CHAPTER I
INTRODUCTION

Background and Rationale

Allergy is a common disease in Thailand and tends to affect more people especially one who lives in the large cities. This is an important health problem for patients themselves, their families, societies and also the nation (Boonyaleepan and Boonyaleepan, 2006). Allergic rhinitis; AR is the most common atopic disorder, affecting 10-25 % of the worldwide population. It was also found that 26 % of the England population and about 20-40 million people in the United States were suffered from this disorder (Storm, 2008). In Thailand, the prevalence of allergic rhinitis was 25-30 % of the total population (Assanasen, 2008). Moreover, the allergy organization of Chulalongkorn hospital studied the prevalence and severity of allergies in children aged 6-18 years in Bangkok and 9 provinces from January 2006 to June 2007 by using the questionnaire and the study showed that most sample were suffered from allergic rhinitis (49.3 %), the second was Urticaria (27 %), atopic dermatitis (25.6 %), allergic conjunctivitis (21.7 %), food allergy (11 %), asthma (6.8 %) and drug allergy (4.9 %) (Ngamphaiboon and Vangveeravong, 2009).

Allergic rhinitis is a disease caused by a malfunction of the immune system in nasal mucosa. It affects quality of life; physical, mental illnesses and also socialization, comparing with healthy persons (Assanasen, 2008). Ngamphaiboon and Vangveeravong (2009) showed that this disease had effect on 38.5 % sleeping, 30.9 % sickness and 28.7 % annoyance. Allergic rhinitis is a common occurrence for several reasons. First, the predisposing factor is the genetic. Second, the primary or specific factor is allergen that is the most common house dust mites, cockroaches, grass pollen and mold (Potirat, 2003). And third, secondary or precipitating factors that increase the allergic rhinitis symptoms such as infection, direct irritants, physical factors, psychological factors and anatomical abnormalities (Vichyanond et al., 2000). Allergic rhinitis can be divided into two categories; seasonal allergic rhinitis triggered by pollen, grass, and weeds and

perennial allergic rhinitis caused by indoor allergens such as dust mites, pet dander, and mold. People who have seasonal allergic rhinitis commonly suffer from the disease only a period of time or season (Kemp, 2009). In the nose allergens are processed by antigen- presenting cells (dendritic cells expressing CD1a and CD11c and macrophages) in the nasal epithelial mucosa, with subsequent presentation of allergenic peptides by MHC class II molecules to T-cell receptors on resting $CD4^+$ T lymphocytes in regional lymph nodes. With costimulatory signals, allergen-stimulated T cells proliferate into Th2-biased cells that release IL-3, IL-4, IL-5, IL-13, and other cytokines. These cytokines then lead to a cascade of events that promote B-cell isotype switching with subsequent local and systemic production of allergen-specific IgE antibody production by plasma cells, eosinophilic infiltration into the nasal epithelium and mucosa, and mast cell proliferation and infiltration of airway mucosa (Dykewicz, 2010). The symptoms of allergic rhinitis include; itching, nasal congestion, sneezing, rhinorrhea caused by allergic reactions between allergen and Immunoglobulin E (IgE). This reaction causes the secretion of mediator such as histamine, leukotriene and prostaglandin to cause the rhinitis symptoms (Banjapolpitak et al., 2001). In addition, the symptoms for patients are red itchy eyes and headaches (Storms, 2008). The nasal congestion caused by the direct effect of the mediator to the blood vessels and nerve endings, it was stimulating vasodilatation of vessel and increases blood permeability cause to swelling in nasal mucosa and nasal passages. The runny nose or rhinorrhea is reflex mechanism in the vidian nerve, which is important in stimulating the secretion of mucus. This symptom is caused by a mucous glands produce more mucus (Vichyanond, 2000).

There are many problems that the patients suffering from allergic rhinitis have to cope with. First, the discomfort caused by the symptoms of the disease. The survey found that most patients have a stuffy nose (43 %), followed by runny nose (31 %). Second, a study showed that allergic rhinitis patients have worse quality of life. The symptoms of nasal congestion, runny nose, make them cannot sleep well at night. Third, the complications of allergic rhinitis can cause sinusitis, reduced odor, ear tubes malfucntion, chronic hoarseness, sore throat and asthma. Last, the treatment of the disease costs, both direct and indirect costs. Direct costs are nasal and oral

medications or immune therapy. Indirect costs are the cost of associated complications treatment, and quality of life in recognition and work life (Potirat, 2003). In 2000, the United States paid for the treatment of allergic rhinitis about 6 billion dollars (Stempel and Woolf, 2002). In Thailand, a survey found that the cost dealing with the symptoms of allergic rhinitis was 777.12 baht per month (Sudchai, 2006).

