의학석사 학위논문

Comparative outcome in acute stroke model after hypoxia and exercise

저산소 및 운동 후 급성 뇌졸중 모델에서 예후 연구

2015년 2월

서울대학교 대학원

의학과 뇌신경과학 전공

김 태 준

저산소 및 운동 후 급성 뇌졸중 모델에서 예후 연구

Comparative outcome in acute stroke model after hypoxia and exercise

지도교수 이상건

이 논문을 의학석사 학위논문으로 제출함.

2014년 10월

서울대학교 대학원
의학과 뇌신경과학 전공
김 태 준

김태준의 석사학위논문을 인준함.
2014년 12월

위 원 장 장 인 진 (인)

부위원장 이 상 건 (인)

위 원 김 만 호 (인)

ABSTRACT

Obstructive sleep apnea and exercise and have conflicting effect on the ischemic stroke. Obstructive sleep apnea has negative effect on ischemic stroke, but exercise prevents and protects deficit from ischemic stroke. In this study, we show that chronic hypoxia and exercise result differently in mice ischemia model. Chronic hypoxia resulted in high mortality in acute period after carotid occlusion compared with the control group, and showed worse neurological outcome compared with the control group in hyper-acute stroke period (24 h after ischemia) in neurological scoring. Exercise group showed better neurological outcome compared with the control group in acute stroke period (up to 3 days after ischemia) in neurological scoring and Y-maze tests, but the infarction size was not definitely smaller in exercise group ($P = 0.051$, mean 57% reduction), although the tendency was positive. The amount of exercise was correlated with the neurological outcome in Y-maze test. These results show that chronic hypoxia might lead to poor outcome after ischemic stroke, whereas exercise can have importance role in reducing the neurological deficit by acute ischemic stroke.

Keywords: Exercise, physical activity, chronic hypoxia, obstructive sleep apnea, ischemic stroke

Student Number: 2013-21725

CONTENTS

LIST OF TABLE AND FIGURES

Introduction

Ischemic stroke is a major leading cause of mortality and disability worldwide.[1] Despite its huge socioeconomic impact and high mortality, there are no effective curative therapeutic managements available for stroke patients, other than thrombolytic treatment which is limited by a narrow time window and low availability. Preventive management for ischemic stroke has significance in this regard, such as treatment for conventional risk factors of hypertension and diabetes. Recently, chronic hypoxia, in particular obstructive sleep apnea (OSA), is proved to be associated with ischemic stroke;[2-5] however, the fundamental causality has not been clarified yet. Physical activity is known to have beneficial effect in brain health and might play a role in preventing ischemic stroke,[6-8] but the correlation is not established, also.

OSA is a common form of sleep related breathing disorder affecting about 4% of men with high prevalence of undiagnosed patients.[9] OSA has been established as an independent risk factor for stroke and known to increase stroke risk by about two fold which is adjusted for other contributing factors.[2,3] The severity of OSA was associated with a progressive increase in ischemic stroke risk, and these correlations between OSA and stroke is confirmed by meta-analysis.[4] Furthermore, long-term sojourn at high altitude is associated with increased risk of stroke.[5] However, the mechanisms by which chronic hypoxia increases susceptibility for stroke remain to be elucidated.

Physical activity or exercise, on the contrary, reduced the risk of

stroke morbidity and mortality with adjustment for vascular risk factors.[6,7] The relationship between physical activity and stroke protection has dose-response effect in some degree, and a meta-analysis of physical activity reached the same conclusion.[8] In addition, higher levels of physical activity before stroke occurrence were associated with functional recovery after stroke.[10]

Majority of studies speculated that these two conditions of chronic hypoxia and physical activity have common multifactorial mechanisms affecting the risk of stroke, such as the effect on hypertension and metabolic syndromes, endothelial function or autonomic systems. Yet, two conditions have conflicting effect on the risk of stroke and the underlying mechanisms of two conditions with stroke are not definite. In the present study, we attempted to induce the change of vascular and autonomic functions by exercise and chronic hypoxia 72 h after cerebral ischemia. We assessed the outcome of ischemia by evaluating the size of cerebral ischemia as well as mortality and behavioral outcome in mouse model.

Materials and methods

Animals

Male C57BL6 mice (6 weeks old; Orient Bio, Seoul, Republic of Korea, n = 42), weighing 22–25 g, were randomly assigned to three experimental groups: hypoxia (n = 15), exercise (n = 12), and normal control (n = 8). Animals were housed with a 12-hour light/dark cycle with ad libitum access to food and water. Animal care and handling were carried out according to the guidelines of the Institutional Animal Care and Use Committee of Seoul National University Hospital.

