The effect of acute exhaustive and moderate intensity exercises on nasal cytokine secretion and clinical symptoms in allergic rhinitis patients

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Summary

Background: **Allergic rhinitis is an inflammation of the nasal mucosa in response to allergens. There is evidence that exercise can significantly improve personal health and has positive effects on immune function. However, the effects of acute exercise on the inflammatory response and clinical symptoms in patients with allergic rhinitis are still unclear.**

Purpose: **The aim of the present study was to determine the effects of acute exhaustive and moderate exercises on cytokine levels and clinical symptoms in patients with allergic rhinitis.**

Methods: **Thirteen allergic rhinitis patients (AR) and 14 healthy subjects (C) were required to complete two running exercise protocols, which included an exhaustive exercise bout using the Bruce protocol performed to exhaustion and moderate exercise performed at 65-70% HRR for 30 minutes. Physiological characteristics, allergic rhinitis symptoms, and cytokine secretions and serum levels were comparatively analyzed before and after each type of exercise.**

Results: **The total immunoglobulin E levels in the AR group were significantly higher than in C group (p <0.05). Rhinitis symptoms scores were significantly decreased (p <0.05) after both exhaustive exercise (7.69 to 1.23 points) and moderate exercise (6.46 to 0.53 points) in the AR group. The ratio of interleukin-2 and interleukin-4 (IL-2/IL-4) in nasal secretions after moderate exercise was significantly higher than those after exhaustive exercise in both the C and AR groups (p <0.05).**

Conclusions: **The data demonstrate that both exhaustive and moderate-intensity exercise resulted in a significant improvement in the symptoms of allergic rhinitis. However, a significantly enhanced IL-2/IL-4 ratio was found following acute moderate exercise intensity. We propose that moderate-intensity exercise is more effective than exhaustive exercise in enhancing immune function for allergic rhinitis patients.** ***(Asian Pac J Allergy Immunol 2012;30:185-92)***

Key words: *Allergic rhinitis, Acute exercise, Cytokines, Nasal secretion, Rhinitis symptoms*

Introduction

Allergic rhinitis (AR), is an inflammation of the nasal mucosal in response to natural allergen exposure, and is a common health problem which affects 10-25% of the worldwide population.[1] Common allergens which can cause an allergic reaction are house dust mite, pollen, and animal dander.[2] It has been suggested that an allergic reaction to the house dust mite is the most common cause of persistent rhinitis.[3] The proliferation of allergen-stimulated T cells into Th2 cells can stimulate the release of interleukin (IL); IL-3, IL-4, IL-5, and IL-13, which can promote B-cell isotype switching, which subsequently induces local and systemic production of allergen-specific immune-globulin E by plasma cells, and which results in mast cell proliferation and eosinophilic infiltration in nasal mucosal epithelium.[4] This allergic inflammation stimulates free nerve ending and

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produces itching, sneezing, rhinorrhea, and congestion in nasal mucosal airways.[5]

Exercise can profoundly influence health and there is mounting evidence that the mechanism of these beneficial effects on health is related, in part, to the impact of exercise on immune function.[7] In fact, it has been shown that an acute bout of strenuous exercise has more negative than positive effect on immune function.[6] In addition, it is now well established that acute strenuous exercise can induce bronchoconstriction[7] and asthma,[8] as well as rhinitis in susceptible individuals.[9] However, the impact of moderate-intensity exercise on immune function and/or allergy is extremely limited. The available evidence indicates that low and moderate intensity aerobic exercise can reduce allergic inflammation and airway remodeling, and the expression of Th2 cytokines in a murine model of asthma.[10] In addition, Hewitt et al. has demonstrated that a single bout of moderate intensity aerobic exercise on a motorized treadmill for 45 minutes in mice decreased the levels of Th2-derived cytokines IL-5 and IL-13 and prostaglandin PGE_2, compared to controls. It thus seems that moderate intensity exercise can reduce inflammatory cytokines and allergic inflammation.[11]

However, to our knowledge, no studies to date have compared effect of high intensity exercise and moderate-intensity exercise on airway inflammatory response in patients with allergic rhinitis. Therefore, the purpose of the present study was to determine the effects of acute exhaustive and moderate exercises on cytokine levels and clinical symptoms in patients with allergic rhinitis.

