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# The Harmful Effects of Prolonged Strenuous Treadmill Exercise on Bronchoalveolar System in Rats

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We designed this study to investigate the effects of continuous strenuous aerobic exercise on the respiratory system in a rat model. After exercise for 8 weeks, rats' weights were higher in the exercise groups than in the Control group (non-exercise). Rats in Exercise-120 min group (Ex-120 group) had the lowest weights. Total leukocyte counts in bronchoalveolar lavage fluid (BALF) were higher in exercise groups than in Control group. The Ex-30 and Ex-120 groups had higher neutrophil counts, whereas that in the Ex-60 group was lower than in the Control group, and that in the Ex-30 group was the highest. Lymphocyte and monocyte counts were higher in all exercise groups than in the Control group, and those in the Exercise-120 min group were the highest. Interleukin-6 (IL-6) level was the highest, while IL-10, interferon-γ and nitric oxide (NO) levels were the lowest in the Ex-120 group when compared to the Control and other exercise groups. These findings suggest that strenuous aerobic exercise for short periods (30 min) may have a beneficial effect on decrease in body weight, whereas prolonged-strenuous aerobic exercise (>1 hr) may be adverse to leukocyte and immune levels in the bronchoalveolar system, as well as result in an increased production of oxygen free radicals.

**Key words** : Exercise, bronchoalveolar lavage, leukocyte, cytokines, nitric oxide

## Introduction

Exercise is one of the most important way for improving health in humans and animals. During exercise, coronary blood flow increases to the myocardium with an adequate supply of oxygen and nutrients as well as to remove metabolic by-products.

Numerous studies have reported that regular exercise is known to reduce the risk of chronic disease, such as diabetes [7], cardiovascular disease [15] and cancer [16], to prevent osteoporosis, obesity and aging, and to increase resistance to infections such as the common cold. Investigation by Blair et al. [4] also revealed that regular exercise offers protection against all-cause mortality, primarily by protection against atherosclerosis, type 2 diabetes, colon cancer, and breast cancer. In addition, physical training is effective in the treatment of patients with ischemic heart disease [10], heart failure [27], and chronic obstructive pulmonary disease [14].

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However, physical exercise can, paradoxically, both enhance and suppress immunity, with the response being related to the type, frequency, intensity, and duration of exercise and the level of fitness of individual [25]. Furthermore, the amount of exercise required to achieve beneficial effects has not been clearly defined. To obtain maximal health benefits from exercise while avoiding potentially deleterious effects, it is important to determine the appropriate amount of physical activity. The negative effects of exercise include a systemic inflammatory response [25], leukocyte DNA damage [32], an increased production of reactive oxygen and nitrogen species [28], increased cytokine release [25], acute coronary syndrome [33], increased platelet and leukocyte activations, elevated platelet and leukocyte aggregation, and facilitation of thrombogenesis [12]. Recent studies have shown other damaging effects of exercise, which may induce bronchoconstriction, asthma, or bronchial hyperresponsiveness [1].

Even though exercise clearly, influence all metabolism and physiology in human body, respiratory system is a target to suffer the most vigorous stress of physical activity as well as cardiovascular system. Nevertheless, most studies on the exercise have focused mainly for the brain, cardiovascular system, immune, energy metabolism, and so

forth.

In addition, we have little data to understand the physiological influence of intensity and duration of aerobic exercise on the respiratory system. Therefore, study need to clarify the effect of high intensity exercise on bronchoalveolar space, which well reflects exercise-induced changes of respiratory system.

We have designed this study to investigate the effects of duration of strenuous aerobic exercise on the respiratory system and biochemical metabolism.

## Materials and Methods

### Rat and grouping

Male Sprague-Dawley (SD) rats (aged 12 weeks) were purchased from Joong-Ang Animal Company (Seoul, Korea). The rats were kept in pathogen-free environment and received sterilized food and water at the Laboratory Animal Center. All rats were kept on a 12:12-hrs light/dark cycle at a temperature of 25°C and humidity of 60%. After adaptation for 2 weeks and were divided into four groups: Non-exercise (Control group, n=7), exercise for 30 min (Ex-30 group, n=8), exercise for 60 min (Ex-60 group, n=8), and exercise for 120 min (Ex-120 group, n=8) (Table 1).

