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ORIGINAL ARTICLE

High-intensity interval training-induced inflammation and airway narrowing of the lung parenchyma in male maturing rats

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Abstract

Besides the metabolic beneficial effects of high-intensity interval training (HIIT), it is able to increase the stress on lung parenchyma. This study examined 6 weeks of HIIT-induced inflammation and airway narrowing of the lung parenchyma in male maturing rats. All animals after 2 weeks of familiarization were divided in 3 groups of base ($n = 10$), HIIT ($n = 10$), and control ($n = 10$). HIIT was performed at speed of 20 m/min and ended at speed of 70 m/min (incrementally increase). Twenty-four hours after, the last training session animal was sacrificed and their lung removed. Lung samples were sectioned in 5 μm, stained with H&E, and studied histologically and histometrically. All these variables were measured at the end of exercise intervention. After 6 weeks of HIIT, measures of intima, media, and adventitia anatomical layers of the bronchi and bronchioles of the respiratory tract were significant than the control group ($p = 0.05$). Mechanical stress caused by excessive ventilation due to HIIT created histological inflammation in the bronchi and bronchioles of the respiratory tract. Thus, HIIT exercise causes reduction in the diameter of the lung parenchyma ducts that can affect the amount of oxygen consumption and consequently affect athletic performance.

Keywords High-intensity interval training · Lung parenchyma ducts · Histometric · Histologic

Abbreviation
HIIT High-intensity interval training

Introduction

Exercise training, depending on its frequency, volume, and intensity, can have positive or negative effects on general health (Pedersen and Hoffman-Goetz 2000). High-intensity interval training (HIIT) or interval training is a cardiorespiratory exercise strategy that alternates short periods of intense anaerobic exercise with less intense recovery periods. Various studies have investigated the metabolic effects of HIIT and suggested that these modalities of exercise can stimulate the oxidation of fatty acids by increasing the key enzymes of the lipid oxidation pathway, especially the β-oxidation and cyclic cycles. Thus, coaches have used this type of exercise as an effective way to lose weight or increase endurance (Burgomaster et al. 2005). In addition to the beneficial metabolism effects of HIIT, it has also effects on the cardiovascular system. In some studies, the benefits of HIIT exercises have been attributed to their positive effect on diaphragm muscle. Scott Bowen et al. (2017) stated that some pathological injuries such as hypertension cause impaired contraction of the diaphragm through the mechanism of action oxidative substances and that HIIT able to prevent the harmful effects of oxidants on contraction of the diaphragm (Bowen et al. 2017). It is also suggested that moderate-intensity exercise before and after pulmonary surgery may shorten length of hospital stay, decrease postoperative complications, and increase

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6MWD (Ni et al. 2017). In chronic obstructive pulmonary disease (COPD), the use of moderate and low intensity interval training improves the performance of the respiratory muscles and had some beneficial effects (Helenius et al. 2002). However, the increasing intensity and duration of exercises can enhance stress in the upper and lower respiratory tract.

