RESEARCH ARTICLE

Effects of exercise combined with hypoxia on vascular function in rats with insulin resistance

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Insulin resistance (IR) is a fundamental pathological factor in a variety of chronic non-communicable diseases (CNCDs) such as type 2 diabetes and cardiovascular disorders. The main goal of this research was to investigate the influences of intermittent hypoxic exposure combined with aerobic exercise on vascular function in rats with IR. 12 healthy male Sprague-Dawly (SD) rats were adopted as normal control group and 48 diet-induced IR rats were divided into four intervention groups as model control, hypoxic quiet, normoxic exercise, and intermittent hypoxic exercise with 12 rats in each group. Following an intervention period of 4 weeks, the intermittent hypoxic exercise group presented the most significant improvement in vasoconstrictor function ($P < 0.05$). The insulin sensitivity indices (ISIs) of both intermittent hypoxia and exercise intervention groups were significantly higher than that of model control group ($P < 0.05$). The IR indices of intermittent hypoxia intervention alone and exercise intervention alone were significantly smaller than that of model control group ($P < 0.05$), while intermittent hypoxia exercise group presented a slight decrease relative to model control group with no significant difference. Angiotensin II (Ang II) and nitric oxide synthase (NOS) were significantly decreased ($P < 0.05$) and nitric oxide was significantly increased ($P < 0.05$) in the intermittent hypoxic quiet group compared with model control group. However, Ang II was slightly reduced in normoxic and intermittent hypoxic exercise groups compared to model control group, but the difference was not significant. Intermittent hypoxic exercise was found to improve IR and lipid metabolism degrees in rats with high-fat diet-induced IR. Intermittent hypoxic exercise improved the vasoconstriction function of rats with insulin resistance induced by high-fat diet, and the effect was the best in the intermittent hypoxic exposure combined with exercise group.

Keywords: insulin resistance; hypoxia; aerobic exercise; vasoconstrictor function; angiotensin II; nitric oxide.

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Introduction

By improving material standard of living, irrational dietary structure, and working style of people, chronic non-communicable diseases (CNCDs) including obesity, type 2 diabetes, abnormal lipid metabolism, hypertension, hyperinsulinemia, *etc*. have become the main threat to people's health. The common soil for all these diseases is insulin resistance (IR) [1]. The common danger of the CNCDs is IR, and the effective prevention and treatment of IR play an

essential role in solving CNCDs [2].

Through the rreviewing of the prevalence data on diet and exercise intervention in the prevention of diabetes in high-risk groups published domestically and internationally, it has found that exercise can significantly improve the body's IR and effectively reduce the incidence of diabetes [3]. However, the specific mechanism by which exercise improves IR is still unclear. Studies have found that there are many potential mechanisms that exercise improves IR, among which changes in vascular function are closely related to the occurrence and development of IR [4]. In recent years, hypoxia has not only been widely used in sports training but has also been increasingly valued in fitness and the treatment of certain diseases. There are continuous research reports on hypoxic exercise and health, and it is pointed out that hypoxia has broad application prospects in rehabilitation and the treatment of certain diseases [5]. Recent studies have suggested that hypoxia might enhance metabolic adaptations [6-8], but the combined effects of hypoxia and exercise on vascular function in IR remain unexplored [9].

This research aimed to investigate whether intermittent hypoxic exercise improved vascular function in IR rats and evaluate the roles of Ang II and NO in this process by using a rat high-fat diet-induced insulin resistance (IR) animal model and aerobic exercise and intermittent hypoxia as intervention measures to monitor the changes in blood glucose, insulin, and IR index to explore the effects of hypoxia and exercise on IR. The change trends of angiotensin II (Ang II), nitric oxide (NO), and nitric oxide synthase (NOS) were compared, and the effects of intermittent hypoxia on the vascular function of IR rats were analyzed. This research provided some effective information for improving cardiovascular function in IR patients with hypoxia exercise. The findings of this study would provide novel insights into therapeutic strategies for IR-related cardiovascular disorders.