### Exercise program

The rats in exercise groups were adjusted by running at 10 m/min (corresponding to 0.6 km/hr) with 0% gradient on a motorized treadmill (TM motor 2000, korea) for 1 week. Then, the rats were aerobically trained (by running) for 30 min (Ex-30 group), 60 min (Ex-60 group), or 120 min (Ex-120 group), respectively.

During the exercise, the rats were warmed up at 13.33 m/min (corresponding to 0.8 km/hr) with 0% gradient and the speed was increased in increments of 33.33 m/min (corresponding to 2.0 km/hr) with 0% gradient. This speed is strenuous exercise (maximal $0_2$ uptake, $VO_2max > 80$-85%) [18]. This exercise program was applied daily for 8 weeks

### Sacrifice

All rats were anesthetized with inhalation of ether in a bottle and placed on the rat operating table (Dong Seo Science, Korea) with supine position. The heart was exposed with upper abdominal incision.

### Collection of bronchoalveolar lavage fluid (BALF)

For the collection of BALF, the right bronchus was ligated with surgical thread. After incision of trachea, 4 mm catheter filled with 5 ml of heparinized phosphate buffer saline (PBS) was inserted into left bronchus. At the least 4 times, left bronchus and lung were washed by the PBS and bronchoalveolar lavage flued (BALF) was collected. Leukocyte counts were measured immediately after collection of BALF. Render BALF was centrifuged into supernatant at 4°C, 6,000× *g* for 10 min and kept in -70°C until determination of cytokines levels.

### Analysis

#### Leukocyte counts

For measuring total leukocyte & diff-counts in the BALF, 1 ml of BALF was analyzed with Animal Auto Hematology Analyzer (BC-2800 ver., Shenzhen Mindary Bio-Medical

Table 1. Characteristics of four groups

| Variable | Group | | | |
|---|---|---|---|---|
| | Control | Ex-30 | Ex-60 | Ex-120 |
| Sample size (n) | 7 | 8 | 8 | 8 |
| BE-Age (wk) | 12 | 12 | 12 | 12 |
| AE-Age (wk) | 20 | 20 | 20 | 20 |
| Exercise type | Non | Aerobic | Aerobic | Aerobic |
| Ex-speed (m/min) | 0 | 33.33 | 33.33 | 33.33 |
| Ex-duration (wk) | 0 | 8 | 8 | 8 |
| Species (rat) | SD | SD | SD | SD |
| BE-Wt (g) | 353.79±19.63 | 362.58±20.42 | 321.60±18.38 | 351.10±22.85 |
| AE-Wt (g) | 452.50±33.55 | 418.50±26.12* | 382.57±31.04**‡ | 364.21±21.64**‡ |

Data were expressed as the mean±standard error (SE).

*, $p<0.05$ (compared with Control); **, $p<0.01$ (compared with Control); ‡ , $p<0.05$ (compared with Ex-30 min).

Abbreviation: Control, no exercise; Ex-30, daily exercise for 30 min; Ex-60, daily exercise for 60 min; Ex-120. daily exercise for 120 min; Ex, exercise; BE, before exercise; AE, after exercise; Wt, weight; SD, Sprague-Dawley.

Electronics Co., Ltd., Germany).

### Cytokines

#### Interleukin-6 (IL-6)

ELISA (Enzymed-Linked Immunosor-bent Assay) method was applied for measuring concentration in BALF. 100 μl of BALF were analyzed by Emax Precision Microplate Reader(Molecular Device, America) with Quantikine Rat IL-6 kit (R&D system, America). Each 100 μl of standard solution and BALF was put into 96 well-microplate and 100 μl of conjugate was added. The microplate was incubated for 2 hrs at room temperature (on 100-120 rpm) and it was washed with washing solution (3 times). 200 μl of substrate was added per well and placed for 30 min at room temperature with protection from light (on 100-120 rpm). 50 μl of stop solution (tacrine) was dispensed to each well of microplate. The optical density of each well was determined within 30 min using a microplate reader set to 450 nm.