Hypoxia and exercise model

Chronic hypoxia was exposed to 15 mice using automated hypoxic chamber (Coy Laboratory Products, Grass Lake, MI, USA). All mice were bred at hypoxic chamber for two hours per day during light phase (when the animals typically sleep). O_2 was replaced by N_2 in a stepwise manner to create normobaric oxygen levels of 15% (day1), 12% (day2), and finally 10% on day 3, from the previous studies with some modification.[11,12] The latter oxygen concentration, 10% O_2, was maintained for the remainder of the experiment. Total duration of hypoxia was 40 hours, that is, two hours daily for 20 days.

12 mice in exercise group were exposed to voluntary chronic aerobic exercise for total two weeks. During the period, the mice were fed in the cage with wheel running (Model 80820F, Lafayette Instrument Co.,

Lafayette, IN, USA) with wheel diameter of 12.7 cm, and amount of exercise was evaluated by wheel running counter (Model 86060, Lafayette Instrument Co., Lafayette, IN, USA).

Induction of focal cerebral ischemia

Cerebral ischemia was induced by performing intraluminal filamentous occlusion of the MCA permanently, according to the previously described methods.[13] In brief, after the anesthetization by intraperitoneal injection of 1% ketamine (30 mg/kg) and xylazine hydrochloride (4 mg/kg), the left common carotid artery was exposed at its bifurcation by a midline cervical incision. The branches from the external carotid artery (ECA) were then coagulated and the pterygopalatine artery was ligated with a 4-0 silk suture. The ECA was then transected and a 3-0 nylon monofilament suture, its tip rounded by heating, was inserted into the ECA stump. To occlude the origins of the MCA and proximal anterior cerebral artery, the suture was advanced into the ICA 15 mm beyond the ICA–pterygopalatine artery bifurcation. Permanent focal cerebral ischemia was induced by leaving the intraluminal filament in place after occluding the MCA. The suture was then secured in place with a ligature and the wound closed. No case of seizure occurred during the experiments at any time following the MCA occlusions. Rectal temperature was maintained at 37 ± 0.5 °C using a thermistor-controlled heating blanket. Free access to food and water was allowed after recovery from anesthesia. Animals were allowed to recover for 24 h and were subjected to analyses of ischemic volume and neurologic function tests.

Behavioral tests

The Y-maze test and neurological function scoring were conducted by 2 individuals blinded to the mouse treatment status. They were performed daily after ischemia for 3 days until ischemic volume evaluation, as previously described.[14] Mice were placed at the center of Y-maze and allowed to move freely through the maze during an 10-min test session. Two results from Y-maze test were number of all entries, and spontaneous alternation testing the tendency of mice to enter an arm of a Y-maze that was not explored in the last two choices. The series of arm entries was recorded visually. Alternation was defined as successive entries into the three arms on overlapping triplet sets. The effect was calculated as percent alternation according to the following formula: percent alternation = {(number of alternation) / (total number of arm entries – 2)} × 100 (%).

Neurological function scoring was maximum score evaluated by each individual and 12 points were normal (Table 1).[15]

Measurement of ischemic volume

At 72 h after the ischemic insults, ischemic volume (infarcted tissue and penumbra) was evaluated in the ischemia model using 2,3,7-triphenyltetrazolium chloride (TTC; Sigma) staining, as described previously.[16] The brain was removed, and cut from the frontal tip by 1 mm thickness, which was then immersed in a 2% solution of TTC. The stained slices were then fixed in phosphate-buffered 4% paraformaldehyde, and the ischemic and total hemispheric areas of each section were traced and measured using an image analysis system (MIPAV, Center for Information

Technology, National Institutes of Health, Bethesda, MD, USA). The hemisphere cortical volume was calculated by summing the infarct volumes in the brain slices, and the results were analyzed statistically. In addition, we selected a standard section at the level of the anterior commissure, and compared the percentage areas of infarction in the striatum and the cortex. Ischemic volumes were determined by two independent investigators blinded to the type of section, and were expressed as percentages of total hemispheric volumes. The corrected ischemic volume was calculated to compensate for the effect of brain edema, as follows: corrected ischemic area = measured ischemic area × {1 − [(ipsilateral hemisphere area − contralateral hemisphere area) / contralateral hemisphere]}. Infarct volumes were expressed as a percentage of the contralateral hemisphere.