The diagnosis of AR can usually be made from the history and physical examination. Allergy testing can be performed to identify which allergens are responsible for the symptoms. There are 2 methods used to determine the presence of immunoglobulin (Ig)-E antibodies to specific allergens: skin testing, and radioallergosorbent (RAST) testing (Lehman and Lieberman, 2007). The symptoms were diagnosed in many ways in clinical and research including the rhinoscopy; a method for analyzing anterior and posterior of nasal cavity (Windsor and Johnson, 2006; Rawlings, 2009), rhinomanometry; a method for measuring nasal resistance (Nathan et al., 2005; Priftis et al., 2006; Ciprandi et al., 2009), peak nasal flowmetry; a method for measuring the volume of air exhaled from the nose (Martin, et al., 2008; Pinar et al., 2008), acoustic rhinometry; a method for measuring volume of the nasal cavity based on the reflection of sound waves to the cross-sectional area or width of the nasal cavity in various positions (Kim et al., 2008; Warrier et al., 2009). In addition, there are other allergy test methods i.e. cytokine analysis in blood, nasal lavage fluid, and nasal secretion by using flow cytometry (Howarth et al., 2005).

In 2003, Scavuzzo et al. (2003) were found that the cytokines IL-6 and IL-10 in allergic rhinitis patients were significantly higher than healthy, but there were no significant difference in Interferon-gramma. Moreover, Rondon et al. (2007) studied the immunoglobulin E and cytokine in nasal lavage fluid of allergic rhinitis patients by dropping saline 10 ml. into the nose and analyzed by flow cytometry. They found that flow cytometry could detect the difference of cytokine in patients with allergic rhinitis and normal people. Furthermore, the study of nasal mucosa fluids in occupational rhinitis, which measured after nasal challenge showed an increase in eosinophils but the level of neutrophils and myeroperoxidase did not change (Castano et al., 2010).

The treatment for allergic rhinitis were avoiding or eliminating allergen, using drugs to relieve symptoms and taking vaccine. It is

reasonable to conclude that no one treatment is totally effective and that the different treatments target the different symptoms and signs of the disease (Al Suleimani and Walker, 2007). The patients with allergic rhinitis should be take care themselves; have a healthy diet, have a good sleep, maintain good mental health and perform exercise regularly (Assanasen, 2008).

Recently, there were many studies about acute exercise or single bout exercise that induced the symptoms of allergy, such as exercise induced bronchoconstriction; EIB (Zietkowski et al., 2008, Manjra et al., 2009, Randolph, 2010) and exercise induced rhinitis; EIR (Silvers and. Poole, 2006, Schwartz et al., 2008). These researches used high intensity exercise (Strenuous exercise) induced acute symptoms of allergy. Valero et al. (2005) studied in patients with allergic rhinitis and asthma by cycling ergometer for 6 minutes at 80 - 90% of maximum heart rate. They found that exercise increased nasal volume, but decreased forced expiratory volume in 1 second (FEV1). In 2006, Silvers and Poole, (2006) reported that exercise-induced rhinitis, predominantly rhinorrhea, commonly occurs in athletes regardless of underlying nasal cavity. In 2010, Aldred et al. (2010) investigated the effect of an acute steady state moderate intensity exercise task on circulating immunoglobulin E. The results shown that IgE levels increased in airborne allergic volunteers but decreased in food allergic volunteers, after exercise at 60% of maximal power output for 40 minutes. This study indicated that acute steady state moderate exercise significantly altered circulating IgE concentrations in volunteers with known allergy, while IgE concentrations in non-allergy sufferers did not change (Aldred et al., 2010).

