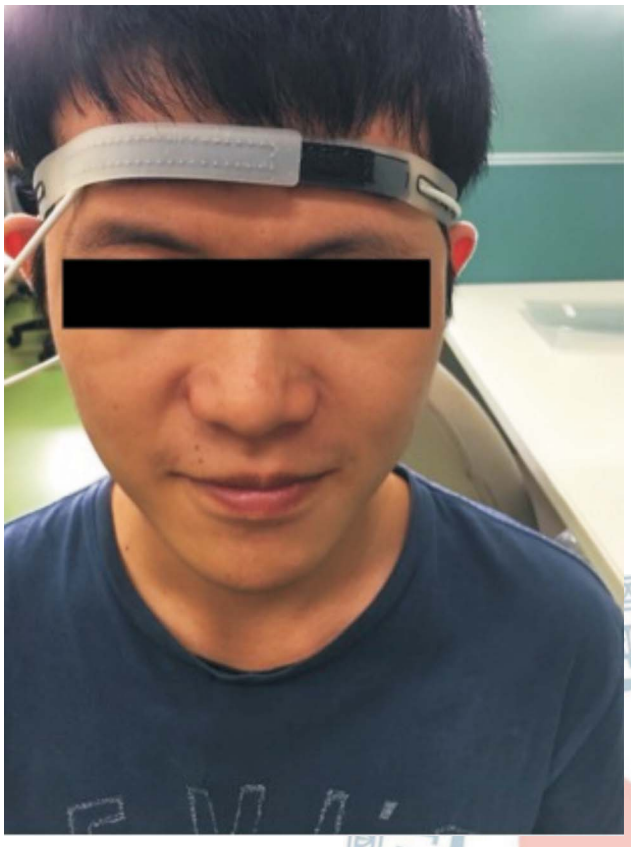

Figure 2. *A near-infrared spectroscopy (NIRS) was placed at mid forehead of patients to detect hemoglobin that went under the headband and reflect the oxygen saturation of cerebral tissue during cardiopulmonary exercising test (CPET).*

tively. The mean resting STO2 before CPET started was 50.87 ± 1.33% over the left brain and 50.78 ± 1.46% over the right brain. The mean oxygen consumption (VO2) while reaching maximal STO2 was 4.42 ± 1.05 METs over the left brain and 4.34 ± 1.17 METs over the right brain. The average maximal VO2 during CPET was 5.25 ± 1.20 METs. The exercise intensity upon reaching maximal STO2 was 84.91 ± 11.70% over the left brain and 83.16 ± 14.64% over the right brain. The mean maximal STO2 over that of resting was 1.02 ± 0.011% over the left brain and 1.02 ± 0.012% over the right brain. The mean STO2 upon peak exercise was 51.58 ± 1.50% over the left brain and 51.41 ± 1.74% over the right brain (Table 2).

Peak_METs was significantly correlated to maxSTO2_METs over the left brain (Figure 3) (R = 0.805, p < 0.001) and right brain (Figure 4) (R = 0.739, p < 0.001). Moreover, there was a significant difference in maxSTO2_METs in the patients with peak_METs ≤ 5.429 and > 5.429 METs over both hemispheres (left hemisphere: p < 0.001; right hemisphere: p < 0.001) (Table 3). In pa-

Table 2. Results of cerebral oxygenation during exercise

Variables	Mean	Standard deviation
maxSTO2*		
Left	51.85	1.57
Right	51.75	1.90
restSTO2#		
Left	50.87	1.33
Right	50.78	1.46
maxSTO2_METs†		
Left	4.42	1.05
Right	4.38	1.17
peak_METs‡	5.25	1.20
maxSTO2_METs/peak_METs		
Left	84.91%	11.70
Right	83.16%	14.64
maxSTO2/restSTO2§		
Left	1.02	0.011
Right	1.02	0.012
pSTO2**		
Left	51.58	1.50
Right	51.41	1.74

* maxSTO2, maximal oxygen saturation of cerebral tissue during exercise; # restSTO2, oxygen saturation of cerebral tissue while resting; † maxSTO2_METs, metabolic equivalents obtained while reaching maximal oxygen saturation of cerebral tissue; ‡ peak_METs, metabolic equivalents upon peak exercise; § max/restSTO2, maximal oxygen saturation of cerebral tissue divided by resting oxygen saturation of cerebral tissue; ** pSTO2, oxygen saturation of cerebral tissue obtained during peak exercise.