Methods

Subjects

Twenty-seven individuals between the ages of 18 and 45 years were divided into 2 groups: healthy subjects (C; n = 14; male/female=5/9) and patients with allergic rhinitis (AR; n = 13; male/female=5/8). The C group had no history of allergic rhinitis and had a negative skin prick test. The AR group had a clinical history of persistent rhinitis, and had positive skin prick test (wheal diameter $\geq$ 3 mm) to house dust mite (*D. pteronyssinus*). Subjects with known asthma, chronic rhinosinusitis, hypertension or cardiovascular diseases were excluded. The AR subjects were asked to abstain from taking antihistamine medications, leukotriene receptor antagonist and nasal steroids for 5 days, 1 week and 2 weeks respectively prior to the start of the experiment.

All subjects gave written informed consent prior to participation in the study. Medical and activity history were obtained via questionnaires. The study was approved by Institutional Review Board, Faculty of Medicine, Chulalongkorn University, COA No. 481/2011.

Study Design

Before each exercise protocol, the subjects reported to the laboratory in the morning after an overnight fast for 8 hrs. Their physiological characteristics and rhinitis symptoms score were assessed. A blood sample was collected from a forearm vein. After having breakfast for 2 hrs, the subjects were asked to perform a maximal incremental exercise until exhaustion. In a subsequent visit (2 wks later), a moderate-intensity exercise was performed following the earlier mentioned assessment. Rhinitis symptom scores assessment and nasal secretion collection were performed at pre and immediately post exercise for each exercise protocol.

Exercise protocol

Two exercise protocols were used in this study. Exhaustive exercise was performed using the Bruce treadmill protocol.[12] Subjects were asked to run on a treadmill (Landice, USA) in which the grade and intensity were increased every 3 minutes until exhaustion. Heart rate, oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured throughout the test using a breath-by-breath gas analysis system (Cortex Metamax 3X, Germany). Hereafter, we refer to this VO_2max test as the exhaustive exercise protocol. After 2 weeks, each subject performed a moderate-intensity exercise bout, which comprised of running on the treadmill at an intensity corresponding to 65-70% heart rate reserve for 30 minutes.

Physiological characteristics

The resting heart rate, and blood pressure were measured using a heart rate monitor (Polar Electro S810, Finland), and mercury sphygmomanometer (Spirit, UK), respectively. Body weight and percent body fat using whole a body bioelectrical impedance analysis (BIA) analyzer (Inbody 220, Biospace, Korea) were also assessed.

Pulmonary function

Pulmonary function tests (FVC and FEV_1) were conducted on all subjects using a calibrated computerized pneumotachograph spirometer (Spirotouch; Burdick, Inc., Deerfield, Wisconsin

USA.) according to American Thoracic Society (ATS) recommendations.[13]

Blood collection and analysis

Blood samples were obtained from an antecubital vein. A portion of the blood was collected into a tube containing ethylenediamine tetraacetic acid and was placed immediately on ice for the determination of hematological parameters and vitamin C level. Another portion of the blood was collected in plain tubes, left on ice for 30 min to clot and centrifuged at 1200 g for 20 min at 4 ºC for serum separation. Lipid profiles including total cholesterol, triglyceride, high density lipoprotein (HDL-C), and low density lipoprotein (LDL-C) were analyzed using the homogenous enzymatic colorimetric method. The rest of the serum was transferred into tubes and was stored at -70 ºC until analysis.[14]

Rhinitis symptom scores

Nasal symptoms were recorded using rhinitis symptom score questionnaires. The patients were asked to score symptoms of persistent allergic rhinitis; nasal congestion, itching, sneezing, and rhinorrhea before and after each exercise protocol. The score ranged from 0 to 3 points (0 = none, 1 = mild, 2 = moderate, 3 = severe).