Aerobic exercise training has been recommended as an effective adjuvant treatment in the management of symptoms in patients with many disease including hypertension (Smith et al., 2007), diabetes (Zoppini et al., 2006; Gill et al., 2007), heart disease (Swain and Franklin, 2006; Hirschhorn et al., 2008) and obesity (Ozcelik et al., 2006; Ghroubi et al., 2009; Shang and Hasenberg, 2010). However, the study in the effects of aerobic exercise training in the patients with allergic rhinitis are very few and still unclear. Most of these studies were done in animal. In 2007, Vieira et al. (2007) studied in allergic asthma mice. They found that running on

treadmill 50% of maximum speed and 75% of maximum speed for 60 minutes per day, 5 days per week, for 4 weeks could infiltrate eosinophil and no significant difference in the presence of Th2 cytokines such as interleukin 4 (IL-4) and interleukin 5 (IL-5) found. It indicated that mild and moderate aerobic exercise training decrease airway inflammation and remodeling in a murine model of asthma. After that, in 2008, Vieira et al. (2008) have reported that aerobic conditioning decrease pulmonary vascular and parencymal inflammation and remodeling in this experimental model of chronic allergic lung inflammation in mice. Moreover, recent study has reported that aerobic exercise increased the immunoglobulin E (IgE) and immunoglobulin G (IgG) but reduced eosinophils, $CD3^{+}$, $CD4^{+}$, IL-4, IL-5, IL-13, nuclear factor-kappa-B; NF-kB, airway remodeling, mucus synthesis, the thickness of smooth muscle and nasal resistance in a chronic model of allergic lung inflammation in mice (Silva et al., 2010). However, there is hypothesis that engaging in moderate activity may enhance immune function, but excessive amounts of prolonged, high-intensity exercise may impair immune function (Gleeson, 2007).

Vitamin C or ascorbic acid is an important antioxidant of the body. The vitamin C is water soluble vitamins. It does not cause accumulation of toxins in the body and has no side effects (Thornhill and Kelly, 2000; Michael, 2008). In addition, vitamin C is also essential for the synthesis of collagen, a fiber produced by the various tissues and is essential for wound healing and maintenance of bones and teeth (Maggini, 2010). Vitamin C supplementation is used to prevent and treat various diseases including cardiovascular disease (Houston, 2010), diabetes (Chen et al., 2006; Ceriello et al., 2007), hypertension (Sato et al. 2006; Mahajan et al. 2007; Plantinga et al. 2007; Block et al. 2008; Hatzitolios et al. 2008; Ledlerc et al. 2009) common cold (Douglas and Hemila, 2005; Sasazuki et al., 2006) and cancer (Verrax and Calderon, 2008). Furthermore, there are some reports in the studied effects of vitamin C supplementation combined with exercise diabetes (Chakraphan et al., 2007) and heart disease (Angus et al., 2002). It has been suggested that vitamin C deficiency causes reduction of immune function, the adequate amount of vitamin C could enhance phagocytic cell and T lymphocyte functioning in the immune system (Anderson et al., 1990; Wintergerst et al., 2006). In 2004, Hartel et al. (2004) reported that vitamin C could

inhibit cytokine secretion such as tumor Necrosis Factor Alpha; TNF-α, interleukin 2; IL-2 and interleukin 6; IL-6 in the inflammatory process. However, the effects of vitamin C supplementation in allergic rhinitis patients are conflicting. Some studies reported that vitamin C had no effect on the reaction of allergic sensitisation (Forastiere et al., 2000; McKeever and Britton, 2004), hay fever (Nagel et. al., 2003) and allergic rhinitis (Kompauer et al., 2006). Some studies reported that vitamin C was good for allergy sufferers. Helms and Miller (2006) demonstrated the application of vitamin C sprayed into the nose three times a day for 2 weeks improved the symptoms of patients with allergic rhinitis by reducing fluids to stimulate the congestion and swelling in the nasal cavity. Moreover, Thornhill and Kelly (2000) suggested that using vitamin C at least 2 grams per day could prevent the release of histamine from white blood cells for naturally allergic rhinitis treatment

Despite the known effects of exercise training and vitamin C supplementation on healthy and patients with chronic disease individuals, few studies have investigated the effect of exercise training and supplemented vitamin C on allergy inflammatory response. Moreover, there is no report showing a synergistic protective role of exercise training combined with vitamin C supplementation. Therefore, the present study was designed to establish whether exercise training and/or dietary supplementation of vitamin C have favorable effect in the immune function. Additionally, we interested to investigate the effects of moderate aerobic exercise training and vitamin C supplementation on physical fitness, cytokines response and symptoms in patients with allergic rhinitis. The knowledge arised from this study will be the guidelines for the care of patients with allergic rhinitis in order to reduce the cost of treatment for both themselves and the nation.