Statistical analysis

Mortality and hyper-acute stroke outcome data of the groups were analyzed statistically using the Kruskal–Wallis one-way analysis of variance. When the P-values from Kruskal-Wallis test were below 0.05, a Mann–Whitney U test was further used for post-hoc intergroup comparisons. Mann–Whitney U test were again used for acute stroke data between exercise and control group. The correlation between exercise amount and stroke outcome were analyzed using the Spearman's rank order. $P < 0.05$ was considered statistically significant. All data are shown as means ± SEMs.

Results

Chronic hypoxia causes higher mortality rate after cerebral ischemia

Chronic hypoxia group showed higher mortality during acute period (up to 3 days) of ischemia compared with the control group ($P < 0.05$, Figure 1). Mortality rate of control group was 25 % (2 from 8 mice), hypoxia group was 93.3 % (14 from 15 mice), and that of exercise group was 42.7 % (5 from 12 mice). According to variance analysis three groups were found to be significantly different from each other in respect of mortality ($P = 0.01$), and intergroup comparisons done with Mann–Whitney U-test revealed that there was statistical difference of mortality rate between hypoxia and control groups ($P = 0.003$).

Chronic hypoxia results in poorer neurological functional outcome during hyper-acute period after cerebral ischemia

24 h neurological function tests showed poorer outcome in chronic hypoxia group (Figure 2). Number of entries in Y-maze test showed no statistical differences ($P = 0.2$, Figure 2A); mean number was 0.13 ± 0.33 in control group, 0.94 ± 0.64 hypoxia group, and 5.56 ± 6.72 in exercise group. Spontaneous alternation in Y-maze test revealed statistical differences according to variance analysis ($P = 0.011$), but the intergroup comparisons showed no differences between each two group. On the contrary, neurological function score demonstrated statistical differences between control-hypoxia and hypoxia-exercise groups; variance analysis of three

groups were found to be significantly different from each other in respect of mortality (P = 0.01, Figure 2B), and intergroup comparisons done with Mann–Whitney U-test revealed that there was statistical difference of neurological function score between hypoxia and control groups (P = 0.003); mean score was 5.50 ± 1.00 in control group, 2.10 ± 1.97 in hypoxia group, and 6.67 ± 3.20 in exercise group.

Exercise prevents functional deficit after cerebral ischemia

Exercise group showed the better functional outcome during acute period of ischemia compared with the control group (Figure 3). In Y-maze test, number of entries (P = 0.035, Figure 3A) and spontaneous alternation (P = 0.035, Figure 3B) were higher in exercise group than control group. Mean number of entries per day was 12.24 ± 7.38 in exercise group and 3.06 ± 3.86 in control group, which shows 4.01 times higher in exercise group compared with control group. Mean spontaneous alternation per day was 43.30 ± 20.56 in exercise group and 12.78 ± 10.88 in control group, which indicates 3.39 times higher in exercise group compared with control group. Moreover, the exercise group demonstrated higher neurological function score than control group (P = 0.022, Figure 3C); mean neurological function score of exercise group was 8.43 ± 1.40, which was 1.50 times higer than control group with mean score of 5.61 ± 1.85.

Additional analysis showed that the amount of exercise was related with number of entries (P < 0.001, Figure 4), but not with neurological functional scoring (P = 0.185) and spontaneous alternation (P = 0.159). Overall, exercise reduces functional deficit after cerebral infarction, and the

superiority of neurological function was partially proportional to the quantity of exercise.

Exercise may reduce infarction volume

The exercise group exhibited reduced infarct volume compared with the control group at 3 day, but the difference was not statistically significant. The mean ratios of the corrected infarct volume to the total hemisphere were 10.97 ± 11.67 % in exercise group and 25.43 ± 19.73 % in the control group (P = 0.051, Figure 5 and 6). The mean infarct volume of exercise group was 43.12 % compared with the control group, which indicates 56.88% decrease in infarcted area.

Additional analysis showed that the amount of exercise was not correlated with the infarct size (P = 0.846). In addition, hypoxia group could not be analyzed with the other two groups due to high mortality as described above.