Nasal secretion collection and handing

Nasal secretions collection was performed bilaterally with filter paper strips (7x30 mm Whatman No.42, Whatman, Clifton, NJ). Three filter paper strips were sequentially placed on each anterior portion of the inferior turbinate for 10 min. This filter paper strips were collected into appropriate tubes and centrifuged at 3,000 rpm for 5 min at 4 °C and immediately frozen at -70 °C until later analysis.

Cytokines analysis

The levels of cytokines, IL-2, IL-4 and IL-13, and tumor necrosis factor (TNF)-α in blood and nasal secretion were determined by using the flow cytometry technique.[1] Data were acquired using the Flow cytometer (BD FACSCalibur Flow Cytometer, USA) and analyzed by Flowcytomix™ Pro software (eBioscience, USA.). The data are presented as percent difference pre-to-post-exercise (% diff = $\frac{\text{Post-Pre}}{\text{Pre}}$ x 100).

Statistical analysis

Data were analyzed using SPSS version 17 for Windows statistical software (SPSS Inc., Chicago, USA). The normality of the distribution of the variables was tested using a Shapiro-Wilk test. The dependent variables between pre-test and post-test were analyzed by a paired t-test. Two-way analysis of variance was used to determine the significant differences in rhinitis symptom scores and cytokines level before exhaustive exercise, after exhaustive exercise, before moderate exercise and after moderate exercise. Differences were considered significant at $p < 0.05$. Data were expressed as mean ± SEM. Only total IgE data were expressed as median values and compared by the Mann-Whitney test.

Results

Physiological characteristics and blood chemical data

The physiological characteristics and blood chemical data of the subjects are summarized in Table 1. Body fat, cholesterol, and low density lipoprotein in the AR group were significantly lower than the C group (p <0.05). Moreover, the AR group exhibited a significantly higher total IgE than the C group (p <0.05). There were no significant differences (p <0.05) in heart rate, systolic blood pressure, diastolic blood pressure, maximal oxygen consumption (VO_2max), forced vital capacity (FVC), forced expiratory volume (FEV_1), hemoglobin, hematocrit, triglyceride, and high density lipoprotein cholesterol between the C and AR groups.

Rhinitis symptoms scores

The baseline rhinitis symptoms scores, including nasal congestion, itching, sneezing, and rhinorrhea, are shown in Table 2. After both exhaustive and moderate-intensity exercise, all rhinitis symptoms were significantly lower than before exercise (p<0.05); they were decreased from 7.69 to 1.23 points and 6.46 to 0.53 points, respectively.

Cytokines determination

The cytokines levels of IL-2, IL-4, IL-13, and those of TNF-α measured in serum and nasal secretions at baseline were shown in Table 3. The concentrations of the cytokines were expressed as pg/ml. The cytokines concentration in nasal secretions were significantly higher (p <0.05) than the levels in serum in both groups. Moreover, all cytokines levels at baseline in the AR group were significantly higher than those for the C group (p <0.05). The percent difference of IL-2, IL-4, IL-13, and TNF-α after exhaustive exercise in the C:AR group were 21.13:35.25, -2.31:-2.46, 0.15:1.49 and -16.21:-15.42, respectively. The percent difference of IL-2, IL-4, IL-13, and TNF-α after moderate

Table 1. Physiological and blood chemical data in healthy subjects (C) and allergic rhinitis patients (AR) groups