Research questions

Study I

1. How does acute exhaustive and moderate intensity exercise effect on physiological changes and rhinitis symptoms in patients with allergic rhinitis?

2. How difference effects of acute exhaustive and moderate intensity on physiological changes and rhinitis symptoms in allergic rhinitis patients?

Study II

1. How does moderate exercise training effect on physiological changes and rhinitis symptoms in patients with allergic rhinitis?

2. How does moderate exercise training combined with vitamin C supplementation effect on physiological changes and rhinitis symptoms in patients with allergic rhinitis?

3. How difference effects of moderate exercise training and moderate exercise training combined with vitamin C supplementation on physiological changes and rhinitis symptoms in allergic rhinitis patients?

The purposes of this study

1. To determine the effects of acute exercise on physiological changes and rhinitis symptoms in patients with allergic rhinitis.

2. To determine the effects of exercise training on physiological changes and rhinitis symptoms in patients with allergic rhinitis.

3. To determine the effects of vitamin C supplementation on physiological changes and rhinitis symptoms in patients with allergic rhinitis.

Scope of research

Study I

1. The sample group consisted of 14 healthy subjects and 13 patients with allergic rhinitis, who were students and official personnel in Chulalongkorn University.

2. The variables used in the study include;

2.1 Independent variables were acute exhaustive exercise and acute moderate intensity exercise (65-70% HRR).

2.2 Dependent variables

- Physiological characteristics such as body weight, percent body fat, resting heart rate and blood pressure.

- Blood chemical variables such as complete blood count, lipid profile and total immunoglobulin E and

- Cytokine levels in blood and nasal secretion such as IL-2, IL-4, IL-5, IL-13, and TNF-α.

Study II

1. The participants were the nineteen patients with allergic rhinitis who were students and official personnel in Chulalongkorn University. Nineteen patients with allergic rhinitis, aged 18-45 years old, were recruited. They were randomized into 3 groups;

- Group I: Control group (CON; n=8) (non exercise)

- Group II: Exercise group (EX; n=9) (moderate exercise training 65-70% HRR)

- Group III: Exercise combined vitamin C supplement group (EX + Vit. C; n=10) (moderate exercise training 65-70% HRR and intake vitamin C 2,000 mg./day)

2. The variables used in the study include;

2.1 Independent variables were a moderate exercise training and vitamin C supplements.

2.2 Dependent variables were

- Physiological variables as to body weight, percent body fat, resting heart rate and blood pressure.

- Blood chemical variables as to complete blood count, lipid profile, malondialdehyde, total immunoglobulin E, specific IgE *(D. pteronyssinus)*

- Cytokine levels in blood and nasal secretion as to IL-2, IL-4 and IL-13.

- Rhinitis symptoms variables as to nasal blood flow, peak nasal inspiratory flow and rhinitis symptoms score.

Operational definition

Allergic rhinitis is an allergic inflammation of the nasal airways. It is caused by the allergens and inflammation of the lining of the nose. The patient has a nasal congestion, itching, sneezing, runny nose, etc.

Acute exercise is a single bout of exercise done at a specific time for a specific amount of time.

Aerobic exercise training is an activity that raises the body's demand for oxygen, resulting in a temporary increase in rate of respiration and heart rate. In this study we use treadmill to exercise training.

Vitamin C is an essential nutrient found mainly in fruits and vegetables. The body requires vitamin C to form and maintain bones, blood vessels, and skin. It is one of many antioxidants. Antioxidants are nutrients that block some of the damage caused by free radicals.

Nasal blood flow is rate of the subcutaneous blood flow as measured by the speed and the average concentration of hemoglobin in the tissue samples (Flux) by using laser Doppler.

Peak nasal inspiratory flow is a clinical trial that has been instituted in clinical practice in order to determine the extent of nasal airway patency and it is used to assess the degree of nasal obstruction.

Lung function is a total lung capacity refers to the total amount of air in the lungs after taking the deepest breath possible by used spirometer.