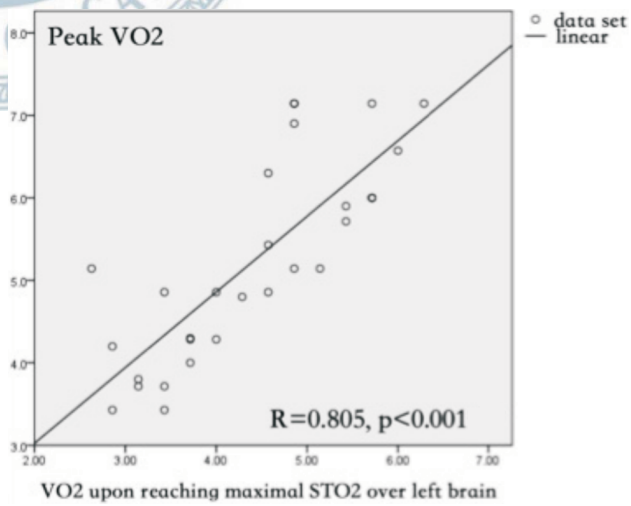

Figure 3. *Peak oxygen consumption (VO2) significantly correlated to VO2 upon reaching maximal oxygen saturation of cerebral tissue (STO2) over left brain (R = 0.805, p < 0.001).*

tients with peak_METs ≤ 5.429, the mean maxSTO2_METs were 3.749 ± 0.721 and 3.643 ± 0.869 over the left and right brains, respectively, while in patients with peak_METs > 5.429, the mean maxSTO2_METs were 5.429 ± 0.531 and 5.381 ± 0.687 over the left and right brains, respectively (Table 3). MaxSTO2 was significantly positively correlated with pSTO2 (left hemisphere: R = 0.992, p < 0.001; right hemisphere: R = 0.984, p < 0.001), atSTO2 (left hemisphere: R = 0.963, p < 0.001; right hemisphere: R = 0.968, p < 0.001), rcpSTO2 (left hemisphere: R = 0.981, p < 0.001; right hemisphere: R = 0.968, p < 0.001) and restSTO2 (left hemisphere: R = 0.943, p < 0.001; right hemisphere: R = 0.961, p < 0.001) in both hemispheres. In addition, pSTO2, atSTO2, rcpSTO2 and restSTO2 were also significantly reciprocally correlated to one another over the left and right brain (Table 4).

MaxSTO2_METs was significantly positively correlated to rcpSTO2 (left hemisphere: R = 0.388, p = 0.034; right hemisphere: R = 0.430, p = 0.018), pSTO2 (left hemisphere: R = 0.444, p = 0.014; right hemisphere: R = 0.447, p = 0.013), maxSTO2 (left hemisphere: R = 0.433, p = 0.017; right hemisphere: R = 0.477, p = 0.008), maxSTO2_time (left hemisphere: R = 0.760, p < 0.001; right hemisphere: R = 0.871, p < 0.001), rcp_METs (left hemisphere: R = 0.657, p < 0.00; right hemisphere: R = 0.550, p = 0.002), peak_METs (left hemisphere: R = 0.805, p < 0.001; right hemisphere: R = 0.739, p < 0.001) and max/restSTO2 (left hemisphere: R = 0.415, p = 0.022; right hemisphere: R = 0.610, p < 0.001) over both brains.

Age was significantly negatively correlated to maxSTO2_METs (left hemisphere: R = -0.378, p = 0.039; right hemisphere: R = -0.513, p = 0.004), max/restSTO2 (left hemisphere: R = -0.455, p = 0.012; right hemisphere: R = -0.512, p = 0.004), maxSTO2_time (left hemisphere: R = -0.530, p = 0.003; right hemisphere: R = -0.513, p = 0.004) over the left and right brain, and peak_time (R = -0.540, p = 0.002). Furthermore, there was a significant difference in max/restSTO2 between the patients aged > 40 and ≤ 40 years (left hemisphere: p = 0.048; right