Discussion

In the present study, we demonstrated that chronic hypoxia increases mortality after cerebral ischemia, in contrast, exercise has beneficial effect on functional recovery after stroke in animal model. Chronic hypoxia worsened mortality 68 % more than control, whereas exercise reduced ischemia volume by about 57%. Moreover, functional outcome after cerebral ischemia exhibited a dose-response relationship with the amount of exercise.

The precise mechanisms of negative effect of chronic hypoxia on stroke remain unknown. However, several studies have suggested that cerebrovascular function affected by chronic hypoxia plays a crucial role in the pathophysiology of the animal model of cerebral ischemia.[17,18] One report revealed that animals exposed to chronic hypoxia exhibited increased sympathetic nerve activity due to enhanced reflexes from carotid bodies.[17] Another study demonstrated that chronic hypoxia reduced cerebrovascular reserves by attenuating endothelial responses through endothelin 1 and NADPH oxidase-derived radicals.[19] In our study, the hypoxia group showed high mortality, and we assumed that extreme cerebrovascular deterioration affected the result negatively.

On the contrary, physical activity has multiple protective effects for stroke.[20] Physical activity reduces blood pressure and controls other risk factors for stroke including diabetes mellitus, obesity and dyslipidemia. It also prevents thrombogenic condition by reducing plasma fibrinogen and platelet activity and elevating plasma tissue plasminogen activator activity. In animal model, exercise has been shown to reduce infarction size and

neurological deficits after cerebral ischemia,[21] as in the present study. The previous study attempted to attribute the risk reduction to increased expression and activity of eNOS, NO-dependent vasodilatation and regional cerebral blood flow.[21] In addition, exercise inhibits injury due to inflammation by decreasing ICAM-1 expression and consecutive lower leukocyte accumulation in damaged brain and causes an overexpression of neutrophils as BDNF.[22] In conclusion, exercise promotes short- and long-term effects that increase cerebral perfusion and functional outcome by activation and expression of eNOS after experimental ischemia in the mouse model.

These two conflicting effects from chronic hypoxia and exercise can be attributed to the same mechanisms through carotid chemoreflex. A growing amount of evidence suggests that the carotid chemoreflex in response to hypoxia plays a role to prevent stroke.[23-25] Especially, although some reports demonstrated that chronic hypoxia can be beneficial for stroke risk in human and animal model,[26-28] selective potentiation of autonomic responses by carotid reflex can be thought to contribute to this apparently contradicting results. Physical activity also plays a role in endothelial function and cerebral autoregulation,[29] suggesting the relationship with carotid reflex.

Carotid body is a peripheral chemoreceptor that resides in carotid bifurcation and sensor the plasma oxygen, carbon dioxide partial pressure and acidity continuously.[25] In that sense, carotid body is neural tissue that control and interact with other parts of body. In the hypoxic environment, cells in carotid body are activated and send afferent parasympathetic signals

to brainstem which negatively feedback to the sympathetic nerve activation with hyperpnea, increased cardiac output and hypertension to compensate hypoxia. Carotid body contains cells that divide, proliferate and differentiated, thus its activity can be variable according to the individuals by innate or acquired effects and tissue damage due to hypoxia would be induced if this sensor system does not activate properly. Therefore, the patient whose carotid body has decreased activity would undergo more severe damage when acute ischemic insult was applied.[2-4] On the other hand, those who have chronically increased activity of carotid body may retain higher capacity that minimizes the ischemic damage,[6-8] but chronic increase of sympathetic tone would result in various cardiovascular diseases.[26]

There are several limitations in this study. First, the key mechanism connecting two conditions and carotid body cannot be elucidated due to the insufficient result. The quantitative polymerase chain reaction failed to show the meaningful consequences since the sample size of mouse carotid body was not sufficient. Second, mortality of the hypoxia group was too high to analyze further results. High mortality of hypoxia group may be caused by inadequate hypoxia condition. Third, the number of mice model was not large enough to show statistical significant, especially with the infarction size. Large number of models would guarantee the positive relationship with the infarction volume, as well as behavior tests. Further evaluations are needed to clarify these underlying processes.

References

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson L, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M, Murray C; Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014;383:245-254.
2. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med.* 2005;353:2034-2041.
3. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Ali T, Lebowitz M, Punjabi NM. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med.* 2010;182:269-277.
4. Loke YK, Brown JW, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2012;5:720-728.
5. Jaillard AS, Hommel M, Mazetti P. Prevalence of stroke at high altitude (3380 m) in Cuzco, a town of Peru. A population-based study. *Stroke* 1995;26:562-568.