Maximal oxygen Consumption (Vo_2max) is the maximal oxygen uptake or the maximum volume of oxygen that can be utilized in one minute during maximal or exhaustive exercise. It is measured as milliliters of oxygen used in one minute per kilogram of body weight.

Cytokine is a generic term for nonantibody proteins released by one cell population on contact with specific antigen, which act as intercellular mediators, as in the generation of an immune response. The cytokines in this study included IL-2, IL-4, and IL-13.

Nasal secretion is mucus produced in the nasal mucosa. In this study used the filter paper and analyzed by flow cytometry method.

Rhinitis symptom scores is the symptoms of allergic rhinitis that using questionnaires to assess symptoms. The symptoms including nasal congestion, itching, sneezing and rhinorrhea.

Expected benefits and applications

1. To understand the maximum oxygen consumption (VO_2max) between healthy subjects and allergic rhinitis patients.

2. To understand the effects of acute exhaustive and moderate intensity exercise on physiological changes and rhinitis symptoms in patients with allergic rhinitis.

3. To understand the effects of aerobic exercise training on physiological changes and rhinitis symptoms in patients with allergic rhinitis.

4. To understand the effects of aerobic exercise training combined with vitamin C supplementation on physiological changes and rhinitis symptoms in patients with allergic rhinitis.

5. To understand the comparative effects between aerobic exercise training and aerobic exercise training combined with vitamin C supplementation on physiological changes and rhinitis symptoms in patients with allergic rhinitis.

6. To providing exercise training recommendations for protection and rehabilitation in allergic rhinitis patients.

7. Providing the sciencetific data for the further research.

Conceptual Framework

Study I: The effect of acute exhaustive and moderate intensity exercise on physiological changes in allergic rhinitis patients.

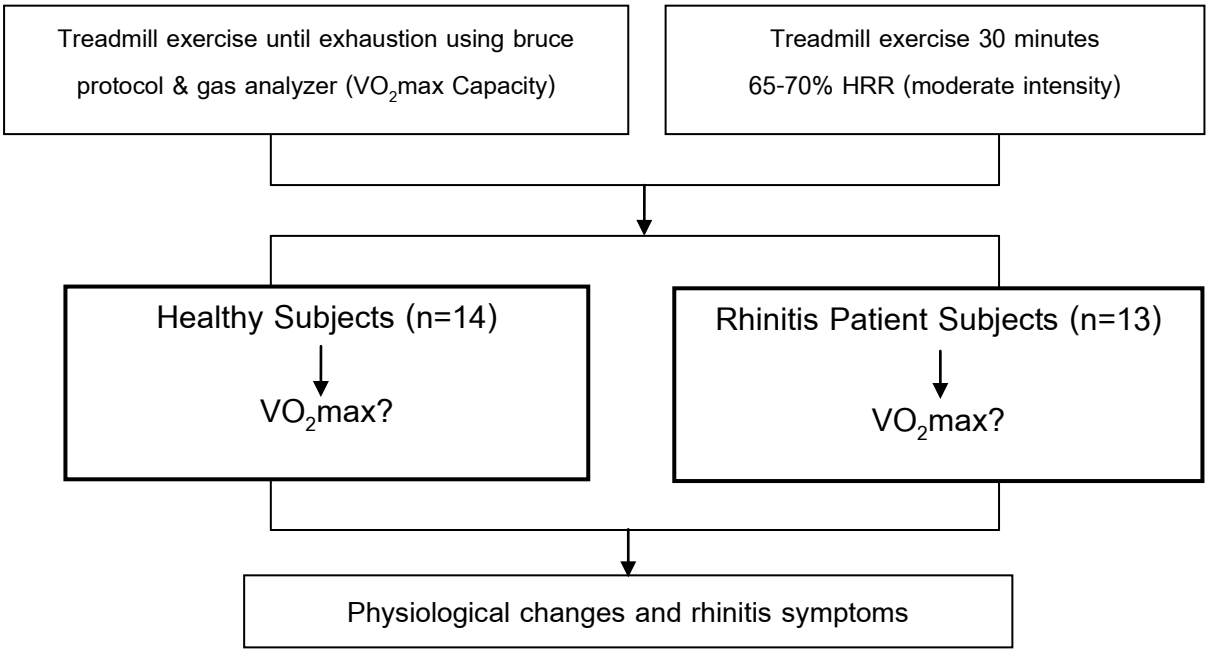

Fig 1.1 Study I conceptual framework

Study II: The effects of moderate exercise training combined with vitamin C supplementation on physiological changes and symptoms in allergic rhinitis patients.