Variables	C (n=14)	AR (n=13)	*P*-values	t
Age (years)	28.93 ± 1.40	26.30 ± 2.28	0.32	-1.00
Body weight (kg)	51.30 (46.70)	54.20 (43.40)	0.73	Z=-0.34
BMI (kg/m^2)	21.46 ± 1.05	21.50 ± 1.24	0.88	.02
Body fat (%)	24.42 ± 2.01	22.60 ± 3.37*	0.03	-.47
Heart rate (bpm)	82.66 ± 3.28	80.53 ± 2.12	0.11	-.52
Systolic BP (mmHg)	120.73 ± 4.11	111.69 ± 2.43	0.13	-1.81
Diastolic BP (mmHg)	71.13 ± 2.15	68.46 ± 2.95	0.64	-.74
Vo_2max (ml/kg/min)	32.6 ± 2.36	33.30 ± 2.35	0.87	.21
FVC (L)	2.85 ± 0.15	2.97 ± 0.22	0.08	.46
FEV1 (L)	2.60 ± 0.14	2.38 ± 0.19	0.45	-.91
Hemoglobin (g/dl)	14.01 ± 0.58	13.82 ± 0.37	0.34	-.26
Hematocrit (%)	46.00 ± 1.77	41.54 ± 1.28	0.16	-1.97
Cholesterol (mg/dl)	218.67 ± 10.38	182.92 ± 4.06*	0.00	-3.02
Triglyceride (mg/dl)	117.93 ± 20.40	67.38 ± 7.67	0.34	-2.18
HDL-C (mg/dl)	67.47 ± 2.81	66.69 ± 3.68	0.38	-.16
LDL-C (mg/dl)	129.87 ± 9.27	104.23 ± 3.96*	0.00	-2.40
Total IgE (IU/ml)	71.00 (390.00)	249.00 (1064.00)*	0.01	Z= -2.37

Values are means ± SEM. (Body weight and total IgE are median)

* P <.05, C group versus AR group.

BMI=Body mass index, BP=Blood pressure, VO_{2max}=Maximal oxygen consumption, FVC=Forced vital capacity, FEV1= Forced expiratory volume, HDL-C=High density lipoprotein Cholesterol, LDL-C=low density lipoprotein Cholesterol, IgE=Immunoglobulin E

exercise in the C:AR group were 35.25:58.36, -40.67:- 11.74, -1.76: -1.29 and -28.7:-27.23, respectively.

The percent difference in cytokine levels in the nasal secretions of the C and AR groups are shown in Figure 1. The data demonstrate that there are no significant differences (p >0.05) in the percent difference of nasal secretion cytokines when compared between exhaustive exercise and moderate exercise in both the C and AR groups. It was found that both the C and AR groups had relatively lower percent differences in pro-inflammatory cytokines (IL-4, IL-13, and TNF-α) and relatively higher percent differences in anti-inflammatory cytokine (IL-2) after moderate exercise but the difference was not significant. However, the ratio of IL-2 and IL-4 (IL-2/IL-4) after moderate exercise was significantly higher than that for exhaustive exercise in both the C and AR groups (p <0.05) (Figure 2.). The IL-2/IL-4 levels of the C and AR groups after exhaustive exercise were 0.5 and 0.7, respectively. The IL-2/IL-4 levels of the C and AR groups after moderate exercise were 6.32 and 2.18, respectively.

Discussion

Our results demonstrate that the baseline cytokines in nasal secretion of patient with allergic rhinitis were higher than those of healthy controls. Both acute exhaustive and moderate-intensity exercise reduced rhinitis symptoms but only moderate-intensity exercise had beneficial effects on the cytokine response in nasal secretions, increasing the ratio of IL-2 and IL-4 in both the C and AR groups.