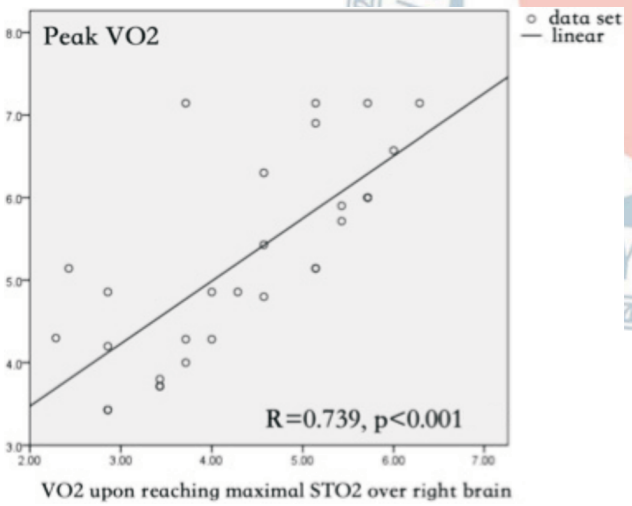

Figure 4. *Peak oxygen consumption (VO2) significantly correlated to VO2 upon reaching maximal oxygen saturation of cerebral tissue(STO2) over right brain (R = 0.739, p < 0.001).*

Table 4. Correlation between oxygen saturation of cerebral tissue (STO2) during different exercising phase

	maxSTO2	pSTO2	atSTO2	rcpSTO2	restSTO2
maxSTO2*	1				
L**		R = 0.992	R = 0.963	R = 0.981	R = 0.934
R##		R = 0.984	R = 0.968	R = 0.981	R = 0.961
pSTO2#		1			
L			R = 0.957	R = 0.976	R = 0.926
R			R = 0.968	R = 0.983	R = 0.955
atSTO2†			1		
L				R = 0.982	R = 0.979
R				R = 0.976	R = 0.984
rcpSTO2‡				1	
L					R = 0.958
R					R = 0.961
restSTO2					1
L					
R					

All p values are < 0.001***.

* maxSTO2, maximal STO2 during exercise; # pSTO2, STO2 obtained during peak exercise; † atSTO2, STO2 obtained at anaerobic threshold; ‡ rcpSTO2, STO2 obtained at respiratory compensatory point; § restSTO2, STO2 while resting; ** L, left brain recorder; ## R, right brain recorder.

Table 3. Mean metabolic equivalents (METs) upon maximal cerebral oxygenation in patients with different exercising capacity

	≤ 5.429 METs (n = 18)	> 5.429 METs (n = 12)	p value
Left maxSTO2_METs*	3.749 ± 0.721	5.429 ± 0.531	< 0.001***
Right maxSTO2_METs	3.643 ± 0.869	5.381 ± 0.687	< 0.001***

* maxSTO2_METs, metabolic equivalents obtained while reaching maximal oxygen saturation of cerebral tissue.

hemisphere: p = 0.001) (Table 5). In the patients aged > 40 years, their mean max/restSTO2 values were 1.017 ± 0.010 and 1.015 ± 0.010 over the left and right brain, respectively. In the patients ≤ 40 years old, their mean max/restSTO2 values were 1.027 ± 0.133 and 1.032 ± 0.004 over left and right brain, respectively.

In the patients excluded from this study due to maximal STO2 fall in warm-up or recovery phase, 33% (n = 20) reached their maximal STO2 during the warm-up phase and 67% (n = 41) during the recovery phase. The main diagnoses of these patients were 13% (n = 8) mitral valve regurgitation (MR), 1.6% (n = 1) atrial septal defect, 3.4% (n = 2) chronic obstructive pulmonary disease, 5% (n = 3) aortic dissection, 1.6% (n = 1) chemical pneumonitis, 1.6% (n = 1) rib fracture, 26% (n = 16) congestive heart failure (CHF), 1.6% (n = 1) stroke, 1.6% (n = 1) myocarditis, 30% (n = 18) acute myocardial infarction status post percutaneous coronary intervention (AMI s/p PCI), 13% (n = 8) acute myocardial infarction status post coronary artery bypass graft (AMI s/p CABG), and 1.6% (n = 1) coronary disease without intervention. Patients with maximal STO2 fall in warm-up phase included 15% (n = 3) MR, 15% (n = 3) AMI s/p PCI, 20% (n = 4) AMI s/p CABG, and 40% (n = 8) CHF. Meanwhile, the patients with maximal STO2 fall in recovery phase included 12% (n = 5) MR, 37% (n = 15) AMI s/p PCI, 10% (n = 4) AMI s/p CABG, and 20% (n = 8) CHF.