6. Wannamethee G, Shaper AG. Physical activity and stroke in British middle aged men. *BMJ* 1992;304:597-601.
7. McDonnell MN, Hillier SL, Hooker SP, Le A, Judd SE, Howard VJ. Physical activity frequency and risk of incident stroke in a national US study of blacks and whites. *Stroke* 2013;44:2519-2524.
8. Lee CD, Folsom AR, Blair SN. Physical activity and stroke risk: a meta-analysis. *Stroke* 2003;34:2475-2481.
9. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993;328:1230-1235.
10. Stroud N, Mazwi TM, Case LD, Brown RD Jr, Brott TG, Worrall BB, Meschia JF; Ischemic Stroke Genetics Study Investigators. Prestroke physical activity and early functional status after stroke. *J Neurol Neurosurg Psychiatry* 2009;80:1019-1022.
11. Eurlings IM, Reynaert NL, van den Beucken T, Gosker HR, de Theije CC, Verhamme FM, Bracke KR, Wouters EF, Dentener MA. Cigarette smoke extract induces a phenotypic shift in epithelial cells; involvement of HIF1α in mesenchymal transition. *PLoS One* 2014;9:e107757.
12. Bishop T, Talbot NP, Turner PJ, Nicholls LG, Pascual A, Hodson EJ, Douglas G, Fielding JW, Smith TG, Demetriades M, Schofield CJ, Robbins PA, Pugh CW, Buckler KJ, Ratcliffe PJ. Carotid body hyperplasia and enhanced ventilatory responses to hypoxia in mice with heterozygous deficiency of PHD2. *J Physiol.* 2013;591:3565-3577.
13. Jung KH, Chu K, Ko SY, Lee ST, Sinn DI, Park DK, Kim JM, Song EC, Kim M, Roh JK. Early intravenous infusion of sodium nitrite

protects brain against in vivo ischemia-reperfusion injury. *Stroke* 2006;37:2744-2750.

14. Oka J, Suzuki E, Kondo Y. Endogenous GLP-1 is involved in beta-amyloid protein-induced memory impairment and hippocampal neuronal death in rats. *Brain Res.* 2000;878:194-198.
15. Abella BS, Zhao D, Alvarado J, Hamann K, Vanden Hoek TL, Becker LB. Intra-arrest cooling improves outcomes in a murine cardiac arrest model. *Circulation* 2004;109:2786-2791.
16. Jung KH, Chu K, Lee ST, Park HK, Kim JH, Kang KM, Kim M, Lee SK, Roh JK. Augmentation of nitrite therapy in cerebral ischemia by NMDA receptor inhibition. *Biochem Biophys Res Commun.* 2009;378:507-512.
17. Prabhakar NR, Kumar GK. Oxidative stress in the systemic and cellular responses to intermittent hypoxia. *Biol Chem.* 2004;385:217-221.
18. Crossland RF, Durgan DJ, Lloyd EE, Phillips SC, Reddy AK, Marrelli SP, Bryan RM Jr. A new rodent model for obstructive sleep apnea: effects on ATP-mediated dilations in cerebral arteries. *Am J Physiol Regul Integr Comp Physiol.* 2013;305:334-342.
19. Capone C, Faraco G, Coleman C, Young CN, Pickel VM, Anrather J, Davisson RL, Iadecola C. Endothelin 1-dependent neurovascular dysfunction in chronic intermittent hypoxia. *Hypertension* 2012;60:106-113.
20. Gallanagh S, Quinn TJ, Alexander J, Walters MR. Physical activity in the prevention and treatment of stroke. *ISRN Neurol.* 2011;2011:953818.
21. Endres M, Gertz K, Lindauer U, Katchanov J, Schultze J, Schröck H,

Nickenig G, Kuschinsky W, Dirnagl U, Laufs U. Mechanisms of stroke protection by physical activity. *Ann Neurol.* 2003;54:582-590.