During exercise at high intensity and duration, there are many reasons that can limit pulmonary function. Airflow limitation in the thoracic respiratory tract during exercise may be due to bronchoconstriction phenomena (exercise-induced bronchoconstriction, EIB) or due to a severe ventilation demand superimposed on normal maximum flow-volume envelope (Guenette et al. 2007). The narrowing of the upper respiratory tract also occurs in some athletes during high-intensity exercises (Nielsen et al. 2013). Also, exercise-induced arterial hypoxemia occurs when oxygen pressure of arterial alveolar is widely spread (Dempsey et al. 1984) that is attributed to the opening of intrapulmonary shunting (Stickland et al. 2004) during exercise and the formation of interstitial edema (Bussotti et al. 2015; Cremona et al. 2002). An increase in duration of the training can produce an upper respiratory tract infection (URTI). During high-intensity exercises, lower respiratory tract particularly bronchial epithelial may be damaged (Kippelen and Anderson 2012). Studies have shown that high-intensity exercise may increase the air flow rate of more than 200 l per minute for speed and strength athletes as well as runners and swimmers of long distances (Helenius et al. 2002); as a result, inhalation of high air volume, lack of water, and heat in breathing occur during exercise (Daviskas et al. 1991). Studies have suggested that even breathing at 60 l per minute (much less than 200 l per minute for elite athletes) requires the need to pass at the last 12 generations of ways to temper and heat up (26.7 °C) (Daviskas et al. 1991). The volume of airway surface liquid is limited in the first 10 generations of airways (less than 1 ml). During exercise, the increase in water evaporation decreases from airway surfaces that leads to dehydration of the airway surface volume and a rise in airway surface liquid osmolality (Anderson and Holzer 2000). All of these factors can have effects on the diameter of respiratory tract in the intima, media, and layers. In endurance sports, especially marathon, the damage of the respiratory system caused by heavy exercise is examined and numerous articles have discussed URTI caused by these exercises. Recently, many studies have been considered EIB (Anderson and Kippelen 2005), in this research; different training modalities are less discussed. Therefore, the aim of this study was to examine 6 weeks of HIIT-induced inflammation and airway narrowing of the lung parenchyma in male maturing rats. In this study for assessing the effects of exercise on lung parenchyma, we used histological images.

Materials and methods

Animals

Thirty male Wistar rats, at the age of 2 weeks, were purchased from the Center of Pasteur Institute Amol, Iran. Animals were transferred to the physical education group of Mazandaran University. They were randomly divided into 3 groups (base, HIIT, and control) and placed polycarbonate cage (each groups with 10 rats). Then, the rat groups of HIIT were familiarized with treadmill running for 2 weeks.

Exercise program

Familiarization for the HIIT group included a 4-day interval of training, with a speed of 10 to 25 m/min that is implemented incrementally. HIIT program was performed in 10 repetitions of 1 min and active rest for 2 min. The total daily workout time per rat head lasted 30 min. The rats started their training program at a speed of 20 m/min and finished at a speed of 70 m/min (Fig. 1). In addition to the time spent on the main activity, a period of 5 min was assigned as warm-up and 5 min to cool down. Training protocol for the HIIT group was performed for 6 weeks (5 days/week) (Ogura et al. 2006).

Measurements

Tissue sampling from the lungs of the rats was performed at the beginning of the training protocols for the base group and at the end of the HIIT period for HIIT and control groups (Fig. 1). **This study was conducted according to the Declaration of Helsinki guidelines and approved by the Ethical Committee of Mazandaran University.** For this purpose, by injection of ketamine (30–50 mg/kg) and xylazine (3–5 mg/kg) (Arabzadeh et al. 2016), the rats were anesthetized and their lung tissues were removed. The lung tissue was weighed by a Sartorius BI 1500 balance with a precision of 0.001 mg/kg. To study the histological structure, the right lobe of the lungs was placed in a 10% formalin solution.

In order to prepare microscopic sections of the samples, the usual method of preparing tissue sections was used. In this method after confirmation, different stages of the passage including water purification, clarification, and paraffin exposure were performed using the histokinette device 2000, manufactured by Leica Germany. Then, the samples are molded and, with a rotary microtome model 2035 manufactured by Leica Germany, were prepared into sections in the thickness of 5–6 μm and were stained of hematoxylin-eosin (H&E), periodic acidic staining (PAS), and Trichrome Mallory. Ultimately, microscopic slides were studied for structural and cellular changes. For histometric study and quantitative changes in the tissue and cell structure of lung tissues, at