Materials and methods

Experimental animals

A total of 60 male specific pathogen-free (SPF) Sprague Dawley (SD) rats with the average body weight of 160 ± 15 g were purchased from the Animal Center of Southern Medical University (Guangzhou, Guangdong, China). The rats were housed in a controlled environment at 22 ± 2.5°C and 39 - 59% humidity with free access to food and water. The rats were randomly divided into 2 groups of the normal control group (n = 12) and high-fat meal group (n = 48). The normal group consumed normal feed while the high-fat group received high-fat feed formulated as rodent feed with 67.5% basal feed, 17% sucrose, 12% lard, 2.5% cholesterol, and 1% sodium cholate provided by South China Sea Hip Lik Feed Co. (Fushan, Guangdong, China). All animals were fed for 6 weeks before the starting of experiments. All procedures of this research were approved by the Ethics Committee of Guangzhou Institute of Physical Education (Guangzhou, Guangdong, China).

Establishment of IR rat model

At the end of the 6^{th} week, 8 rats were randomly selected from the normal and high-fat meal groups. The fasting insulin (FINS) and the fasting blood glucose (FBG) were measured. The insulin sensitivity indices (ISI) and IR index (HOMA-IR) were separately calculated using the internationally recognized HOMAMODEL equation as below. Due to the non-normal distribution, the ISI was taken as its natural logarithm.

$$ISI = -\log (FBG \times FINS)$$

$$Homa\text{-}IR = (FBG \times FINS) / 22.5$$

The glucose tolerance test (GTT) was conducted through subcutaneous abdominal injection of glucose solution at 2 g/kg body weight. Blood glucose levels were measured at 0, 30, 60, and 120 minutes using a Kyoto GT-1640 blood glucose meter (Arkray, Kyoto, Japan).

Animal grouping and treatments

The animals in IR group were additionally divided into four subgroups with 12 animals in each group, which included model control group that housed in a normoxic environment, hypoxic quiet group that received hypoxic stimulation for 4 hours per day, normoxic exercise group that housed and exercised under normoxia, and intermittent hypoxic exercise group that received hypoxic stimulation for 4 hours per day and in normoxic environment for housed and exercise for the remaining of the day. The rats were trained with 4 weeks of running table exercise at a slope of 0 and a speed of 25 m/min. The normoxic exercise was 1 hour a day, 5 days a week, while the intermittent hypoxic exercise was 4 hours a day, 7 days a week. The intermittent hypoxic stimulation used 14.5% oxygen concentration. During these 4 weeks, the rats in the high-fat meal group were fed with high-fat chows, while the healthy group was fed with normal food and also selected as the normoxic quiet group.

Sample collection

Rats were sampled 24 hours after rest following the last exercise and hypoxic stimulation and anesthetized with 50 mg/kg sodium pentobarbital. Blood samples were collected from abdominal aorta in test tubes with or without anticoagulant. Serum was then separated by centrifugation at 3,000 rpm for 20 min. The supernatant was stored at -70℃ for further analyses.

Indicators tests

Fasting blood glucose (FBG) was determined using a Kyoto GT-1640 blood glucose meter (Arkray, Kyoto, Japan). Collected blood samples were allowed to clot for 2 hours at room temperature before centrifugation at 3,000 rpm for 20 minutes to separate serum. Serum glucose levels were directly measured using pre-calibrated glucose test strips (Arkray, Kyoto, Japan) according to the manufacturer's instructions. Serum nitric oxide (NO) levels were quantified *via* the nitrate reductase method. Briefly, serum samples were incubated with nitrate reductase (Adlitteram Diagnostic Laboratories, San Diego, CA, USA) and NADPH to reduce nitrate to nitrite before reacted with Griess reagent made by mixing 1% sulfanilamide and 0.1% N-1-naphthylethylenediamine dihydrochloride in 5% phosphoric acid. The absorbance was measured at 540 nm using a spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). Total nitric oxide synthase (T-NOS) and inducible nitric oxide synthase (iNOS) activities were measured by chemical colorimetric assay. Serum samples were incubated with L-arginine (substrate), NADPH, and $CaCl_2$ (cofactors) at 37°C for 60 minutes. The reaction was terminated by adding a stop solution, and the generated nitrite was detected using the same Griess reagent system. Absorbance values at 540 nm were recorded *via* a spectrophotometer, and enzyme activity was calculated based on a standard curve provided in the NOS assay kit (Adlitteram Diagnostic Laboratories, San Diego, CA, USA). Serum angiotensin II (Ang II) concentrations were determined using Ang II enzyme-linked immunosorbent assay (ELISA) Kit (Adlitteram Diagnostic Laboratories, San Diego, CA, USA). Serum samples were added to antibody-precoated microplates and incubated with horseradish peroxidase-conjugated secondary antibodies. After washing, tetramethylbenzidine (TMB) substrate was added, and the reaction was stopped with 2 M sulfuric acid. Absorbance was measured at 450 nm using an RT-2100C multifunctional microplate reader (Rayto Life Sciences, Shenzhen, Guangdong, China), and the concentrations were interpolated from a standard curve. All assays were performed in duplicate following the manufacturer's protocols.