22. Ding YH, Young CN, Luan X, Li J, Rafols JA, Clark JC, McAllister JP 2nd, Ding Y. Exercise preconditioning ameliorates inflammatory injury in ischemic rats during reperfusion. *Acta Neuropathol.* 2005;109:237-246.
23. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev.* 2010;90:47-112.
24. Narkiewicz K, van de Borne PJ, Pesek CA, Dyken ME, Montano N, Somers VK. Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. *Circulation* 1999;99:1183-1189.
25. Gonzalez-Martín MC, Vega-Agapito MV, Conde SV, Castañeda J, Bustamante R, Olea E, Perez-Vizcaino F, Gonzalez C, Obeso A. Carotid body function and ventilatory responses in intermittent hypoxia. Evidence for anomalous brainstem integration of arterial chemoreceptor input. *J Cell Physiol.* 2011;226:1961-1969.
26. Lavie P, Lavie L, Herer P. All-cause mortality in males with sleep apnoea syndrome: declining mortality rates with age. *Eur Respir J.* 2005;25:514-520.
27. Stowe AM, Altay T, Freie AB, Gidday JM. Repetitive hypoxia extends endogenous neurovascular protection for stroke. *Ann Neurol.* 2011;69:975-985.
28. Jackman KA, Zhou P, Faraco G, Peixoto PM, Coleman C, Voss HU, Pickel V, Manfredi G, Iadecola C. Dichotomous effects of chronic intermittent hypoxia on focal cerebral ischemic injury. *Stroke*

2014;45:1460-1467.

29. Schmidt W, Endres M, Dimeo F, Jungehulsing GJ. Train the vessel, gain the brain: physical activity and vessel function and the impact on stroke prevention and outcome in cerebrovascular disease. *Cerebrovasc Dis.* 2013;35:303-312.

Level of consciousness	
1. No reaction to pinching of tail	0
2. Poor response to tail pinch	1
3. Normal response to tail pinch	2
Corneal reflex	
1. No blinking	0
2. Sluggish blinking	1
3. Normal blinking	2
Respirations	
1. Irregular breathing pattern	0
2. Decreased breathing frequency, normal pattern	1
3. Normal breathing frequency and pattern	2
Righting reflex	
1. No turning attempts	0
2. Sluggish turning	1
3. Turns over spontaneously and quickly	2
Coordination	
1. No movement	0
2. Moderate ataxia	1
3. Normal coordination	2
Movement/activity	
1. No spontaneous movement	0
2. Sluggish movement	1
3. Normal movement	2
Total possible score	12

Table 1. Neurological function score. Referred from reference[13]

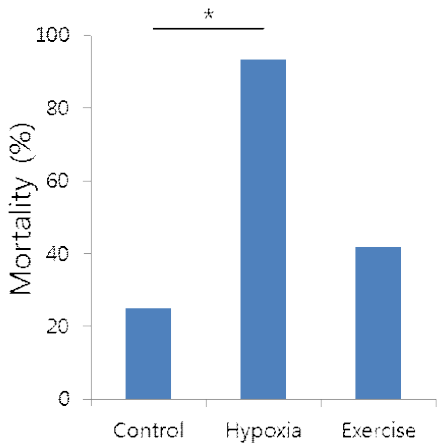

Figure 1. Mortality rate during acute stroke period according to each group. Mortality rate of control group was 25 %, hypoxia group was 93.3 %, and that of exercise group was 42.7 %. Intergroup difference was validated between control and hypoxia groups ($P < 0.05$)

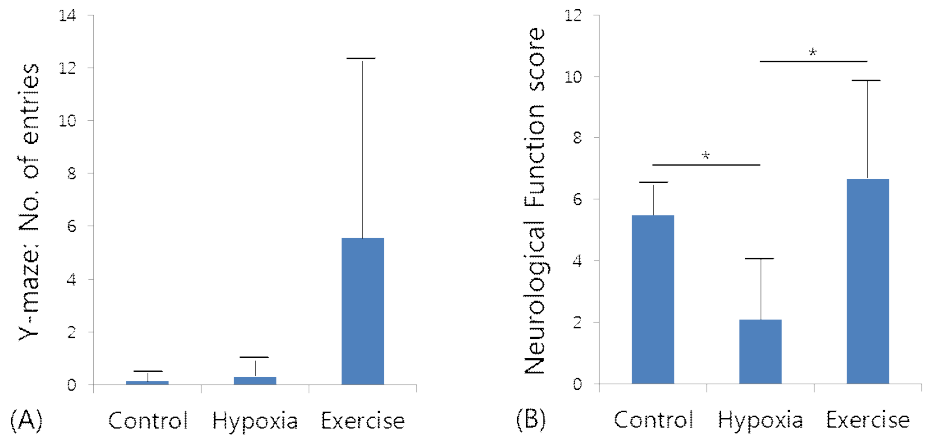

Figure 2. Functional outcome during hyper-acute stroke period according to each group. (A) Number of entries in Y-maze test showed no statistical differences; mean number of control group was 0.13 ± 0.33, hypoxia group was 0.94 ± 0.64, and that of exercise group was 5.56 ± 6.72. (B) Neurological function score showed statistical differences between control-hypoxia and hypoxia-exercise groups; mean score of control group was 5.50 ± 1.00, hypoxia group was 2.10 ± 1.97, and that of exercise group was 6.67 ± 3.20.