Allergic rhinitis is a significant cause of widespread morbidity, high medical treatment costs, reduced work productivity, can affect a patient's quality of life and can be associated with conditions such as fatigue, headache, cognitive impairment, and sleep disturbance.[15] In the present study, the AR group had lower body fat and lipid profile than the healthy subjects. The data from the present study are in contrast to other studies, which found that body mass index in allergic rhinitis patients was higher than control subjects.[16] Moreover, Erel et al. investigated the serum levels of leptin and lipid profiles on allergic rhinitis and found that they were not different than those in controls.[17]

In our study, the level of total immunoglobulin E (IgE) in the AR group (416.50 ± 352.69 IU/ml) was significantly higher than in the C group (77 ± 52.06

Table 2. Severity of rhinitis symptoms in allergic rhinitis patients (AR) group

Variables (Level)	AR (n=13)					
	Exhaustive exercise			Moderate exercise		
	Pre	Post	% diff	Pre	Post	% diff
Congestion	2.07 ± 0.17	0.23 ± 0.16*	-89.74	1.61 ± 0.26	0.15 ± 0.10*	-74.35
Itching	2.15 ± 0.22	0.30 ± 0.17*	-88.46	1.84 ± 0.24	0.15 ± 0.10*	-82.05
Sneezing	1.61 ± 0.26	0.23 ± 0.16*	-75.64	1.46 ± 0.24	0.00 ± 0.00*	-84.61
Rhinorrhea	1.84 ± 0.24	0.46 ± 0.18*	-73.07	1.53 ± 0.21	0.23 ± 0.12*	-76.92
Total symptoms scores	7.69 ± 0.77	1.23 ± 0.63*	-88.07	6.46 ± 0.88	0.53 ± 0.31*	-82.94

Values are means ± SEM. (Level: 0 = none, 1 = mild, 2 = moderate, 3 = severe)

* *P* <.05, Different from pre test.

IU/ml), which agrees with previous studies that have also reported that the IgE in patients with rhinitis is higher than in healthy controls.[18] Patients with allergic rhinitis present an inflammatory IgE-mediated response characteristized by a Th2 immunologic pattern, with mast cell and eosinophil activation and release of inflammatory mediators in response to an allergen.[18] IgE levels greater than 140 IU/ml are suggestive of an atopic etiology for patients with signs and symptoms of rhinitis.[19]

The mechanism of nasal symptom generation in allergic rhinitis is more complex. Some symptoms, i.e. rhinorrhea, can be produced by direct effects of allergic reaction products on nasal end organs, while typical symptoms of rhinitis can be produced through neural mechanisms.[20] In the present study, the data demonstrate that rhinitis symptoms scores decrease after a single bout exercise in both exhaustive and moderate-intensity exercise. These findings lead to the assumption that nasal symptoms improve rather than worsen with exercise. The mechanisms by which acute exercise improve nasal rhinitis symptoms are not completely understood. It has been thought that these changes could be caused by sympathetic activity induced nasal vasoconstriction that reduced the volume of the venous sinusoids.[21] In addition, the improvement is most likely related to both acute exhaustive and moderate-intensity exercise reducing nasal congestion by decreasing blood flow and increasing sinus emptying in the capacitance vessels,[22] since the nasal mucosa is composed of both resistance and capacitance blood vessels.[23] It has been shown that nasal resistance decreases with exercise.[24] However, a few studies have demonstrated an increase in rhinitis symptoms with exercise.[25] Silvers WS. suggested that exercise-induced rhinitis, with varying degrees of rhinorrhea, congestion, and sneezing, has been increasingly recognized in athletes who run, cycle, and ski.[26]

Using flow cytometry, we found that cytokines in nasal secretion contained significantly higher concentrations than those in serum in both the C and AR groups. This indicates that cytokine

Table 3. Cytokines in serum and nasal secretion at baseline in healthy subjects (C) and allergic rhinitis patients (AR) groups

Cytokines (pg/ml)	C (n=10)		AR (n=10)	
	Serum	Nasal secretion	Serum	Nasal secretion
IL-2	6.85 ± 3.62	68.79 ± 8.11*	16.81 ± 4.86	104.25 ± 12.49*†
IL-4	0.00 ± 0.00	6.93 ± 2.66*	2.38 ± 2.16	23.36 ± 5.08*†
IL-5	0.00 ± 0.00	1.41 ± 0.74*	0.00 ± 0.00	14.30 ± 5.32*†
IL-13	42.13 ± 10.55	100.24 ± 2.20*	76.17 ± 6.14†	116.62 ± 4.98*†
TNF-α	1.53 ± 0.38	8.07 ± 1.13*	3.68 ± 0.97	15.78 ± 2.24*†

Values are means ± SEM.