#### Interleukin-10 (IL-10)

ELISA method was applied for determining IL-10 level in BALF.

100 μl of BALF were analyzed by Emax Precision Microplate Reader (Molecular Device, America) with Quantikine Rat IL-10 kit (R&D system, America). Each 50 μl of standard solution and BALF was put into 96 well-microplate and 100 μl of conjugate was added. The microplate was incubated for 2 hrs at room temperature (on 100-120 rpm) and it was washed with washing solution (3 times). 200 μl of substrate was added per well and placed for 30 min at room temperature with protection from light (on 100-120 rpm). 50 μl of stop solution (tacrine) was dispensed to each well of microplate. The optical density of each well was determined within 30 min using a microplate reader set to 450 nm.

#### Interferon-γ (IFN-γ)

ELISA method was applied for determining IFN-γ level in BALF. 100 μl of BALF were analyzed by Emax Precision Microplate Reader (Molecular Device, America) with Quantikine Rat IFN-γ ELISA kit (Abcam, England). Each 100 μl of standard solution and BALF was put into 96 well-microplate and 50 μl of diluted biotinylated anti-γ IFN gamma was added. The microplate was incubated for 3 hrs at room temperature (on 100-120 rpm) and it was washed with washing solution (2 times). 100 μl of HRP (horse radishi peroxidase) was dispensed into all wells, including the blank wells and microplate strips were incubated at room temperature for 20 min. The was washed 2 times. 100 μl of substrate was added per well and placed for 12-15 min at room temperature with protection from light (on 100-120 rpm). 50 μl of stop solution (tacrine) was dispensed to each well of microplate. The optical density of each well was determined within 30 min using a microplate reader set to 450 nm.

#### Nitric oxide (NO)

NO levels in BAL fluid (100 ul) (ELISA method) were analyzed by Emax precision microplate reader (Molecular Device, America) with Total NO/Nitrite/Nitrate kit (R&D System, America). The assay procedures were as follows: After nitrite and nitrate reduction assays, the result of the nitrate reduction assay was subtracted from that of the nitrite assay, and the results were the final NO levels. This assay procedure was designed to measure the concentration of endogenous nitrite present in the sample. All reagents, working standards, and samples were prepared as directed in the previous sections. 50 μl of reaction diluent (1X) was added to the blank wells. 50 μl of nitrite standard or sample was added to the remaining wells. 50 μl of reaction diluent (1X) was added to all wells. 50 μl of griess reagent I was added to all wells. 50 μl of griess reagent II was added to all wells. It was mixed well by tapping the side of the plate gently and was then incubated for 10 min at room temperature. The optical density of each well was determined by using a microplate reader set at 540 nm.

### Data analysis and statistics

A series of ANOVA were applied for data analysis. If significant differences were between groups, Dunncan tests as post-hoc were used to further analysis. Statistical significance was accepted with $p<0.05$. All data was expressed as the Mean ± standard deviation (SD).

## Results and Discussion

### Body weight

There were not significant different in the body weights between the four groups at pre-exercise period. However, after exercise for 8 weeks, the rats' body weights in all exercise groups were lower than that in Control group ($p<0.05$ or $p<0.01$, Table 1). The body weight in Ex-120 group was the lowest ($p<0.05$), suggesting that prolonged-strenuous exercise is effective for reducing body weight.