Statistical analysis

SPSS 20.0 (IBM, Armonk, NY, USA) was employed for statistical analysis of experimental data. One-way ANOVA was applied after normality and chi-square test. The results were expressed as mean ± standard deviation (SD). The *P* value less than 0.05 was defined as a statistically significant difference and the *P* value less than 0.01 was defined as a very significant difference.

Table 1. Comparison of relevant indexes in modeling rats (mean ± standard deviation).

Groups	No.	FINS (μg/L)	ISI	HOMA-IR	GTT (mmol/L)			
					FBG (min)			
					0	30	60	120
Normal dietary (NC)	8	4.18 ± 1.21	-1.83 ± 0.14	0.79 ± 0.14	4.69 ± 0.92	10.80 ± 1.75	6.38 ± 1.74	5.40 ± 1.13
High-fat dietary (HC)	8	5.29 ± 1.33$^{\#}$	-1.96 ± 0.12$^{\#}$	1.10 ± 0.15*	4.20 ± 0.61	16.36 ± 2.23$^{\#}$	10.62 ± 2.08*	6.36 ± 0.82

Notes: Comparison between the modeling group and the control group. $^{*}P < 0.05$. $^{\#}P < 0.01$.

Table 2. Comparison of ISI and Homa-IR in rats of each group (mean ± standard deviation).

Groups	No.	Blood glucose (mmol/L)	Insulin (ng/mL)	Insulin sensitivity index (ISI)	IR index (Homa-IR)
Normal control	12	4.19 ± 0.37	4.87 ± 0.57	-1.30 ± 0.14	0.94 ± 0.32
Model control	12	5.60 ± 0.33*	6.35 ± 1.33**	-1.54 ± 0.16**	1.64 ± 0.54**
Hypoxia quiet	12	5.15 ± 0.43	5.04 ± 0.15$^{\#}$	-1.38 ± 0.16$^{\#}$	1.12 ± 0.39$^{\#\#}$
Normoxic exercise	12	5.35 ± 0.51	5.03 ± 0.39$^{\#}$	-1.38 ± 0.19$^{\#}$	1.15 ± 0.49$^{\#}$
Hypoxia exercise	12	5.18 ± 0.48	5.30 ± 0.29$^{\#}$	-1.45 ± 0.16$^{*\#}$	1.28 ± 0.28

Notes: Comparison with the control group, $^{*}P < 0.05$, $^{**}P < 0.01$. Comparison with the model control group, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$.

Results

IR rat model

The results showed that the high-fat diet induced significant IR in rats after 6 weeks ($P < 0.01$), which successfully established the IR rat model. The ISIs of rats in normal and high-fat dietary groups did not differ significantly from IR index at week 4. However, a significant or very significant difference was observed by week 6 (Table 1).

Changes of blood glucose and insulin indexes in rats after intermittent hypoxic exercise intervention

After 4-week intervention period of exercise and hypoxia, the blood glucose value of the model control group was much higher than that of the normal control group ($P < 0.05$), and there were no significant differences in comparison to the remaining other three intervention groups. Insulin of the model control group was very significantly higher than that in normal control group ($P < 0.01$) and was also significantly higher than that of the other three intervention groups ($P < 0.05$). The insulin sensitivity index of model control group was very significantly lower than that of the normal control group ($P < 0.01$) and was also significantly lower than that of other three intervention groups ($P < 0.05$). The hypoxia exercise group demonstrated the highest insulin sensitivity index but was still significantly lower than that in normal control group ($P < 0.05$). The IR index of the model control group was very significantly higher than that of the normal control group ($P < 0.01$). A significant decrease in the IR index was observed in the normoxic exercise group compared to that in the model control group ($P < 0.05$), while a very significant difference was observed in the hypoxia quiet group ($P < 0.01$). No significant difference was identified between the intermittent hypoxic exercise group and the model control group, as well as between hypoxia exercise group and normal control groups, although the IR index in hypoxia exercise group was slightly higher than that in the normal control group (Table 2).