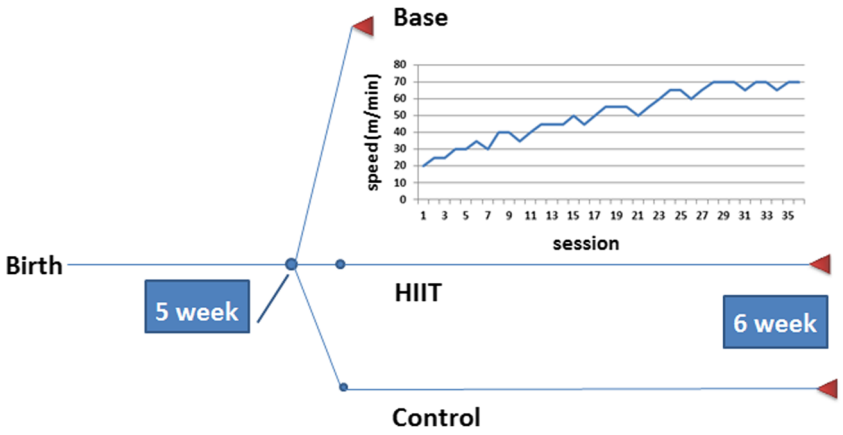

Fig. 1 HIIT protocol

least 10 tissue cuttings from each sample and in each cutting at least 10 microscopic fields of view were counted and evaluated. All micrometer studies were carried out using a graded eye lens and Slide Calibrate. Finally, the results of the changes in the parenchymal structure of the lung tissue in different groups with micrograph were presented and identified.

Statistical analysis

The data are reported as mean ± standard error. Data normality test and homogeneity of variances were measured by Kolmogorov-Smirnov (K-S) and Levene's test. One-way analysis of variance (ANOVA) and LSD post hoc test were used to compare the groups. Statistical analysis was performed by SPSS software version 16 (SPSS Inc., Chicago, IL, USA) and the significance level of the tests was considered ($p \leq 0.05$).

Results

Histometric

Histometric measurements of pulmonary bronchi and bronchial were reported in Tables 1 and 2. Results obtained from intra-pulmonary bronchi variables including the thickness of the epithelial bronchi ($F = 166.99$, $p = 0.001$), thickness of the tunica media (muscle) ($F = 64.92$, $p = 0.001$), thickness of the tunica adventitia bronchi ($F = 930.3$, $p = 0.001$), and number of goblet cells of the bronchi ($F = 41.02$, $p = 0.001$) showed a significant increase compared to the control group, as shown in Table 1.

Also, results obtained from pulmonary bronchiole variables included the thickness of the epithelial bronchi ($F = 102.39$, $p = 0.001$), thickness of the tunica media (muscle) ($F = 62.7$, $p = 0.001$), and thickness of the tunica adventitia ($F = 166.07$, $p = 0.001$) and the significance of these variables was confirmed from the control group (Table 2).

Histologic

Description of the results of histological lung rats was showed in Fig. 2. Histological images showed that intense exercise causes inflammation in the lung parenchyma, which leads to bronchial constriction and reduce air crossing of the dipper respiratory tract.

Discussion

We investigated the air duct responses following these exercise modalities as a method that recently considered in the

Table 1 Internal bronchi variable

Variable	Groups		
	Base	High-intensity interval training	Control
Epithelial (thickness, μm)	16.32 ± 0.83	37.6 ± 1.12*	23.4 ± 1.02
Tunica media (muscle) (thickness, μm)	23.98 ± 0.86	46 ± 1.87*	32 ± 1.22
Tunica adventitia (thickness, μm)	17 ± 1.43	63 ± 1.55*	27.6 ± 1.12
Goblet cells (number, per 100 μm of epithelial cell)	9 ± 0.89	22.4 ± 1.36*	13 ± 0.89

Mean (± SE)

*Significant compared to the control group ($p < 0.05$)

Table 2 Internal bronchiole variable

Variable	Groups		
	Base	High-intensity interval training	Control
Epithelial (thickness, μm)	6.08 ± 0.13	15.4 ± 0.68*	10.6 ± 0.4
Tunica media (muscle) (thickness, μm)	12.94 ± 0.64	27.6 ± 1.12*	23.4 ± 1.03
Tunica adventitia (thickness, μm)	12 ± 1.19	48.6 ± 1.86*	25 ± 1.57

