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Review Article

Effects of Exercise on Myocardial Damage and Heart Failure Due to Hypoxia Induced by Obstructive Sleep Apnea

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SUMMARY

Obesity and intermittent hypoxia (IH) occurring during obstructive sleep apnea (OSA) are two independent risk factors for impaired ventricular function; cardiac dysfunction is exacerbated when the two factors co-occur. Regular exercise provides beneficial effects to attenuate cardiac fibrosis by reducing body fat percentage and preventing adipokine dysregulation. However, the mechanisms by which myokines, muscle-derived factors released during exercise, play a role in the prevention of IH-induced cardiac dysfunction, are still unclear.

This study investigates the effects of myokines on ventricular dysfunction. The important role that myokines play in cardiac function in patients with OSA is discussed in the literature review.

The conclusion of this study is that in obese individuals, excess adipose tissues trigger the dysregulation of adipokines. This dysregulation leads to myocardial inflammation, resulting in left ventricular dysfunction. Physical activity induces an increase in energy expenditure and triggers the release of myokines into the circulation by skeletal muscles, accelerating lipid metabolism, and improving the altered secretion profiles of adipokines. This process helps to alleviate myocardial inflammation and prevents the impairment of ventricular function.

The paper suggests that future studies can investigate the effects of myokines on lipid metabolism, including how to reduce fat deposition and alleviate inflammation efficiently.

In effect, muscle-derived cytokines (myokines) can be considered as anti-inflammatory mediators. This similarity provides support for advocating that regular exercise provides cardioprotective effects against cardiac function impairment in obese patients with OSA.

1. Introduction

Obesity is an important public health problem worldwide and one of the major virulence factors for many chronic diseases such as type 2 diabetes, cardiovascular diseases, and metabolic syndromes.[1] The main causes of obesity are excessive energy intake, lack of exercise, and genetic predisposition, genetic mutations, endocrine disorders, drug use, and mental disorders.[2] Studies have shown that about 60–90% of patients with obstructive sleep apnea (OSA) are obese, and weight gain would worsen the severity of OSA.

Conversely, weight loss can alleviate OSA symptoms.[3] Obesity is characterized by the accumulation of adipose tissue in subcutaneous tissues or peripheral visceral organs. Studies have shown that adipose tissue is an endocrine organ that secretes a variety of cytokines, such as adipokines. Adipokines increase the inflammatory response of the entire body, especially the circulation system. Cytokines secretion within fat tissue may lead to chronic inflammation. However, physical activity and exercise are the best non-pharmaceutical way to treat obese patients. Physical activity and exercise can reduce whole-body inflammation and reconstruct lipid distribution.[4] In addition, studies have shown that three hormones, interleukin-6 (IL-6), myoceptin (CTRP15), and irisin are related to fat metabolism.[5] Interestingly, one of the most important adipokines, leptin, regulates the expression and activity of irisin in skeletal muscle and adipose tissue,[6] confirming the crosstalk between adipokines and myokines. Dysregulation of the expression, function, or both of adipokines and myokines due to a sedentary lifestyle might contribute to the onset of obesity and its associated comorbidities.[7]

Although the impact of exercise training on the apnea-hypopnea index in patients with OSA is not clear, exercise alone can improve subjective daytime sleepiness and reduce certain inflammatory reactions levels in serum and lipid concentrations. Therefore, understanding the effects of obesity on cardiac function in OSA patients and exploring the muscle hormones released by skeletal muscles is worth considering in the role of obesity in patients with OSA.[8]

In order to understand the complex association between obesity, obstructive sleep apnea (OSA), and cardiovascular diseases, it would be notable to point out that the severity of OSA is associated with left ventricular mass independent of other cardiovascular risk factors in patients with morbid obesity.[9] At present, the prevalence rate of OSA among the general public is about 2% to 32.8%, which is regarded as a major health problem in public health.[10] OSA increases the risk of heart failure, stroke, acute coronary syndrome, and coronary heart disease by 140%, 60%, 30%, and 30%, respectively.[7] It is

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considered to be a risk factor for cardiovascular diseases.[11]

OSA is characterized by repeated or partial obstruction of the upper respiratory tract during night sleep, and its apnea and hypopnea persist for at least 10 seconds. The severity of the general diagnosis of OSA is based on the hourly occurrence during sleep. The low ventilatory index of apnea, the higher the index, the higher the severity.[12–14]