### Leukocyte counts in BALF

Total leukocyte counts in the three exercise groups were higher than that of Control group (300±25/ul) ($p<0.05$, Fig. 1). Among the exercise groups, Ex-30 group had the highest total leukocyte count (723±41/ul). Such increased leukocyte counts in the exercise groups may result from the stimulation of strenuous aerobic exercise on the bronchoalveolar system. Deep breathing or hyperventilation during aerobic exercise can cause inhalation of dust and/or particles into bronchoalveolar (respiratory) system. In the mechanism of elevated leukocyte counts, Ex-30 and Ex-120 group were slightly different from Ex-60 group. In the both groups, increase of total leukocyte count was due to elevated neutrophil, lymphocyte, and macrophage (monocyte) count (Figs. 2, 3, and 4), whereas, in Ex-60 group, it was attributable mainly to increased lymphocyte and macrophage (monocyte) count (Figs. 2 and 4). Among the three exercise groups, total leukocyte count in BALF was the highest due to elevated neutrophil in Ex-30 group. These findings indicate that short-term strenuous exercise may improve neutrophil- mediated immunity, whereas longer-period strenuous exercise may impair it.

Nevertheless, longer-period strenuous exercise (Ex-120

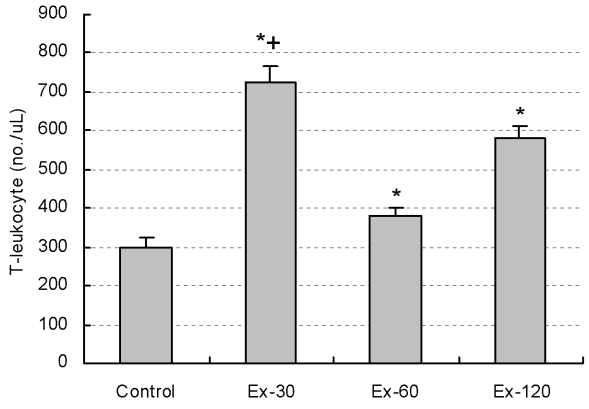


Fig. 1. Change of total leukocyte count in BALF (bronchoalveolar lavage fluid) following aerobic exercise for 8 weeks. Three exercise groups had higher total leukocyte counts than Control group (*, $p<0.05$). Exercise-30 min group (Ex-30) had the highest total leukocyte count (+, $p<0.05$; compared with Ex-60 and Ex-120 group).

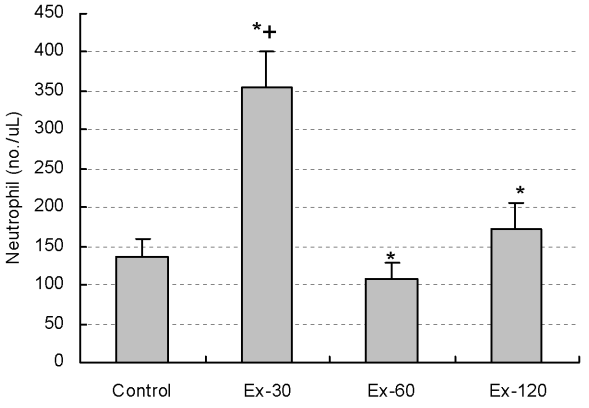


Fig. 2. Change of neutrophil count in BALF following aerobic exercise for 8 weeks. Exercise 30 and 120 group (Ex-30 and Ex-120, respectively) had higher neutrophil count, whereas Exercise 60 min (Ex-60 group) had lower that than Control group (*, $p<0.05$). Exercise-30 min group (Ex-30) had the highest neutrophil count (+, $p<0.05$; compared with Ex-60 and Ex-120 group).

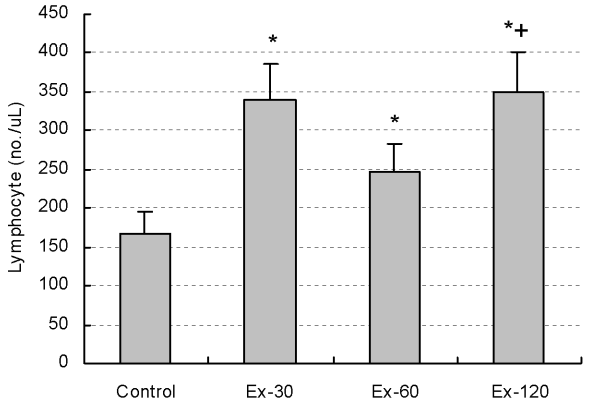


Fig. 3. Change of lymphocyte count in BALF following aerobic exercise for 8 weeks. Three exercise groups had higher lymphocyte counts than Control group (*, $p<0.05$). Exercise-120 min group (Ex-120) had the highest lymphocyte counts (+, $p<0.05$; compared with Ex-30 and Ex-60 group).