Changes of Ang II, NO, and NOS in IR rats by hypoxic exercise

The results showed that the Ang II in the model control group was significantly higher than that in both the normal control group and hypoxia-quiet group ($P < 0.05$). In addition, a slight but non-significant decreases of Ang II were observed in both normoxic and hypoxia-exercise groups compared to the model control group (Table 3). NO was significantly lower in the model control group than the normal control, hypoxic quiet,

Table 3. Angiotensin II (Ang II), nitric oxide (NO), total nitric oxide synthase (T-NOS), and inducible nitric oxide (iNOS) changes in intermittent hypoxic exercise group.

Groups	No.	Ang II (ng/mL)	NO (μmol/L)	T-NOS (U/mL)	iNOS (U/mL)
Normal control	12	0.72 ± 0.17	38.48 ± 8.08	31.39 ± 3.47	11.34 ± 2.17
Model control	12	0.85 ± 0.10*	28.59 ± 8.78*	37.55 ± 4.67*	17.12 ± 2.99*
Hypoxia quiet	12	0.74 ± 0.12$^{\#}$	49.20 ± 6.3$^{*\#}$	26.53 ± 4.44$^{\#\#}$	10.85 ± 2.22$^{\#}$
Normoxic exercise	12	0.79 ± 0.08	38.03 ± 8.52	27.88 ± 3.93$^{\#\#}$	8.59 ± 1.44$^{*\#}$
Hypoxia exercise	12	0.83 ± 0.16	41.86 ± 8.64$^{\#}$	27.97 ± 3.21$^{\#\#}$	6.42 ± 1.16$^{*\#}$

Notes: Comparison with the control group, $^{*}P < 0.05$. Comparison with the model control group, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$.

and intermittent hypoxic exercise groups ($P < 0.05$). In the hypoxic quiet group, NO was significantly higher than those in the normal control and normoxic exercise groups ($P < 0.05$), but no significant difference was observed between the model control and intermittent hypoxic exercise groups. The total nitric oxide synthase (T-NOS) in the model control group was significantly higher than that in the normal control group ($P < 0.05$) and very significantly higher than those in the other three intervention groups ($P < 0.01$). No significant differences were found among the hypoxic quiet, normoxic exercise, and intermittent hypoxic exercise groups. The inducible nitric oxide synthase (iNOS) of the model control group was significantly higher than those of the normal control, hypoxic quiet, normoxic exercise, and intermittent hypoxic exercise groups ($P < 0.05$), while the iNOS in intermittent hypoxic exercise group was significantly lower than those in the other groups ($P < 0.05$).

Discussion

Insulin resistance (IR) refers to a decrease in insulin sensitivity, which is mainly manifested in peripheral tissues such as muscle and fat. The ability of insulin to promote skeletal muscle and adipose tissue to absorb, utilize or store glucose is weakened. IR may arise due to small mutations in genes that are members of multiple insulin signaling networks and several genes regulating energy metabolic processes and interacting with environmental risk factors [10]. Abnormalities in the secretion and action of different active substances in the body such as Ang II and leptin are closely related to IR development. Exercise was found to be able to prevent and attenuate IR and vascular aging by improving the expression of insulin signaling proteins and vasoconstrictor function [11].

Effects of exercise and hypoxia intervention on blood glucose and insulin in IR rats

Exercise reduces IR and is one of the basic principles in the treatment of diabetes mellitus. In the treatment of type 2 diabetes, exercise and diet are the basis and guarantee of all treatments [12]. It was found that exercise therapy mainly improved tissue sensitivity to insulin, enhanced the metabolism of sugar and fat, and improved the ability of the body to maintain hormonal regulation of blood glucose stability, while exercise promoted weight loss and acted as an effective adjunct in the prevention and treatment of all cardiovascular diseases [13]. Hypoxic stimulation also improved the efficiency of insulin action and increased plasma insulin levels [14], which is contributed by many factors. As hypoxia was prolonged, the regulation of pancreatic islets by the endocrine system and gradual improvement of the oxygen supply of pancreatic islet restored insulin secretion function. Meanwhile, after hypoxia exercise, the lack of tissue oxygen supply was no longer the main contradiction due to pulmonary ventilation enhancement, increase of tissue capillary density, *etc*. Then, selective utilization of energy substances is changed and dependence on glucose is decreased, which increases blood glucose level and, therefore, is an important reason for the increase of insulin level. Hypoxia