Mean (± SE)

*Significant compared to the control group ($p < 0.05$)

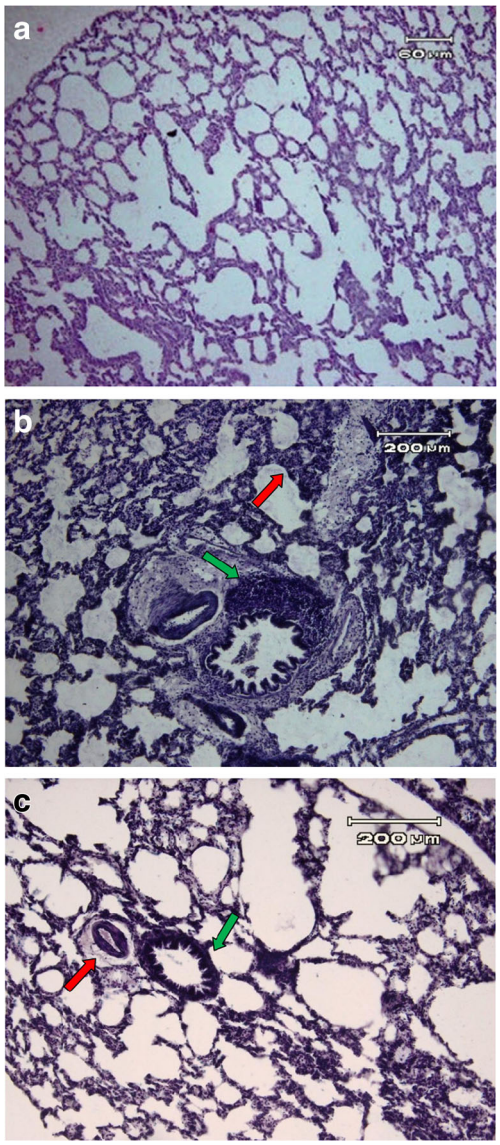

Fig. 2 HIIT lessened sensitization-induced changes in inflammatory cells and lymphocyte infiltration and lung architecture (**a** Base group, H&E stain, 60× original magnification. **b** HIIT group, H&E stain, 200× original magnification. **c** control group, H&E stain, 200× original magnification)

research. The present study data showed that air flow restriction due to airway changes was significantly higher in the HIIT than the control group. Histologic images also confirmed severe inflammation immunologic change of the lung tissue (Fig. 2). Researchers have examined immune changes induced by high-intensity exercises. Gleeson (2000) state that immunoglobulin A (SIgA) is one of the important elements of internal immunity and protects salivary immunity (Gleeson 2000). Low levels of SIgA have been reported in over-trained athletes (Gleeson 2000; Gleeson and Bishop 2000) and associated with upper respiratory tract infection (URTI) (Mackinnon et al. 1991). In other studies with intense training courses, subjects reported that their health was reduced and there were signs of URTI. In repeated studies, it was mentioned that increasing the amount of exercise and extreme competition can cause suppression of immunity (Berk et al. 1990; D. Nieman et al. 1995) and increase susceptibility to URTIs (D. C. Nieman et al. 1998). The reasons for reducing neutrophilia during intensive exercise can be two factors: First, the high intensity of exercise during a short period of time may result in the loss of immature neutrophils in the bloodstream of the bone marrow that is affected by cortisol due to intense exercise (McCarthy and Dale 1988). Secondly, neutrophils may have low respond to secondary stimuli when they are exposed to bacterial stimuli (Prasad et al. 1991). Histologic images of HIIT compared to the control and base group indicate increasing stresses on the bronchi and bronchiole airways (Fig. 1). The passage of high air volume from the respiratory tract causes the mucosal surface to dry, which can lead to local inflammation (Cox et al. 2004). Kilian et al. (2016) considered markers of biological stress in response to a single session of HIIT and high-volume training (HVT) in young athletes. They concluded that cardiorespiratory stress was higher during HIIT compared to HVT (Kilian et al. 2016). In recent studies, showed that HIIT significantly increases the hormonal and metabolic stresses. In addition to the prolonged periods of intense exercise, salivary alpha-amylase (Gómez et al. 2013) and levels of salivary immunoglobulin A reduced, as well as salivary cortisol concentration increased