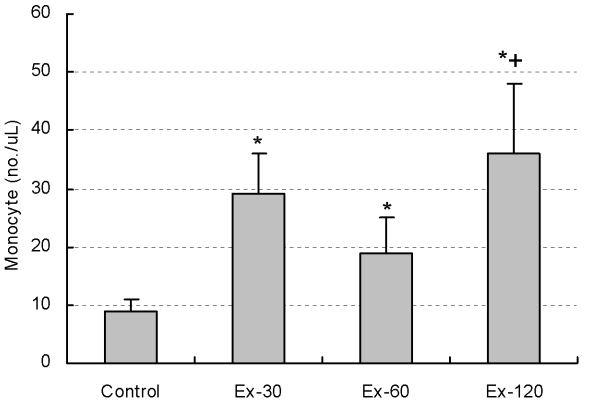


Fig. 4. Change of monocyte count in BALF following aerobic exercise for 8 weeks. Three exercise groups had higher monocyte counts than Control group (*, $p<0.05$). Exercise-120 min group (Ex-120) had the highest monocyte counts (+, $p<0.05$; compared with Ex-30 and Ex-60 group).

group) had higher lymphocyte and macrophage count than Control and short-term exercise group (Ex-30 group), suggesting that prolonged-exercise may lead to stimulation of cellular immunity. Our results were consistent with previous study, which reported exercise-induced increase of neutrophil counts [6]. As well known, T-lymphocyte generate a variety of cytokines, which are representative cytokines include IFN-γ, IL-2, IL-5, IL-6, and IL-10 [21].

Several studies have shown that exercise induces characteristic alterations of blood lymphocyte counts. An initial lymphocytosis during exercise is followed by a lymphocytopenia in the recovery phase after exercise [23]. The initial rise of blood lymphocytes is supposed to reflect cell mobilization both from the marginal pool and from peripheral lymphoid organs [13]. Environmental stress such as exercise induces a substantial re-distribution of T-cells within lymphoid and non-lymphoid organs. A uniform response pattern seems to exist with a decrease in lymphocyte numbers in the spleen which is accompanied by an increase in lymphocytes in lung, bone marrow and Peyer's patches.

This study demonstrates that short-term exercise (Ex-30 group) induces a increased BALF neutrophil count, whereas longer-period strenuous exercise (Ex-120 group) leads to elevated lymphocyte and monocyte count. This finding represents an exercise-induced re-distribution of lymphocytes. Recruit meat of lymphocytes into lungs contributes to an increase of lymphocyte counts in bronchoalveolar spaces.

Our observations agree with other authors opinions that strenuous exercise induces recruitment of lymphocytes to the circulation and bronchoalveolar spaces [24]. However, we did not determine lymphocyte subset in blood and BALF, and thus, further study should be performed for identifying the subset. Exercise enhances or reduces the immune function depending on its frequency, duration, and intensity [26]. Exhaustive exercise decreases the functional capacity of neutrophils and lymphocytes and increases susceptibility to infections.