**P* <.05, Different between serum and nasal secretion in the same group.

†*P* <.05, Different from C group.

IL-2 = Interleukin 2, IL-4 = Interleukin 4, IL-13 = Interleukin 13, TNF-α = Tumor necrosis factor-alpha

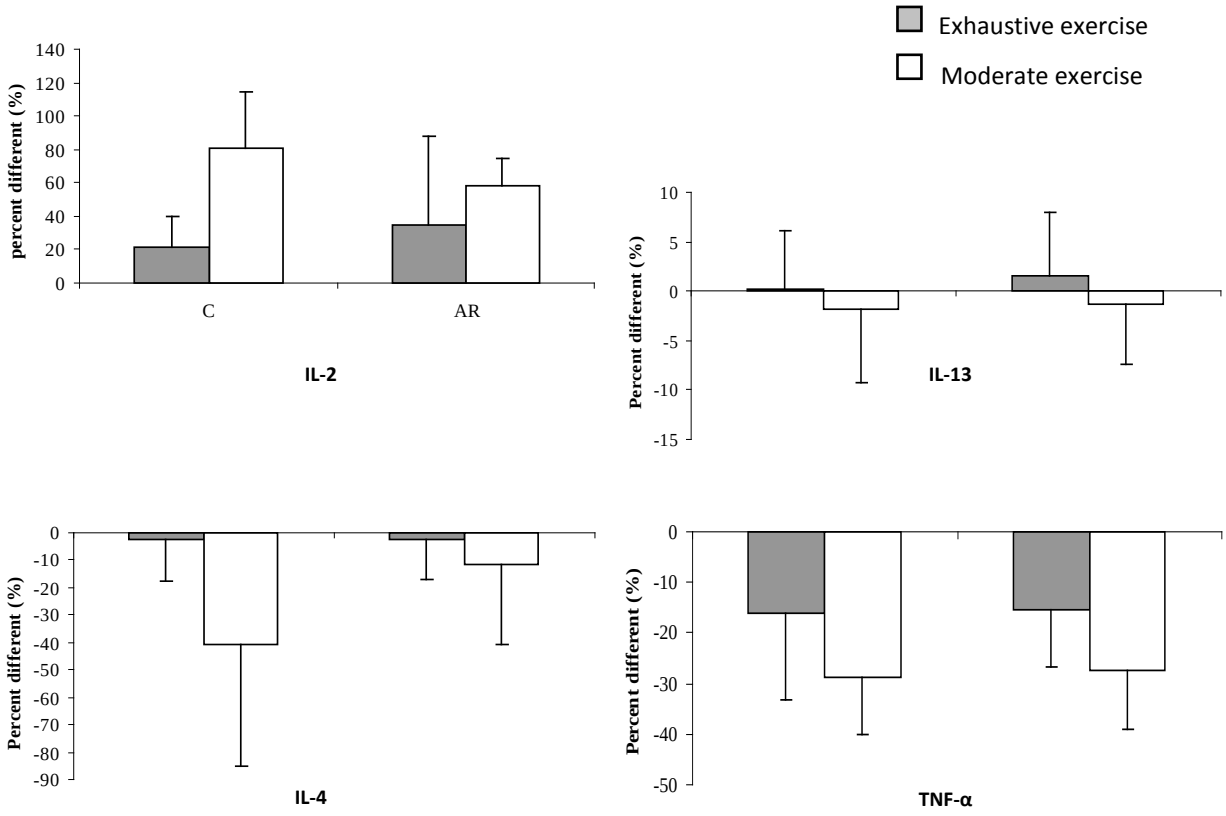
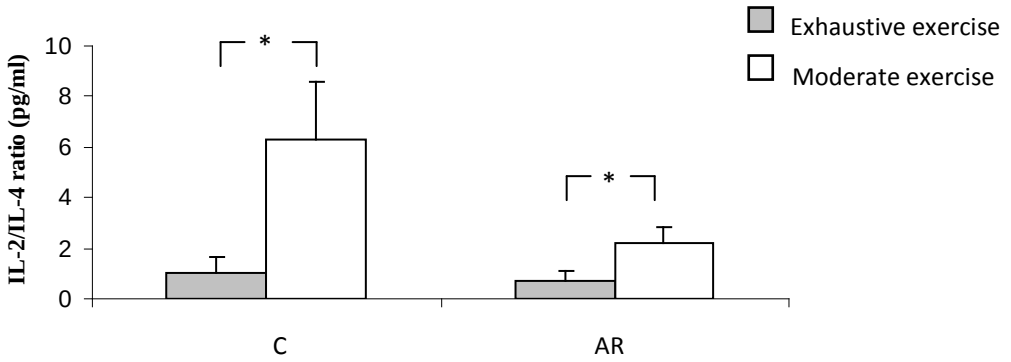


