Research Article

Effect of incremental interval training on levels of Fasl protein in lung tissue of mature male Wistar rats: Does exercise training reduce lung inflammation?

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Abstract

Intense exercise training is associated with Lung inflammation. Fasl protein on the cell surface is responsible for the initiation of the inflammatory response that finally leads to cell death at the site of inflammation, and can be interpreted as Fasl induced apoptosis. Therefore, the aim of this study was to investigate the effects of increasing and intense interval exercise training on Fasl levels of mature rat lungs. 30 rats within three weeks of birth with mean weight 68±9 g were randomly divided into three basic, control, and exercise groups. Increasing interval training for 6 sessions per week, each session 30 minutes at a speed of 15 to 70 meters per min was employed and Fasl levels were measured using the kitby Elisa method. The data were analyzed with two-way ANOVA and LSD test was done at p≤0.05 significant level. The results showed that Fasl protein levels in the interval training group compared to baseline group increased by 23.75 % and was significant (p≤0/05). However, although the amount of this protein in the interval training group compared to the control group was high, this value was not significant. In addition, Fasl protein levels in the control group compared to the baseline group increased by13.58 % and was significant (p≤0.05). The findings indicated that intense and prolonged exercise training causes damage of the respiratory tract, and in turn, leads to the increased levels of Fasl.

Key Words: **Incremental interval training, FASL, Lung tissue, Inflammation**

Introduction

Using the best training methods to achieve maximum adaptation in the least possible time is one of the goals of coaches and athletes, which requires the diligence in adopting modern training methods. Intensive and heavy training methods, along with active rest periods, are one of the best and most famous of these methods (Arnardóttir et al., 2007). Interval exercises are one of the most effective exercises in the development of all three energy systems and especially the aerobic system, which results in the best training adaptations in the shortest time (Coppoolse et al., 1992). On the other hand, there is an inverse relationship between training load and immune system performance, which shows the improvement of immune performance in moderate activities while the excessive amount of intense long-term training has destructive effects on immune performance. Intense and overtraining exercises are generally associated with recurrent drowsiness and weakening of the immune system, but immune dysfunction does not seem to be a symptom of overtraining (Vogiatzis et al., 2002).

The reduction and deterioration of immune function after periods of heavy and intense training may be related to various factors. One of these mechanisms that weakens the immune system is inflammation. In fact, inflammation is a response to injury, which occurs through the flow of plasma proteins and the migration of white blood cells into the tissue, in response to injuries, infection or antigens, and the purpose of this function is cleansing the damaged tissue and removing microbial substances so that the tissues are prepared for repair. During the inflammation process, monocytes with an inflammatory phenotype move to the alveolar space. It takes several days for these cells to acquire the suppressive phenotype of alveolar macrophages.

Recently, a mechanism has been proposed claiming that macrophages return to their suppressive phenotypes after exposure to infectious agents, this mechanism explains the fact that a few days after exposure to infectious agents, lymphocytes secrete gamma interferon stimulating the product-

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-ion of matrix metalloproteinase-9 by alveolar macrophages. Matrix metalloproteinase-9 can activate latent β-BGT by the described mechanism. This macrophage switches back to its anti-inflammatory phenotype. The FAS/FASL pathway can be important in the interaction between macrophages and neutrophils in inflammatory areas (De Paepe et al., 2005). Macrophages expressing FASL and FASLS are in the conditioned supernatant of activated macrophages. The favorable supernatant includes FASLS, which accelerates neutrophil apoptosis, but other factors that help induce neutrophil apoptosis are also present. In a report, Leandro et al. (2007) confirmed that FAS and FASL expression decreases after light exercise (>50% VO2max) and moderate exercise (70-60% VO2max). They stated that moderate physical exercise reduces the FAS/FASL system and as a result tends to reduce apoptosis and the production of pro-inflammatory cytokines and their soluble receptors. They are the product of the interaction of endothelial cells with monocytes, and at the same time, they are the biological modifiers of the action of circulating cytokines.

In another study, it was found that immediately after strenuous exercise, the percentage of apoptotic cells increases significantly, while after moderate-intensity exercise, this percentage remains unchanged. In addition, after both methods of passive and moderate exercise training, positive regulation of CD95 receptor expression is revealed. However, a characteristic change in the expression profile of CD95 (FAS) compared to cells with high receptor density was observed only after the inhibitory exercise. The results showed that apoptosis may help regulate the immune response after endurance exercise (Mooren et al., 2002). In a study on the relationship between aging and FASL protein levels in the lungs of rats, De Paepe et al. (2005) stated that with increasing age and the development of the respiratory system, there was a threefold increase in FASL protein levels in the lungs. These results show that along with age, lung FASL protein levels also increased due to the development of the respiratory system. It should be noted that the knowledge of apoptosis in AE2 cells in the physiology and pathology of the adult lung is still in its early stages (Fine et al., 2000). Accordingly, this study aimed to investigate the effect of increasing interval training on changes in the FASL levels of male rats' lungs during inflammation.