2. Discussion

Clinical studies have confirmed that changes in blood oxygen saturation (OS) at night with OSA (hypoxia) and rebound (reoxygenation) are similar to those of chronic IH.[15,16] This phenomenon of IH is an important mechanism leading to an increase in sympathetic nerve activity, endothelial cell dysfunction, systemic inflammation, oxidative stress, and metabolic abnormalities, and eventually progresses into myocardial damage.[17] Although most patients with OSA are obese, some patients with OSA are thin.[18] Studies have shown that both IH and obesity of OSA can cause oxidative damage (through increased activity of lipid peroxidation and superoxide dismutase), activation of an inflammatory response (C-reactive protein), and nuclear factor kappa-B. Nuclear factor kappa-B is a marker for inflammation and sympathetic hyperactivity (increased renal artery catecholamine secretion and synthesis rate); however, when IH coexists with obesity, it aggravates the aforementioned phenomenon deterioration.[19]

Previous studies have pointed out that the heart is repeatedly or temporarily exposed to a hypoxic environment and produces temporary cardioprotective effects, which is an innate defense response of cardiac muscle to adapt to hypoxia; however, prolonged exposure to chronic IH can cause myocardial maladjustment and reduce cardiac function. Therefore, nocturnal OSA with IH is considered the main cause of left ventricular remodeling, including cardiac hypertrophy, myocardial fibrosis, and abnormal cardiac function, which impair myocardial contractility and lead to concurrent heart failure.

In summary, the IH phenomenon combined with OSA causes an additive effect of the inflammatory response, which may aggravate the severity of cardiac dysfunction.[10,20] Lack of activity and obesity has become a worldwide pandemic. It is worth noting that obesity is not only related to cardiovascular diseases caused by abnormal metabolic function, but also has a negative impact on the structure and function of the myocardium, resulting in left ventricular hypertrophy, heart failure, and atrial fibrillation.[21]

Clinical studies have shown that early myocardial structural remodeling, fibrosis, and diastolic dysfunction can be detected in healthy obese individuals. However, myocardial fibrosis and metabolic dysfunction are also closely related to heart failure, ventricular arrhythmia, atrial fibrillation, and sudden death in obese people;[22,23] this may be related to abnormalities in fat metabolism. Obesity increases oxygen intake, increases fatty acid metabolism, and reduces the efficiency of myocardial contraction. When body fat intake is higher than fat oxidation, it will cause accumulation in myocardial tissue, and that accumulated in the myocardium will release lipotoxicity, destroy the oxidative capacity, and increase the reactive oxygen species (ROS) of the heart, thereby increasing abnormal myocardial metabolites, reducing myocardial efficiency, and causing abnormal systolic function.[21] On the other hand, adipose tissue is considered an endocrine organ that secretes a variety of hormones.[4] Some adipokines have only a single source, such as adipsin and acylation-stimulating protein (ASP), which are only produced by adipose tissue. Some adipose hormones have a variety of sources, that can be generated by the liver or macrophages out of fat cells.[24] Excess adipose tissue secretes large amounts of hormones, causing hypercholesterolemia and triglyceridemia, leading to hypertension, vascular dysfunction, and dyslipidemia. Eventually, it leads to atherosclerosis.[25]

Higher serum concentrations of slimmer, tumor necrosis factor-α (TNF-α), PAI-1 (plasminogen activator inhibitor type 1), transforming growth factor-β (TGF-β), and resistin can cause malformation of myocardial remodeling,[26] while TNF-α and IL-6 are important factors in the body's immune system and inflammatory response.[24] Obesity is associated with increased production of proinflammatory adipokines. It is important to point out that overwhelming evidence supports a depot-related expression of adipokines in human visceral and subcutaneous adipose tissue. In this regard, visceral obesity is associated with a higher production of proinflammatory and proatherogenic adipokines that contribute to the onset of metabolic syndrome and its accompanying cardiovascular complications.[27] Importantly, exercise training attenuates the inflammatory response in visceral adipose tissue, as evidenced by a decrease in macrophage recruitment and the production of inflammatory markers in this fat depot.[28] Not all of them are bad; for example, adiponectin is a hormone produced by fat. It has anti-inflammatory effects. It contains a large amount of adiponectin in the plasma of healthy and thin people. Unfortunately, obesity, high blood pressure, and ischemic heart disease reduce the amount of adiponectin. In addition, adiponectin has protective effects against cardiomyocyte hypertrophy, avoiding ischemia-reperfusion injury and avoiding the role of angiotensin II in causing myocardial fibrosis.[29,30]