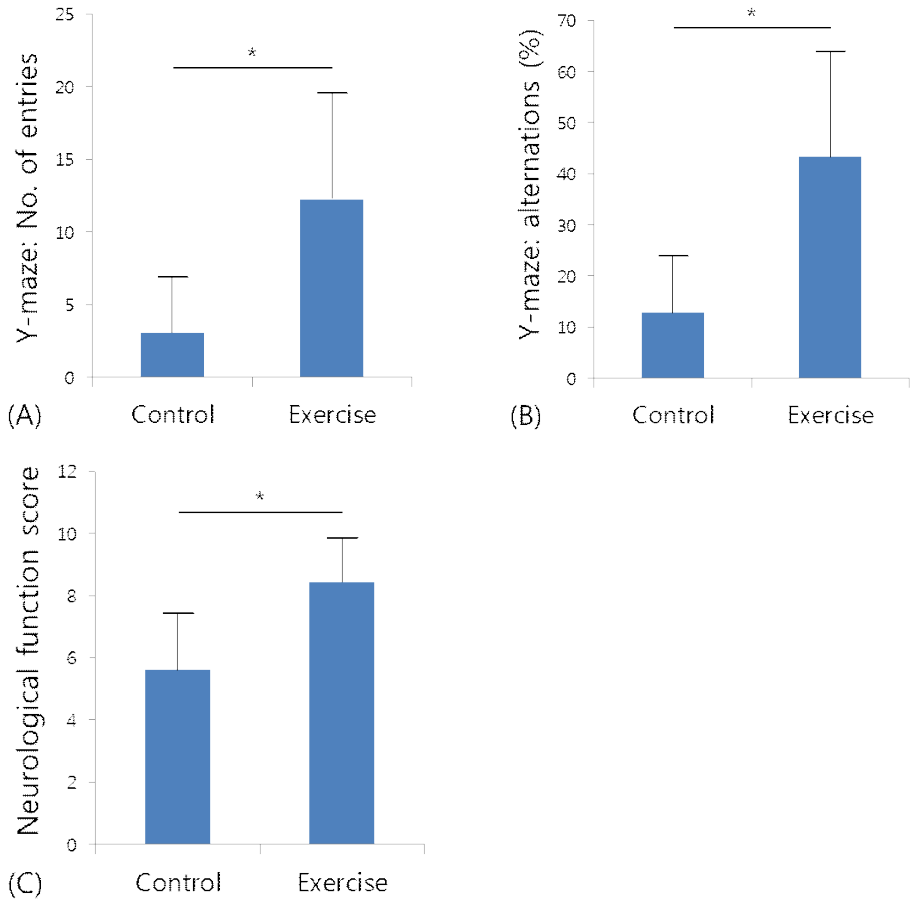

Figure 3. Average neurological deficit during acute stroke period according to each group. (A) Average score of exercise group during acute period after cerebral ischemia was 8.73 ± 1.72, and that of control group was 4.78 ± 0.69. (B) Average number of entries in Y-maze test of exercise group was 11.87 ± 9.53, and that of control group was 1.11 ± 1.02. (C) Average spontaneous alternation in Y-maze test of exercise group was 45.86 ± 25.97 %, and that of control group was 8.15 ± 7.14 %