Materials and Methods

Animals

Thirty male Wistar rats were purchased from the Pasteur Institute at the age of two weeks and transferred to the laboratory animal. Then they were randomly divided into three groups based on weight groups and placed in groups of 10 in each polycarbonate cage. Since the transfer and relocation of the subjects caused stress in them, they were kept there for one week after the transfer in order to adapt to the environment and then to familiarize themselves with the treadmill for one week. They learned how to work on the tape recorder. The treadmill used for rats (made in Iran) had 10 glass compartments made of Plexiglas with the dimensions of 90 cm in length, 10 cm in width, and 15 cm height. It had an automatic shocker, positive slope and the negative was adjustable, with a display screen for speed, distance, time, and shock voltage. The familiarization program included 4 sessions of walking and running at a speed of 10 to 25 meters per minute and zero incline, and was performed in intervals according to the training protocol.

Exercise training

To stimulate running, a mild electric shock was placed at the back of the device. In order to prevent the possible effect of electric shock on the research findings, during the familiarization stage of the activity on the treadmill, the subjects were taught to avoid approaching and resting in the end part of the device by the method of conditioning with sound. The duration of the training period of the rats was 6 weeks, and the training protocol of the research was in the form of increasing wave intervals (Table 1 and Figure 1). The familiarization phase included 4 days of an interval training program with a speed of 10 to 25 meters per minute according to the pattern of the increasing interval training program. The increasing interval training program was performed in the form of 10 repetitions of one minute and active rest of two minutes. In such a way that the resting speed was half of the running speed and total daily training time for each animal was

Table 1. Demographic characteristics of the subjects by research groups

Week	Acquaintance	1	2	3	4	5	6
Speed (M/Min)	10-25	25-35	35-45	45-55	55-65	65-70	65-70
Duration(Min)	1	1	1	1	1	1	1
Rest	2	2	2	2	2	2	2
Frequency	7	8	10	10	10	10	7
Sessions per week	4	5	6	6	6	6	5

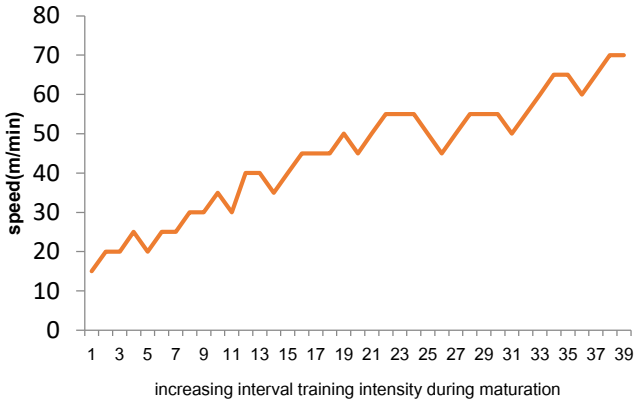

Figure 1. Increasing interval training intensity during maturation.

30 minutes. Subjects practiced throughout the week except for Friday. The subjects started the increasing interval training program with a speed of 25 m/min and finished with a speed of 70 m/min. Apart from the main activity time, 5 minutes for warm-up and 5 minutes for cool-down were considered.

Laboratory measurements

Tissue sampling was done from the lungs of rats at the end of the interval period. For this purpose, by injecting 3 units of ketamine solution (30-50 mg per kg) and xylazine (3-5 mg per kg), the mice were unconscious and their lung tissue was removed. Lung tissues were weighed using a Sartorius BL 1500 scale with an accuracy of 0.001. The dependent variable of the research included FASL levels, which were evaluated and analyzed in the pulmonary parenchymal ducts. FASL levels were determined using a special kit using the ELISA method. For this purpose, lung tissue was first homogenized using liquid nitrogen powder and then in buffer solution and centrifuged for 15 minutes at 3000 g speed. The obtained solution was transferred to the laboratory to measure the desired index using dry ice. To analyze the findings of this research, Kolmogorov Smirnov test, one-way analysis of variance and LSD follow-up tests were used to compare the groups. All calculations were done using SPSS 20 statistical software and at a significance level of $P \leq 0.05$.