In the last 10 years, while accepting adipose tissue is an endocrine organ, pioneering research has confirmed that skeletal muscle is also an active endocrine organ. The secreted muscle hormone is considered to be the benefit of exercise to the body.[31] Although skeletal muscle role in controlling blood sugar and lipid metabolism has been established, skeletal muscle is regarded as an endocrine organ, secreting polyp-like cytokines (myokines), which are involved in the regulation of non-muscle tissue, inflammation, and other physiological metabolisms. Recently, myokines have noticeably improved that health problem.[32] There is much evidence that skeletal muscle can secrete many biologically active proteins to the extracellular fluids. These proteins are affected by exercise and are regulated through autocrine and paracrine pathways, such as metabolic and anti-inflammatory pathways, that impact other organs.[33] Obesity and lack of exercise are high-risk factors for metabolic syndrome and type 2 diabetes, causing mild inflammation of the body. It has been found that in obesity, fat tissue alters endocrine function, resulting in increased release of pro-inflammatory hormones such as TNF-α, chemerin, monocyte chemoattractant protein-1, and dipeptidyl peptidase-4.[31]

Among all the myokines, IL-6, irisin, and myoglobin can affect lipid metabolism. IL-6 is an early explored cytokine. It has been shown that skeletal muscle cells secrete IL-6 during exercise to improve systemic insulin sensitivity and protects against inflammation.[32] IL-6 is also considered as an indicator of inflammation, which is often confused with the anti-inflammatory role of IL-6 secreted by muscle. The main difference is that when IL-6 is regarded as an indicator of inflammation, IL-6 maintains a high concentration in the blood for a long time. When muscle contraction during exercise causes a large increase in IL-6 in a short period of time (hours), it returns to its normal level, at the same time IL-6 is considered as anti-inflammatory role.[34]

For example, *in vivo* (a mouse study), exercise caused an increase in IL-6 levels, which increased the expression of follistatin-like 1 (Fstl-1) and protected cardiac vascular endothelial cells from the

ischemic environment.[35] Vascular remodeling in high fat-diet induced obesity in mice. After they lost weight, serum Fstl-1 concentration was also elevated, which helped to reduce the amount of lipid in mouse skeletal muscle.[27] These results show that myokines play an important role in the interaction between tissues and integrated physiology. In addition, the main role of irisin is to turn white fat into brown fat and to generate calories and reduce insulin resistance. Irisin may be a useful anti-obesity and anti-diabetic factor.[36] In addition, exercise causes an increase in intracellular calcium consumption, which increases the skeletal muscle production of myokines.[32] It is confirmed that in cell and animal models, adenine is an important muscle hormone in metabolism. It is mainly produced and released from skeletal muscle and regulates the interaction between skeletal muscle and other organs such as the liver and regulates the metabolic functions of the entire body.[32]

However, the role of muscle hormones in obesity and IH on cardiac dysfunction is still not well understood. Studies have shown that patients with OSA often experience perceived fatigue, which is associated with low physical activity.[37] The cause may be that OSA causes abnormal skeletal muscle metabolism, impairs skeletal muscle glycolytic capacity, and affects aerobic capacity.[38]

Results of decreased exercise capacity: studies have shown that after exercise testing, the maximal oxygen uptake in patients with OSA was significantly lower than that in the control group and negatively correlated with the hypopnea index.[37,39]