(Li et al. 2012). It has also been shown in young footballers that have prolonged periods of exercise and high levels of overload that lead to URTI and a decrease in sIgA (Moreira et al. 2014).

Research on the size of airway changes in response to HIIT is limited. In the present study, HIIT increased the thickness of the epithelial bronchi and bronchioles. Very fast breathing caused by exercise can stimulate the epithelial surface of the airways, which leads to the release of contraction responses for airway constraints (Kippelen and Anderson 2012). Dynamic inflation caused by trapping air into the lungs during exercise can reduce inspiratory capacity (Stevens et al. 2013). These two mechanisms can cause air flow limitation, which results in the reduction of forced expiratory volume in one second (FEV1) (Parsons et al. 2013).

Measurements obtained from intra-pulmonary bronchi variables including the thickness of the epithelial bronchi ($F = 166.99$, $p = 0.001$), thickness of the tunica media (muscle) ($F = 64.92$, $p = 0.001$), thickness of the tunica adventitia bronchi ($F = 930.3$, $p = 0.001$), and number of goblet cells of the bronchi ($F = 41.02$, $p = 0.001$) showed a significant increase compared to the control group that indicates an increase in the thickness of the bronchial duct. Exercise-induced bronchoconstriction is an acute obstruction of the airways following intense exercise (Parsons et al. 2013). The prevalence of asthma, bronchial hyperresponsiveness (BHR), and EIB has significantly increased in elite athletes (Carlsen et al. 2008). "The influence of water and heat loss in causing the transient bronchoconstriction that occurs shortly after high intensity exercise is now widely accepted" (Anderson and Daviskas 2000). The responsible mechanism for developing EIB and BHR in athletes has been studied over a long time. Anderson and Kippelen (2005) stated that recurrent airway epithelial damage plays an important role in the pathogenesis of respiratory distress in elite athletes (Anderson and Kippelen 2005). Recently, Kippelen and Anderson proposed that various reasons have been noted for damage to the epithelial cells of the airways caused by intense exercise. First, extreme hyperpnoea results in changes in viscosity, elasticity, and volume of the ASL. Secondly, the excessive force created on the epithelial surface of the airways during exercise can cause tension stress and increase the trans-epithelial pressure gradient. As a result of these factors, the destruction of the epithelial cell layer occurs, and injury-repair response may follow. Plasma infiltration, with repetition of damage and restoration process, may alter the contraction characteristic of smooth muscle in airways, causing high sensitivity in athletes (Kippelen and Anderson 2012). Airway epithelial damage after exercise was first confirmed in the animal model, but recent studies have suggested that this injury can also occur in athletic humans. Exercise intensity and environmental factors are considered as degradation and modulation of epithelial airway integrity. In this study, it was also shown that the increase in the intensity of exercise with HIIT strongly affects with changes in the diameter of the airways of the bronchus and branches.

Conclusion

It was shown that intensity and frequency of exercise or both are important determinants for the development of airway epithelial injury. This study showed that HIIT exercise causes reduction in the diameter of the lung parenchyma ducts that can affect the amount of oxygen consumption and consequently affect athletic performance. Therefore, it was suggested that other research in the program of exercise should also consider the effect of training intensity on the respiratory system.

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Compliance with ethical standards This study was conducted according to the Declaration of Helsinki guidelines and approved by the Ethical Committee of Mazandaran University.

Conflict of interest The authors declare that they have no conflict of interest.

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