Results

Table 2 presents the mean and standard error of the weight of rats in each research group. The control and the interval-training group had a significant increase in weight compared to the base group. In addition, the interval control group had a considerable increase compared to the interval training group.

The values related to the FASL protein variable of the research groups are shown in Figure 2. The findings show that the amount of FASL protein in the interval-training group had a significant increase of 23.75% compared to the baseline group ($P \geq 0.05$).

In addition, the amount of FASL protein in the interval control group had a significant increase of 13.58 ($P \geq 0.05$) compared to the baseline group. However, the increase of this protein in the interval-training group was not significant compared to the interval control group ($P \geq 0.05$).

Discussion

In the present study, the effect of six weeks of increasing interval training on lung FASL protein levels was investigated. The results showed that six weeks of increasing interval training caused a significant increase in the FASL levels of the interval-training group compared to the baseline group. On the other hand, the FASL levels of the interval control group increased significantly compared to the baseline group, but the difference was not significant. No difference was observed between the FASL levels of the interval control group and the interval-training group. The results of studies have shown that along with age, FASL protein levels in the lung have also increased due to the development of the respiratory system (De paepe et al., 2005). Regarding the effect of interval training on FASL levels, it seems that there is a key factor in increasing FASL levels, and that is the intensity of sports training.

The results of the current research are align with the findings of Moran et al. (2004). In their research, they examined the effect of exercise conditions on apoptosis. These researchers compared the exercise conditions in lymphocyte apoptosis and the expression of cell death receptors and ligands after marathon running and treadmill exercise tests. Their results showed that apoptosis due to FASL can be seen in intense exercise (such as marathons), while no changes in apoptosis were observed after low-intensity exercise (treadmill). Based on this finding, the percentage of apoptotic cells changed after the marathon. An increase in apoptotic cells was observed 3 hours after running, followed by a significant decrease one day after marathon running. Interestingly, an increase in apoptotic cells was not observed in professionally trained athletes while this increase was observed in amateur athletes. The percentage of FAS and FASL proteins also increased after the marathon while the FAS receptor peaked one hour after the marathon, and FASL increased three hours after the marathon. After the treadmill test, FAS receptor expression increased in both groups while FASL protein increased only in the intense training (marathon) group. As a result, they stated that sensitivity to apoptosis depends on exercise intensity. The increase in expression levels of death receptors and ligands may indicate the potential of this type of exercise (marathon) to induce apoptosis. The expression of pre-apoptotic FASL protein after the marathon shows the high apopt-

Table 2. The weight of lung and relative lung weight in different groups (Mean ± SD) (gr).

Period	Group	Average Weight of rats (gr)	Standard error	Average lung weight (gr)
Before starting the protocol	Base group	64	6.59	0.41
Interval (Week 1 to 6 of the protocol)	Interval	123.106	1.81	0.69
	Interval control	145.029	3.96	0.98