habituation enhances the expression and storage of glucose transporter while preparing more receptors for insulin stimulation. Insulin-insulin receptor interaction can mobilize glucose transporters in a reserve state (e.g. glucose transporter-4) to translocate to cell membrane, increasing the density of glucose transporters on cell membrane. Xia *et al*. found that both exercise and hypoxia affected the binding capacity of insulin receptors and after hypoxic exercise, the glucose uptake capacity of skeletal muscles was enhanced and the number of mobilizable glucose transporters increased [15]. Also, the increase of the density of insulin receptors and enhancement of insulin sensitivity of tissues were other mechanisms for enhancing reserve capacity. Both enhancements made it easier for tissues to intensify glucose utilization to conserve oxygen, thus facilitating the survival of the body in more hypoxic environments. Exercise improved IR primarily by enhancing the uptake and transport of muscle glucose, while hypoxia improved insulin sensitivity primarily by increasing the number of insulin receptors and therefore, the amount of insulin binding to them. In this research, the results demonstrated that insulin in the IR group was very significantly higher compared to that in the normal control group ($P < 0.01$). The insulin amounts of the hypoxia quiet, hypoxia exercise, and normoxic exercise groups were significantly lower than that of model control group ($P < 0.05$), but slightly higher than the normal control group. Blood glucoses in the hypoxia quiet, hypoxia exercise, and normoxic exercise groups were slightly lower than the model control group, but higher than the normal control group, which indicated that both hypoxia and exercise increased insulin sensitivity and improved the biological efficiency of insulin. However, insulin concentration in the exercise plus hypoxia group was slightly higher than that in the exercise alone or hypoxia quiet groups, which might be due to the superimposed effect of exercise and hypoxia. The stimulation load of exercise plus hypoxia was much higher than that in exercise alone or hypoxia quiet groups, while the glucose requirement was also higher in exercise plus hypoxia group than that in exercise alone or hypoxia quiet groups because of the increase of energy consumption and demand. On the one hand, a large amount of insulin was needed for the stimulation of hepatic glucose catabolism, while more insulin was required to bind to insulin receptors to promote the transport, absorption, and utilization of glucose by the muscle. Therefore, the body needed to consume more energy, which resulted in slightly higher insulin in the intermittent hypoxic exercise group than the normoxic exercise and hypoxic quiet groups.

Effects of exercise and hypoxia intervention on vasoconstrictive function in IR rats

Exercise as a kind of stress generates various compensatory changes in physiological mechanisms in the body. Previous studies showed that plasma Ang II levels increased significantly after exercise, which were associated with the increase of exercise intensity and time. After long-term systematic training, Ang II increased significantly. During exercise, the increase of Ang II could strengthen the vasoconstriction, promote the venous return, exert time-varying force effect on the heart, improve cardiac output, and ensure the redistribution of blood to meet the oxygen demand of the moving organs and tissues. Exercise-promoted increase in Ang II was related to renin-angiotensin system (RAS) activation and exercise intensity [16-18]. Staessen suggested that too high exercise intensity that was above the anaerobic threshold led to blood acidification, and additional Ang II might be formed through new pathways, decreasing degradation, and resulting in a dramatic increase in blood concentrations of Ang II [19]. Tian *et al*. showed that overtraining could decrease local myocardial content and increase plasma content [20]. The possible mechanisms of RAS activation by exercise could be that sweating during high-intensity exercise led to water and sodium loss, which reduced the amount of extracellular fluid and redistributed blood during exercise, reducing renal blood flow, thereby directly stimulating renin secretion. In addition, the increase of sympathetic nerve tone under the effect of

exercise directly stimulated renin secretion by elevating circulating catecholamines that directly stimulated proximal glomerular juxtaglomerular cells to release renin. Further, decrease of hepatic blood flow during exercise reduced the clearance of renin, Ang I, and Ang II, while the stimulation of aldosterone by RAS compensated the loss of sodium due to prolonged exercise and sweating [21].