### Cytokines and nitric oxide concentrations in BALF

IL-6 and NO levels in Ex-30 group were lower, whereas they in Ex-60 and Ex-120 group were higher than those of Control group ($p<0.05$, Table 2). IL-10 and IFN-γ levels in BALF were lower in all exercise groups than in Control group ($p<0.05$, Table 2). IL-6 and NO levels were the highest, while IL-10 and IFN-r levels were the lowest in Ex-120 group, indicating that prolonged strenuous exercise causes functional immune impairment [9] and increased sensitivity to upper respiratory tract infections [11]. Despite of increased leukocyte (lymphocyte and macrophage) counts in longer-period exercise groups (Ex-60 and 120 group) (Table 2) increase and decrease in the groups mean that prolonged strenuous exercise may lead to the impairment of immune function. IL-6, a pro-inflammatory cytokine, belongs to the family of cytokines, including IL-11, oncostatin M, leukemia inhibitory factor, ciliary neurotrophic factor, cardiotrophin-1, and cardioreophin-like cytokine. Physical exercise creates muscle damage and non-specific inflammatory response, which is manifested by elevated concentrations of circulating pro-inflammatory cytokines such as IL-1, tumor necrosis factor-α (TNF-α) and IL-6 [20].

Our observations indicate that short-term aerobic exercise offers a positive effect (a decrease of IL-6 level), whereas prolonged vigorous aerobic exercise has a negative effect (a increase of IL-6 level, inflammatory reaction) for health.

IL-10 is an anti-inflammatory cytokine and IL-10 acts as an anti-inflammatory cytokine and inhibits the synthesis of a large spectrum of pro-inflammatory cytokines. In this study, IL-10 level in Ex-30 group exceeded itself IL-6 level, whereas IL-6 levels in Ex-60 and Ex-120 group were higher than their IL-10 levels, suggesting adverse effects of longer-

Table 2. The changes of cytokines and nitric oxide concentrations in BALF

| Variable \ Group | Control | Ex-30 | Ex-60 | Ex-120 |
|---|---|---|---|---|
| IL-6 (pg/ml) | 37.61±10.43 | 20.14±7.07* | 39.93±14.45† | 43.59±11.30*† |
| IL-10 (pg/ml) | 67.40±16.68 | 24.36±10.90* | 31.65±12.64* | 22.77±8.27*‡ |
| IFN-γ (pg/ml) | 4.30±1.42 | 1.08±0.09* | 3.24±0.95* | 0.00±0.00*¶ |
| NO (umol/l) | 1.80±0.85 | 1.73±0.93 | 4.07±0.58*† | 5.26±0.60*¶ |

Data were expressed as mean±SD (standard deviation).
*, $p<0.05$ (compared with Control group); †, $p<0.05$ (compared with Ex-30 group); ‡, $p<0.05$ (compared with Ex-60 group); ¶, $p<0.05$ (compared with Ex-30 and Ex-60 group).
Abbreviation: BALF, bronchoalveolar lavage fluid; IL, interleukin; INF-γ, interferon-γ; NO, nitric oxide.

period aerobic exercise on the immune function. Increased production of pro-inflammatory IL-6 and decreased secretion of anti-inflammatory cytokine cause systemic inflammatory reaction. Together with IL-2 and TNF-β, IFN-γ is produced by type 1 T cells and a role in the protection against intracellular pathogens such as several virus [17].

T cells include CD+ T helper and CD8+ T cytotoxic cell phenotypes. Based on their distinct profile of cytokine production, they are classified as type 1, and type 2 cells [22].

Type 2 T cells produce IL-4, IL-5, IL-6, and IL-10 [21]. Even though this study reveals that longer-period strenuous exercise induced increased lymphocyte counts, there were increased IL-6 and reduced IL-10 and IFN-γ levels in Ex-60 and Ex-120 group, indicating that prolonged strenuous aerobic exercise impairs immune function. Exercise-induced immunological impairment may result in chronic low-grade inflammation and increase of risk against infection.

Many studies have demonstrated that strenuous or exhaustive exercise suppresses IFN-γ productions [3].

Nitric oxide (NO) is an important regulatory molecule that plays a central role in a variety of physiological and pathological processed [30].

NO is produced from L-arginine by the actions of three isoforms of nitric oxide synthases, which are constitutively expressed and inducible nitric oxide synthase, which is epithelium expresses constitutive and inducible forms of NO synthases [31]. Additionally, activated alveolar macrophages can produce high levels of NO. Thus the respiratory epithelium can be exposed to elevated levels of endogenous NO, which can adversely affect its function.