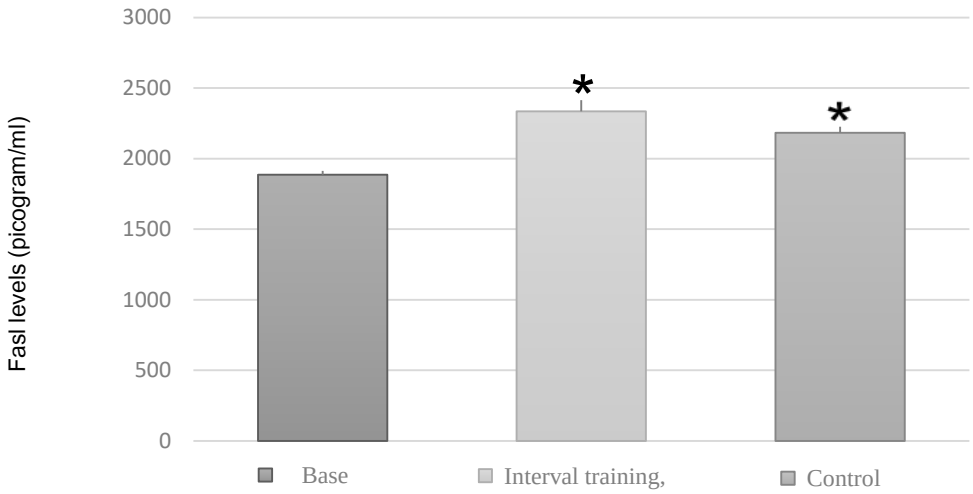

Figure 1. The means of Fasl protein in lung tissue at different research groups

-otic potential of this aerobic exercise. Finally, they stated that intense exercise is a stressful factor and can induce a state similar to inflammation. In another study, Ebrahimi et al. (2013) investigated the effect of two months of adaptation to aerobic exercise on the expression of FAS in peripheral blood lymphocytes of healthy women. In their research, 24 healthy inactive women with an average age of 20±3 years participated, who were divided into two groups: exercise (8 weeks of moderate-intensity aerobic exercise 30 minutes per day) and control groups. Their findings showed that there was no significant difference in the amount of apoptosis of lymphocytes between the first stage and the second stage in the control group. In contrast, FAS levels significantly decreased after two months of exercise training, which indicates that low-intensity physical activity may lead to a decrease in apoptosis in peripheral blood lymphocytes in active subjects compared to non-active subjects (Ebrahimi et al., 2013).

Krueger et al. (2009) also stated that exercise has caused the expression and increase of FAS in lymphocytes in the lungs of mice. They reported that FAS-deficient mice had less T lymphocyte apoptosis in lymphocytes, spleen, lung, and the bone marrow after exercise. This indicates the critical role of FAS in exercise-induced apoptosis. In addition, another study reported that intense exercise increased FAS expression in the lymphocytes of healthy volunteers, but moderate exercise had no effect on FAS expression (Krueger et al., 2009). Adamopoulos et al. investigated the role of physical exercise on pro-inflammatory cytokines and the FAS/FASL system in patients with chronic heart failure. Their training program included 12 weeks of light to moderate physical training (cycling at home, 5 days a week for 30 minutes with a heart rate of about 60-80%) on 24 patients with chronic heart failure and 20 healthy individuals. Their results showed that physical training caused a significant decrease in TNF-α, sTNF-RI, sTNF-RII, IL-6, sIL-6R, FAS and FASL while exercise increased VO2max. There is a good correlation between the increase in VO2max caused by exercise and the decrease caused by exercise in the levels of pro-inflammatory cytokines TNF-α and apoptosis induced by FASL in patients with CHF (chronic heart failure). They concluded that light to moderate physical exercise causes a significant decrease in circulating pro-inflammatory cytokines and their soluble receptors, as well as in soluble FASL inducing and soluble FAS apoptotic receptors, and

these effects may be related to exercise-induced improvement of functional status in patients with CHF (Adamopoulos et al., 2002). Therefore, light to moderate physical training negatively regulates the FAS/FASL system.

Navalta et al. (2007) stated in their research that when exercise intensity increases step by step, the increase of apoptotic cells is observed in exercise intensity beyond 60% of VO2max in human samples. One reason for these different effects can be the different metabolic and hormonal reactions of this type of exercise, such as the level of lactate and catecholamine (Navalta et al., 2007). In another study, Moran et al. (2002) investigated the effect of intense and moderate exercise on lymphocyte apoptosis. In their research, healthy volunteers performed two treadmill tests; the first test was performed with 80% of maximum oxygen until exhaustion (exhausting exercise) and the second test was done two weeks later, at 60% of maximum oxygen and similar to running (moderate exercise). Blood samples were taken one hour after exercise. Their results showed that there was a positive regulation of FAS receptor expression after both exercise tests. However, a characteristic change in FAS expression towards cells with high receptor density was observed only after the passive exercise. FASL expression also remained unchanged after both exercises. Intense exercise training modulates several factors, such as reactive oxygen species, DNA damage, and hormone and cytokine levels that are involved in the regulation of apoptosis in different types of cells. Free oxygen species that increase in response to exercise can induce apoptosis through different mechanisms, such as reducing intracellular glutathione levels and changing mitochondrial proteins or through direct cellular DNA damage. Finally, they reported that an increase in apoptotic cells after exercise was not observed in trained professional athletes, while these cells were significantly increased in untrained athletes (Moran et al., 2002).

In another study, Simpson and et al. (2007) reported increased apoptotic cells caused by exercise. In this study, it was shown that exercise-induced changes in glucocorticoids lead to the induction of lymphocyte apoptosis. Using a glucocorticoid receptor antagonist reduced DNA damage in the thymus of rats that experienced a mild physical effect compared to control group animals (Simpson et al., 2007). In another study, Kruger et al. (2011) examined the role of exercise training on lymphocyte apoptosis and the FASL signaling pathway. They stated that intense exercise causes the activation of blood T lymphocytes, which seems to be terminated by apoptotic processes in the post-exercise period. They reported that apoptosis caused by T lymphocyte exercise is a systemic phenomenon in different lymphatic and non-lymphatic tissues (lung). The amount of apop-tosis can be related to the intensity and type of exercise. Although in some tissues such as the spleen and pieces of lymph nodes, early apoptosis can be detected (1-3 hours after exercise); delayed apoptosis (24 hours after exercise) in the lung, bone marrow and lymph nodes was observed. The percentage of positive FAS and FASL receptors of lymphocytes in lymph nodes increased after exercise. In addition, FASL+ T cells were increased in the lung, while FAS cells were increased in the lymph nodes (Kruger et al., 2011).