Low-oxygen stimulation could transform blood vessels into an improvement in energy utilization. The research found that the prevalences of atherosclerosis, coronary heart disease, and hypertension on people living at high altitudes were lower than those living in plains. In addition to less salt intake and stress, the influence of low oxygen environment played a role that could not be ignored. It was generally believed that, due to the adaptability of the body, peripheral small arterial dilatation, capillary proliferation, collateral circulation opening, and vasoconstrictor factor content were reduced, and therefore, the plateau population basal blood pressure and the prevalence of hypertension were decreased [22]. Du *et al*. also found that the high-density lipoprotein cholesterol (HDL-C) was increased with the increase of altitude [23]. Isotope tracing using positron emission tomography also revealed that chronic hypoxic acclimatization increased the dependence of the body on glucose utilization [24]. Although the mechanism of the increase of glucose utilization in plateau hypoxia is not clearly understood, it is known that glucose is the fuel with the highest oxygen utilization efficiency, which reflects the principle of "low consumption and high efficiency" in plateau acclimatization. The results of this research suggested that environmental factors and IR had a variety of effects on the body. Insulin could promote the endothelial cell NOS activity and increased NO production, while NO could activate soluble guanylate cyclase (sGC), causing endothelium-dependent vasodilatation and lowering blood pressure. Insulin could enhance the expression of smooth muscle cell angiotensinogen mRNA and production of angiotensinogen, promoting smooth muscle cell proliferation and migration. Ang II could activate NADH/NADPH oxidase, increase O^{2-} production and, therefore, cause hypertension. The previous study confirmed that injection of lipid-encapsulated superoxide dismutase (SOD) improved the endothelial function of blood vessels, decreasing blood pressure. Endothelial cells produced various vasoactive substances to maintain vascular tone, which depended on vasodilatory substances such as NO and vasoconstrictive substances such as Ang II remaining in balance [25]. Reaction of NO and O^{2-} produced peroxynitrite ($ONOO^-$), which was a reaction 6-fold faster than SOD-catalyzed metabolism of superoxide catabolism, and O^{2-} reduced the half-life of NO, decreasing endothelium-dependent vasodilatation. However, SOD increased the half-life of NO and enhanced endothelium-dependent vasodilatation. Increase of O^{2-} level decreased NO bioactivity, decreasing endothelium-dependent vasodilatory function and blood flow, leading to endothelial dysfunction. Ang II could also decrease NO bioactivity and insulin could exert its biological effects through 2 signaling pathways of PI-3K and MAPK [26].

Insulin has anti-inflammatory and vasodilatory functions, and its trend should be opposite to Ang II under normal conditions. However, insulin can synergize with Ang II under the condition of IR to jointly promote IR. The results of this study showed that the trends of Ang II and insulin were consistent, and that in the model control group was higher than the normal control group, indicating that IR could promote Ang II secretion and vasoconstriction and hinder vasodilatation. Due to higher blood lipids of model groups, in the case of narrowing blood vessels, lipids were more likely to be deposited in blood vessel walls, resulting in atherosclerosis, hypertension, and other diseases. Hypoxic intervention alone could significantly decrease the Ang II level and significantly increase the NO level, indicating that hypoxic intervention could effectively improve vasoconstriction in IR rats. Exercise alone and hypoxia exercise intervention groups had slightly higher Ang II and slightly lower NO, indicating

that exercise also had some effect on them. However, the influences were not significant, which was probably because the intervention time, exercise load and intensity had not been adjusted to the most appropriate conditions. Under hypoxia and exercise intervention, Ang II and NO were higher than those under exercise or hypoxia alone groups, which were close to those in IR group. This result might be because, when rats exercised after being exposed to hypoxia, their blood vessels constricted to overcome the body's lack of oxygen supply, and then they exercised immediately afterwards, causing their blood vessels to constrict further to meet the body's oxygen supply needs. The effects of exercise load and intensity of intermittent hypoxia stimulation were much higher than that of exercise alone or hypoxia stimulation only groups. Its energy requirements increased while the blood vessels constrict.

Conclusion

High-fat chow induced insulin resistance in rats, resulting in hyperlipidemia. The degree of IR in the organism correlated with vascular damage. Both exercise and hypoxia improved insulin sensitivity in rats with high-fat feed-induced insulin resistance. Intermittent hypoxia reduced Ang II secretion and increased NO content in high-fat chow-induced insulin resistance rats, thereby improving vascular tension. Appropriate hypoxic stimulation and aerobic exercise improved the vascular abnormality of insulin resistance rats. Meanwhile, appropriate exercise and hypoxic stimulation did not cause any damage to the healthy body, which was favorable to vascular health. Therefore, appropriate exercise and hypoxic stimulation may become a promising health care and even therapeutic method, and its mechanism of action needs further in-depth study.

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