As shown in table 2, BALF macrophage counts were increasing with prolongation of exercise duration. Besides, increased BALF macrophage counts were associated with gradual elevation of BALF NO levels (Table 2), implying a harmful effect of prolonged-strenuous aerobic exercise on the respiratory system (bronchoalveolar spaces and lungs). Elevated NO levels negatively regulated SP-B (pulmonary surfactant protein B) gene expression. Reduced SP-B expression due to elevated NO levels can contribute to injury [29]. NO is important as a toxic defense molecule against infectious organisms and also regulates the functional activity, growth and death of many immune cells [5].

However, when NO is generated at high concentrations it is rapidly oxidized to reactive nitrogen oxide species (RNOS) which mediated most of the immunological effects. Reactive nitrogen species include the free radicals nitric oxide (NO) and nitrogen dioxide ($NO^{\cdot}_2$) and the potent oxidant peroxynitrite (ONOO-).

NO is known to be one of the important markers of airway inflammation. That is, NO is a potent vasodilator in the bronchial circulation and may mediate the hyperemia see in asthmatic airways [2]. Thus, NO may increase the exudation of plasma by increasing blood flow to leaky postcapillary venules, thus increasing airway edema [19]. These findings suggest that endogenous NO is likely to play an important role in modulation bronchial microcirculation.

Therefore, it seems likely that excessive production of NO contributes to the increase in airway vascular permeability especially in asthmatics. Water and heat loss by hyperventilation with exercise causes airway narrowing and bronchoconstriction. Exercise-induced bronchoconstriction (EIB) occurs in up to 90% of asthmatic patients and is estimated to occur in >10% of the general population [8]. As recent studied reveal that exercise may bronchoconstriction, our findings in this study are supported by the reports.

In conclusion, our study indicates that longer-period (>60 min) strenuous aerobic exercise can offer harmful effects such as changed leukocyte distribution, elevated proinflammatory cytokines, decreased anti-inflammatory, cytokines and increased NO levels in BALF.

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## 초록 : 장시간의 고강도 트레드밀 운동이 기관지 폐포계에 미치는 유해한 효과

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본 연구는 장시간의 고강도 트레드밀 운동이 호흡기계의 생리를 가장 잘 반영하는 기관지 폐포계에 미치는 생리학적 효과를 규명하기 위해 실시되었다. 랫트를 대상으로 매일 8주간 운동시킨 결과 60분 및 120분 운동 그룹군은 대조군(비운동군)과 30분 운동군보다 체중이 유의하게 낮았으며 운동전보다 체중증가율도 높지 않았다. 기관지 폐포세척액 내 총 백혈구수는 세 운동군(30분, 60분, 120분) 모두 대조군보다 유의하게 높았다. 호중구수는 대조군에 비해 30분군과 120분군은 유의하게 증가하였고 60분군은 감소하였으며 30분군이 가장 높았다. 림프구수는 세 운동군 모두 대조군에 비해 유의하게 높았고 120분군이 가장 높았다. 대식세포(단구) 수는 세군 모두 대조군보다 높았고 120군이 가장 높았다. 기관지폐포액 내 인터루킨-6 농도는 대조군보다 30분군은 낮았고 60분과 120분군은 높았다. 그러나 인터루킨-10과 인터페론 감마 농도는 세 운동군 모두 대조군에 비해 유의하게 낮았다. 산화질소(nitric oxide) 농도는 세 운동군 모두 대조군보다 유의하게 높았다. 본 연구의 결과들은 1시간 이상의 고강도 트레드밀 운동은 기관지 폐포 내 백혈구 분포도에 변화를 유도하고 염증성 사이토카인 및 산화성질소 농도의 증가와 항염증성 사이토카인 농도의 감소와 같은 유해한 효과를 일으킬 수 있음을 시사하고 있다.