Table 5. Mean oxygen saturation of cerebral tissue (STO2) gain in different age group

	> 40 year-old (n = 7)	≤ 40 year-old (n = 23)	p value
Left max/restSTO2*	1.017 ± 0.010	1.027 ± 0.133	0.048*
Right max/restSTO2	1.015 ± 0.010	1.032 ± 0.004	0.001**

* max/restSTO2, maximal STO2 divided by resting STO2.

DISCUSSION

Early cardiopulmonary rehabilitation has been emphasized in patients with acute myocardial infarction.[4] CPET data not only offers precise and individualized information when planning exercise programs for cardiopulmonary rehabilitation, but also predicts outcomes and mortality in certain diseases.[5] In our study, we combined CPET and cerebral oxygenation detection and found that the exercise intensity upon reaching maximal STO2 was 84.91 ± 11.70% over the left brain and 83.16 ± 14.64% over the right brain. A previous study showed similar results that the mean percentage to peak oxygen consumption during highest STO2 in the right hemisphere was 76.27 ± 14.02% and 72.14 ± 17.94% in the left hemisphere, and that there was an inverted U-shaped relationship between cerebral oxygenation and exercise intensity in patients with cardiovascular diseases.[6] Another study also revealed that cerebral oxygenation measured by NIRS increased between moderate and high intensities and dropped at very high intensity in healthy adults.[1] In addition, another study reported a decrease in cerebral oxygenation during high-intensity exercise compared to low- and moderate-intensity exercise in other neuroimaging results.[7] A decline in cerebral oxygenation above respiratory compensation point (RCP) during exercise has been reported in healthy subjects,[8] and fatigue resulting from dynamic severe exercise is regarded to be an important factor associated with a decrease in cerebral oxygenation.[9]

Maximal cerebral oxygenation during CPET was significantly positively correlated with cerebral oxygenation upon peak exercise, anaerobic threshold (AT), RCP and resting phase in both hemispheres in the patients with cardiopulmonary diseases in our study. However, the increase in cerebral oxygenation during the exercising phase was not significantly correlated with either of the parameters of cerebral oxygenation in various phases of CPET. This finding is similar to that of healthy adults without significant changes in cerebral oxygenation upon peak exercise.[10] Thus, we propose that higher maximal cerebral oxygenation indicates higher cerebral oxygenation during the resting phase and exercising phase upon peak exercise, AT and RCP.

In our study, the left and right brains had similar changes in cerebral oxygenation during CPET, however another study reported that the left hemisphere was more susceptible to changes in cerebral oxygenation.[11] As for cognition and cerebral oxygenation during exercise, a recent study demonstrated that lower cerebral oxygenation in the prefrontal cortex was exclusively associated with a slower reaction time in executive condition.[7] In addition, in patients with long-term hemodialysis, lower cerebral oxygenation has been associated with lower cognitive function.[12] Furthermore, a study

focusing on patients with mild cognitive impairment concluded that an intervention with a 6-month exercise program resulted in an increase in cerebral oxygenation and that it could improve or maintain cognitive function.[13] That is to say, better cerebral oxygenation may lead to greater cognitive function, and physicians may improve a patients' cerebral oxygenation with exercise programs in the future.

There was a significant difference in oxygen consumption upon reaching maximal cerebral oxygenation between peak oxygen consumption ≤ 5.429 and > 5.429 METs in the patients with cardiopulmonary diseases during CPET (Table 3). Mean oxygen consumption values upon reaching maximal cerebral oxygenation were 3.749 ± 0.721 and 3.643 ± 0.869 over the left and right brain in patients with a peak_METs ≤ 5.429, and 5.429 ± 0.531 METs and 5.381 ± 0.687 METs over the left and right brain in patients with peak_METs > 5.429. That is to say, those with better work capacity (as evidenced by peak oxygen consumption > 5.429 METs) may require higher oxygen consumption in order to reach maximal cerebral oxygenation.