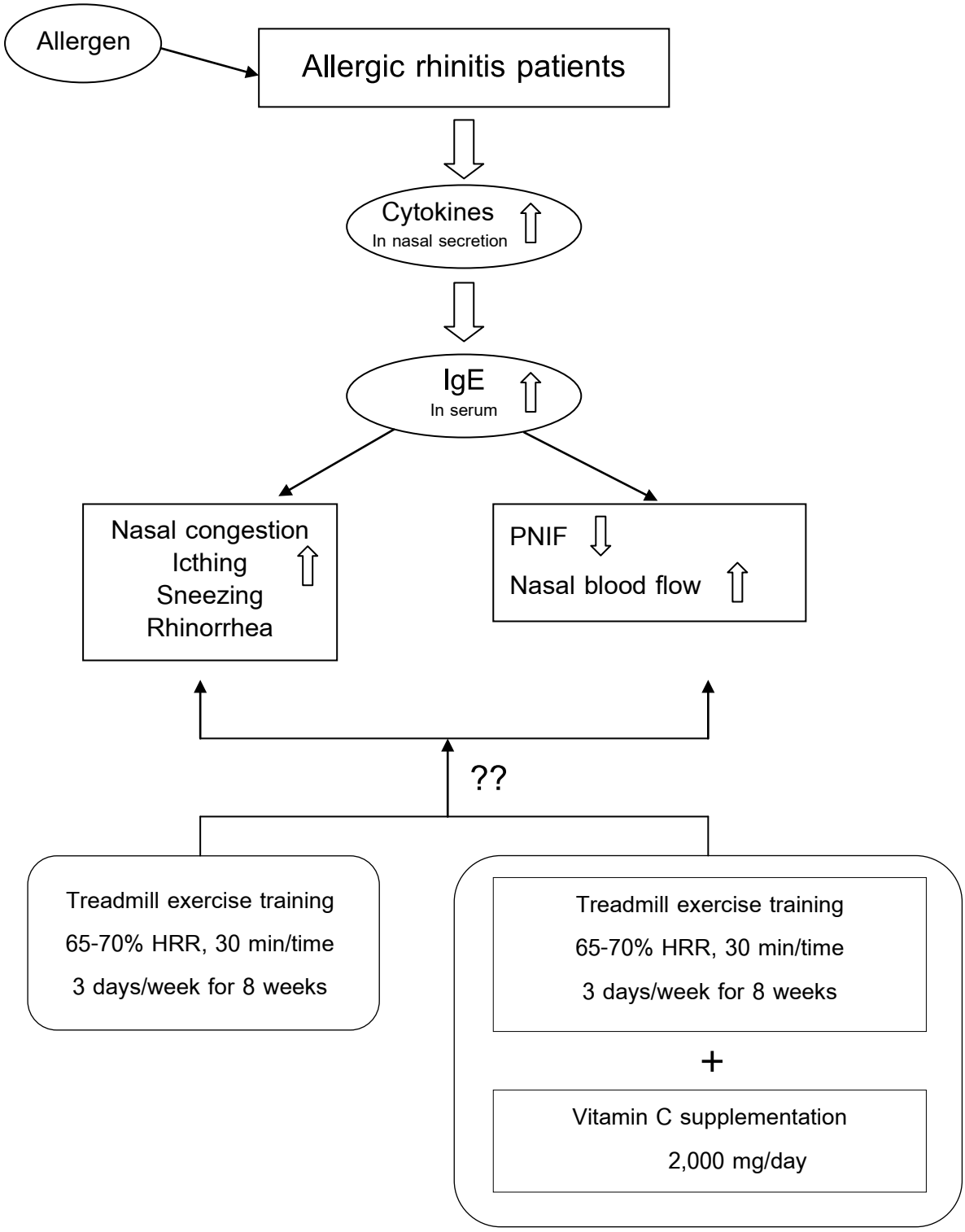

Fig 1.2 Study II conceptual framework