According to Hoffman Goetz and Quadrilatero (2003), intense running on a treadmill leads to an increase in lymphocyte apoptosis in the intestinal epithelium and thymus. These data show that the apoptosis of lymphocytes caused by sports activity may not be limited locally, but as a general process spread throughout different tissues. It is interesting to note that there are certain differences in FASL protein expression in different tissues of the body, such that early changes in the spleen and lymph nodes increase FASL expression immediately after exercise, while in the lung, bone marrow and lymph nodes, this increase is associated with a delay of several hours. Intense running on the treadmill causes massive apoptosis of the thymus and intestinal lymphocytes in 24 hours after exercise. In the bone marrow, the death of T cells increased 24 hours after exercise. The increase in FASL expression in lung lymphocytes 24 hours after exercise corresponds to the beginning of apoptosis. These results show that exercise does not affect the apoptosis of T lymphocytes in MRL/LPR mice. FAS expression increased in lymph nodes while apoptosis of T cells was weak after intense exercise tests in MRL/LPR mice. The expression of FAS and FASL in lymph node T cells significantly increased after exercise (Hoffman Goetz & Quadrilatero, 2003).

Tuan et al. (2008) also in their research stated that pro-apoptotic death receptor ligands (TNF-α and FASL) increased up to 72 hours after 3 days of intense continuous treadmill running in trained individuals. This finding shows that cell sensitivity to apoptosis can exist even 3 days after intense exercise. In addition, intense exercise (40 minutes of cycling with 80% VO2max) shows the compromise of cell resistance to apoptosis caused by oxidants and the activity of pro-apoptotic proteins caspase 8, caspase 9 and caspase 3 in lymphocytes. Increases (Tuan et al., 2008). In a study conducted by Zhang et al. (2008), the results showed that the amount of Bax/Bcl-2 in mRNA increased in response to intense resistance exercise, which causes an increase in procaspase-3 in mRNA in response to acute resistance exercise. In contrast, the results of Lee et al. (2012)'s research showed that 16 weeks of moderate-intensity treadmill training decreased the expression of various apoptotic

markers in the brain, such as; Cytochrome C, caspase 9, caspase 3 and Bax (Lee et al., 2012). Timmons et al. (2007) also pointed out that FASL cells were more during the recovery phase than during the rest phase before exercise. Therefore, although some studies reported that FASL cells increase after exercise, and also considering the knowledge of apoptosis in AE2 cells in the physiology and pathology of the adult lung is still in its infancy, the research emphasized that apart from intense exercise, aging and the growth and development of the respiratory system also lead to an increase in FASL levels (Timmons et al., 2007).

Conclusions

Based on the findings of the current research and according to the results of studies by different researchers in the field of lung injuries, this research supports the hypothesis of an increase in the lung injury response following intense sports activities, with an increase in FASL protein levels in the AE2 cells of the lung.

What is already known on this subject?

Using the best training methods to achieve maximum adaptation in the least possible time is one of the goals of coaches and athletes.

What this study adds?

Intense exercise increasing Fasl levels in lung tissue that can induce inflammation.

Organ Cross-Talk Tips:

- Cross-talk between skeletal muscle and lung by Fas ligand is involved in better understanding of inflammation.
- Cross-talk between skeletal muscle and lung through incremental interval training will have therapeutic application in patients with lung inflammation such as COPD and fibrosis.

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Compliance with ethical standards

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

Ethical approval Experimental protocols were approved by the Ethics Committee of Mazandaran University, Babolsar, Iran.

Informed consent Animal study.

Author contributions

Conceptualization: S.A., R.SH.; Methodology: S.A., R.SH.; Software: R.SH.; Validation: S.A.; Formal analysis: S.A.; Investigation: .M., Z.H.F.; Resources: .M., Z.H.F.; Data curation: S.A., R.SH.; Writing - original draft: S.A., R.SH.; Writing – review & editing: S.A.; Visualization: S.A., R.SH.; Supervision: S.A.; Project administration: S.A., R.SH.; Funding acquisition: S.A.

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