We also found that age was significantly negatively correlated to oxygen consumption upon reaching maximal cerebral oxygenation, increase in cerebral oxygenation compared to the resting phase, duration of reaching maximal cerebral oxygenation, and duration of reaching peak exercise over the left and right brain. In other words, older patients with cardiopulmonary diseases would need less time to reach maximal cerebral oxygenation and peak exercise, less oxygen consumption to reach maximal cerebral oxygenation, and less improvement in cerebral oxygenation during CPET. Moreover, a cut-off value of 40 years old indicated a significant difference in promoting cerebral oxygenation (Table 5). The younger cardiopulmonary patients (≤ 40 years old) had increases of approximately 2.7% and 3.2% over left and right cerebral oxygenation, compared to approximately 1.7% and 1.5% for the older cardiopulmonary patients (> 40 years old). However, a previous study showed that cardiorespiratory and tissue oxygenation response to hypoxia both at rest and during moderate-intensity exercise were similar in healthy young and older people at least until the age of 70 years, and that the response to hypoxia during high-intensity exercise was slightly lower in older adults than in young adults.[14]

Among our recruited patients, 19% (n = 6) had diabetes and 81% (n = 25) did not. The association between diabetes and cerebral perfusion or oxygenation has seldom been discussed, and most studies have focused on diabetes and cerebral blood flow. One study reported that the effect of type 2 diabetes on cerebral blood flow is small and independent of brain atrophy,[15] whereas another showed a significant age-related decline in cerebral blood flow in diabetic and healthy individuals.[16] In addition, mean flow velocity and systolic velocity in the middle cerebral artery have been reported to be higher in hyperglycemic diabetic patients compared to normoglycemic diabetic patients.[17] Moreover, antihypertensive medication and cerebral circulation have been attracting increasing interest. Current research has focused on the relationship between medication and cerebral blood flow rather than cerebral perfusion or oxygenation. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and beta-blocker are regarded to have limited effects on cerebral blood flow. Furthermore, calcium channel blockers were not shown to change cerebral blood flow in a trial of intravenous nimodipine in healthy humans.[18] However, nilvadipine has been shown to increase cerebral blood flow in Alzheimer's hippocampus region.[19] Vasodilators, on the other hand, have not been shown to significantly impair absolute cerebral blood flow but it improve pulsatility and reactivity of the brain.[20] Another study showed that patients with uncontrolled hypertension receiving lisinopril with or without hydrochlorothiazide or nifedipine or an angiotensin receptor blocker reached better blood pressure control as well as increasing cerebral blood flow,[21] while another study revealed that hypertensive patients treated with doxazosin mesilate had improvement in mean cerebral blood flow in the bilateral cerebral cortices.[22] The reason for the enhanced cerebral blood flow could be due to the well-controlled blood pressure in these patients.

There are some limitations to this study. This is a single-center, small sample size study with great disparity in main diagnosis of the participants. In addition, over two-thirds of the patients were excluded due to maximal cerebral oxygenation fell at a point other than the exercising phase. Thus, further multivariate analysis was limited. In addition, the underlying diseases and medications of the patients should be taken into con-

sideration, and future studies could evaluate their correlations with cerebral oxygenation. Although the results may not apply to all patients with cardiopulmonary diseases, they could still be used in future clinical practice when planning cardiopulmonary exercise programs.

CONCLUSION

Cerebral oxygenation increases with higher exercise intensity, and it reaches maximal STO2 between respiratory compensation point and peak exercise during exercise. We found that patients reached maximal oxygen saturation of cerebral tissue upon an average of 84.91 ± 11.70% and 83.16 ± 14.64% of maximal METs over the left and right brain. This could be used to guide exercise programs for patients with cardiopulmonary diseases in order to increase cerebral oxygenation. In addition, the age of the patients was negatively correlated to oxygen consumption upon maximal STO2, which may help physicians to further modify individualized exercise programs for patients.

Moreover, the higher the peak oxygen consumption, the better the oxygen consumption upon reaching maximal STO2. The patients who had higher maximal STO2 also had higher STO2 during whole exercise compared to the patients with lower maximal STO2. This implies that physicians could utilize CPET data and parameters to predict changes in cerebral oxygenation during exercise in patients with cardiopulmonary diseases.

Last but not least, exercise contributed to an average maximal increase of 2% in cerebral oxygenation in patients with cardiopulmonary diseases. Exercise may also be a potential treatment to enhance cerebral oxygenation, cerebral blood flow, cerebral blood volume and even cognitive function.

CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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