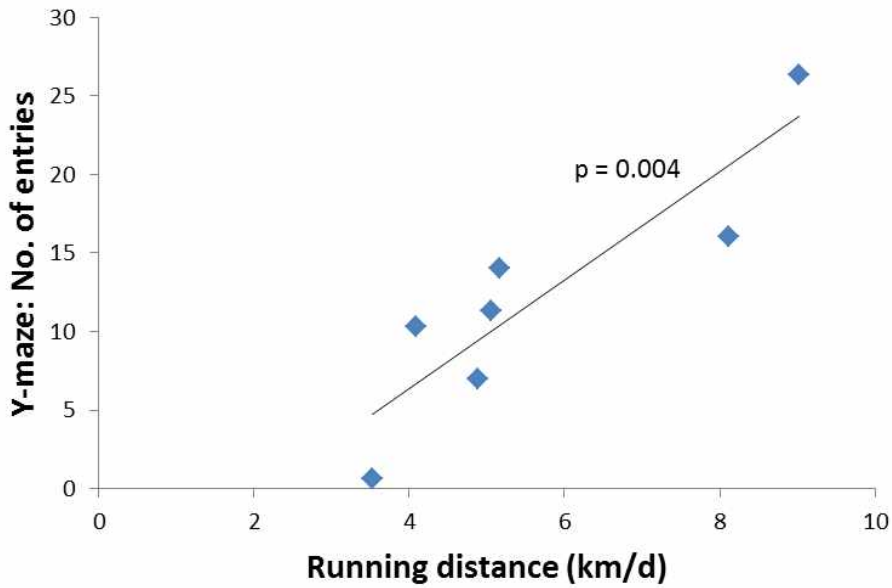

Figure 4. Relationship of the amount of exercise with average number of entries in Y-maze test.

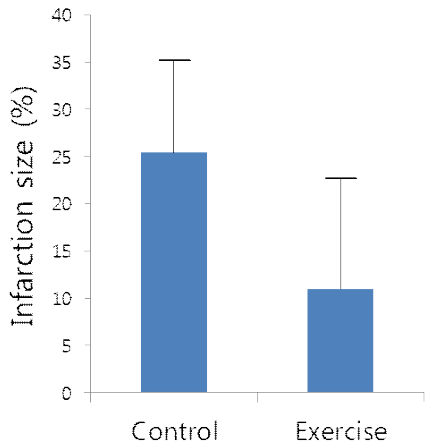

Figure 5. Infarction size according to each group. Infarction size on 3 day after cerebral ischemia of exercise group was 8.59 ± 12.54 %, and that of control group was 19.15 ± 12.71 %.

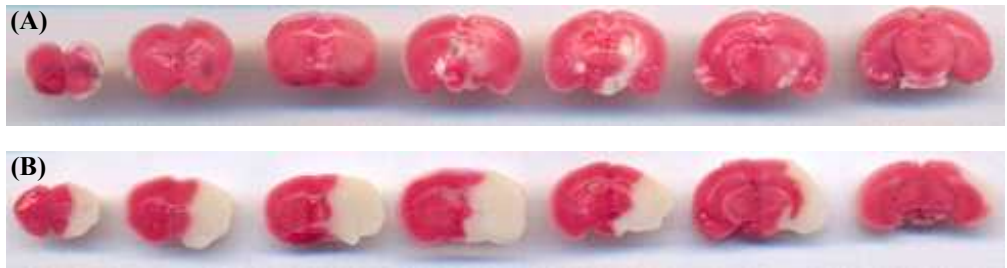

Figure 6. One of each ischemia model, exercise (A) and control (B)

국문초록

수면 무호흡증과 운동은 허혈성 뇌경색에 서로 상반된 영향을 끼친다. 수면 무호흡증은 뇌경색의 위험 인자로 작용하나, 운동은 뇌경색을 예방하고 예후를 좋게 한다. 본 연구에서 저자들은 만성 저산소증과 운동이 뇌경색 동물 모델에서 서로 다른 결과를 가져옴을 보였다. 만성 저산소증은 대조군에 비해 뇌경색 초기의 치사율이 유의하게 높았으며, 초급성기인 24시간 이내에서 신경학적 점수가 유의하게 낮았다. 뇌경색 급성기인 72시간 동안 운동군은 대조군에 비해 신경학적인 예후가 더 좋았으며, 신경학적 점수 및 Y-maze의 entrance 수가 유의하게 우월한 결과를 보였다. 뇌경색 크기는 운동군에서 평균 57% 작았으나 통계적으로 유의하지는 않았다 (P = 0.051). 운동 총량도 위의 내용과 같은 관계를 갖는다는 것을 밝혔다. 이러한 결과로부터 만성 저산소증은 허혈성 뇌경색의 예후에 좋지 않은 영향을 끼치지만, 운동은 급성 허혈성 뇌경색 후에 신경학적 손상을 감소시키는 데에 중요한 역할을 할 수 있음을 보았다.

주요어: 저산소, 무호흡증, 운동, 신체활동, 뇌경색

학번: 2013-21725