Figure 1. The percent difference between pre and post of exhaustive and moderate exercise in cytokine levels in nasal secretions: IL-2, IL-4, IL-13, and TNF-α (pg/ml) in healthy subjects (C) and allergic rhinitis patients (AR) groups

determination should be carried out on samples from the local area (nasal secretion) rather than the systematic system (serum). In the present study, the IL-2, IL-4, IL-13 and TNF-α in the nasal secretions of allergic rhinitis patients were significantly higher than those for healthy subjects, which is in agreement with previous studies.[27]

In terms of the cytokine response following acute exercise, the data showed that there was no significant difference between exhaustive and moderate-intensity exercise in both the C and AR groups. However, we found that IL-2/IL-4 ratio after moderate-intensity exercise was significantly higher than that for exhaustive exercise in both the C and AR groups ($p < 0.05$). This suggests that moderate-intensity exercise is more effective in stimulating a cytokine response than exhaustive exercise for allergic rhinitis patients. IL-2 is critical for supporting T cell activation, and the dominant physiological function of IL-2 signals in vivo is to restrain T cell activation and prevent autoimmunity.[28] IL-2 induces macrophage activation, which is very effective in controlling infection along with intracellular pathogens.[29] Alternatively, IL-4 may play a central role in the IgE synthesis system, the development of Th-2-like cells, and act as a co-ordinator of airway inflammatory processes in allergic disorders.[30] A number of recent studies have shown an increase of IL-4 level in allergic rhinitis patients.[31-32] Those previous studies indicated that moderate exercise induced an increase of anti-inflammatory cytokines but a decrease in pro-inflammatory cytokine. We suggest that moderate-intensity exercise appears to have beneficial effects for allergic rhinitis patients, which is consistent with a previous study.[33] They reported that moderate-intensity exercise could protect against upper respiratory tract infections. Moreover, Pedersen BK. et al. found that strenuous exercise is accompanied by an increase in circulating pro-inflammatory cytokines.[34] The mechanisms for this cytokine response to acute exercise is not known and requires further investigation.

In summary, our data demonstrate that rhinitis symptoms decrease after both acute exhaustive and



*P <.05, Different between exhaustive and moderate exercise in the same group.

Figure 2 The ratio of IL-2 and IL-4 (IL-2/IL-4) in nasal secretions compared between exhaustive and moderate exercise in healthy subjects (C) and allergic rhinitis patients (AR) groups

moderate-intensity exercise, but only moderate-intensity exercise has a positive effect on pro-inflammatory cytokine levels. We therefore conclude that moderate-intensity exercise is beneficial for allergic rhinitis patients.

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