Although hypoxic stimulation of IH causes more accommodative micro vascularization in the skeletal muscle of patients with OSA (this phenomenon seems to be beneficial to aerobic metabolism of skeletal muscle), the fitness of patients with OSA is still lower than that of the healthy control group.[37] It is speculated that the decrease in exercise capacity caused by OSA is mainly due to the impaired mitochondrial glycolytic and oxidative metabolism of skeletal muscle cells, resulting in a decrease in the maximum concentration of lactic acid in the blood during maximum exercise and delay in the clearance of lactic acid after exercise.[39] Another major cause of impaired OSA exercise capacity is cardiovascular dysfunction. Studies have shown that patients with OSA underwent a maximum exercise capacity test with a slow-changing heart rate showed a significant delay in systolic blood pressure response during the early recovery phase, an increase diastolic blood pressure, early recovery, and abnormal cardiovascular responses during exercise and post-exercise recovery, including decreased cardiac output per bit, reduced exercise capacity, and heart rate during recovery.[39,40] In addition to the comprehensive ventricular dysfunction, the ability to regulate the heart rate is reduced.[39] On the other hand, studies of normal-weight and obese children with OSA aged 7 to 12-year-old indicate that OSA is an independent factor that causes a decline in children's athletic ability without a relationship to body weight, leading to cardiovascular dysfunction. In maximum exercise, children with OSA have a lower heart rate, lower output per bit, lower heart volume, and lower VO_2 peak than those of the healthy population. However, obesity and OSA have a multiplier effect on reducing exercise capacity, which is more affected than OSA alone or obesity.[27] Clinical studies have shown that patients with OSA suffer from oxidative damage due to IH, leading to abnormalities in heart function and ventilation as well as affecting muscle energy metabolism and impairing exercise capacity.[39] Disorders that reduce sleep (stopping breathing times) can aggravate the effects.[40] In an eight-year follow-up survey, long-term regular exercise can prevent OSA. Regarding the impact of short-term exercise on OSA, it takes a minimum of 3–4 months to improve sleep disorder breathing.[41] The survey results of 4,275 subjects showed that at least 200 minutes of physical activity per week by which the muscle strength of the skeletal and respiratory muscles of patients with OSA can be increased, and exercise capacity and cardiopulmonary function could be improved.[42] In addition, increasing the amount of exercise helps the secretion of myokines. For example, the concentration of irisin in the blood is increased after exercise.[43] However, in the absence of exercise effects, irisin in the blood is related to body composition. A patient with anorexia nervosa, whose body mass index (BMI) is only 12.6 kg/m^2, has a low level of irisin in the blood, that is, 14% lower than that of normal-weight people, obese people (BMI 30–40 kg/m^2) whose blood is similar to normal-weight people, and severe obesity (BMI 40–50 kg/m^2–BMI > 50 kg/m^2) people whose blood concentration of irisin is significantly higher than that of anorexia patients, probably because it improves the glucose tolerance of obesity.[44]

3. Result

In terms of the effect of regular exercise on irisin, the physical activity of healthy people is divided into three levels: high, medium, and low. High-activity people have significantly higher levels of irisin in their blood than those with low activity. This result indicates that the amount of physical activity is positively correlated with the concentration of irisin.[45] In addition, irisin can promote oxygen intake, and energy supply is considered to beused as a strategy for the treatment of obesity and diabetes.[46] Therefore, it is speculated that increasing the amount of exercise in patients with OSA may increase muscle strength, improve exercise capacity, and promote skeletal muscle release of more irisin to the circulation.[5] Improve fat metabolism and the release of adipokines, which reduces the secretion of pro-inflammatory hormones,[4] avoiding cardiac dysfunction.[10,20] This mechanism is subject to further research in the future. Obesity is an important public health problem worldwide and a major cause of many chronic diseases, such as type 2 diabetes and cardiovascular diseases.

There is evidence that obesity is a key mediator of myocardial fibers, and obesity can effectively reduce the imbalance of adipokines secretion, leading to coronary artery diseases and heart failure. Studies have shown that IH and obesity, similar to OSA, cause oxidative damage, increased inflammatory response, and sympathetic hyperactivity. IH, combined with obesity, will aggravate the aforementioned phenomenon.[19] How to effectively transfer the body's white adipose to brown adipose is important.[47]

4. Conclusion

The commonality of these methods is to increase the training intensity of the muscles to achieve effective consumption of body fat, thereby reducing body weight. Based on the above, the conclusion of this study is that lack of exercise, and excessive diet can cause obesity. Due to the accumulation of excessive adipose tissue in individuals, the secretion of adipokines is imbalanced, increasing inflammation and myocardial fibrosis and finally causing ventricular dysfunction. For decreasing calories consumption and reducing fat tissue, exercise may also promote muscle secretion of myokines, increase adipose metabolism, reduce inflammation and prevent damage to heart function. Therefore, it is recommended that future research can better understand the effects of muscle hormones released from skeletal muscle on the function of adipose metabolism, including how to effectively reduce the accumulation of fat, reduce the inflammatory response, and myokines secreted by skeletal muscle during exercise. It is considered an inflammatory inhibitor; therefore, regular exercise is recommended to improve the health of

patients with OSA and to reduce cardiac function damage in obese patients and patients with OSA.[48]

Declaration

Declaration of any potential financial and non-financial conflicts of interest: none.

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