THORACIC AORTIC REACTIVITY IN OBESE PATIENTS SUBMITTED TO AEROBIC EXERCISE

REATIVIDADE DA AORTA TORÁCICA EM PACIENTES OBESOS SUBMETIDOS AO EXERCÍCIO AERÓBICO

REACTIVIDAD DE LA AORTA TORÁCICA EN PACIENTES OBESOS SOMETIDOS A EJERCICIO AERÓBICO

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ABSTRACT

Introduction: Aerobic exercise can improve the function of the cardiovascular circulatory system, reducing morbidity and mortality from cardiovascular disease by stimulating the production of endogenous self-protection. Activating potassium channels in vascular smooth muscle cells can cause vasodilation and increase blood flow, lowering blood pressure. There is a sensitivity to intracellular ATP and ADP concentration among the variety of potassium channels distributed in vascular smooth muscle cells, which vary mainly during aerobic physical activity. Objective: Explore the effect of aerobic exercise on the vascular reactivity of the thoracic aorta in patients with obesity and hyperlipidemia. Methods: Randomized controlled trial in twenty male Wistar rats weighing 250g and two months old. The control group remained at rest while the experimental group performed aerobic exercise on a treadmill at increasing speed for eight weeks. The rats were dissected, and dilatators and vasoconstrictors drugs stimulated their blood vessels in a tamponade solution. Observation of vascular changes was measured under controlled tensioning. Results: The blockade of KATP channels in vascular smooth muscle caused tonic contraction of vascular smooth muscle cells and increased blood pressure. Conclusion: Long-term regular aerobic exercise may induce changes in rats' thoracic aortic vascular function and vascular smooth muscle reactivity. Aerobic exercise can also significantly improve the activity of KATP channels. ***Evidence Level II; Therapeutic Studies – Investigating the results.***

Keywords: KATP Channels; Aerobic Exercise; Vasodilation; Obesity.

RESUMO

Introdução: O exercício aeróbico pode melhorar a função do sistema circulatório cardiovascular, reduzindo a morbidade e mortalidade de doenças cardiovasculares estimulando a produção de autoproteções endógenas. A ativação de canais de potássio nas células musculares lisas vasculares pode causar vasodilatação e aumentar o fluxo sanguíneo, diminuindo a pressão sanguínea. Há uma sensível a concentração de ATP intracelular e ADP dentre a variedade de canais de potássio distribuídos em células musculares lisas vasculares, que variam principalmente durante a atividade física aeróbica. Objetivo: Explorar o efeito do exercício aeróbico na reatividade vascular da aorta torácica em pacientes com obesidade e hiperlipidemia. Métodos: Estudo randomizado controlado em vinte ratos Wistar machos de 250g e 2 meses de idade. O grupo controle permaneceu sob repouso enquanto o experimental realizava exercícios aeróbicos em esteira com velocidade crescente durante 8 semanas. Os ratos foram dissecados e seus vasos sanguíneos estimulados com drogas vasoconstritoras e dilatadoras em solução tampão. A observação das alterações vasculares foi mensurada sob tensionamento controlado. Resultados: O bloqueio dos canais KATP no músculo liso vascular causou contração tônica das células musculares lisas vasculares e aumento da pressão arterial. Conclusão: Exercícios aeróbicos regulares de longo prazo podem induzir alterações na função vascular da aorta torácica e reatividade do músculo liso vascular em ratos. O exercício aeróbico também pode melhorar significativamente a atividade dos canais KATP. ***Nível de evidência II; Estudos terapêuticos - investigação dos resultados do tratamento.***

Descritores: *Canais KATP; Exercício Aeróbico; Vasodilatação; Obesidade.*

RESUMEN

Introducción: El ejercicio aeróbico puede mejorar la función del sistema circulatorio cardiovascular, reduciendo la morbilidad y la mortalidad de las enfermedades cardiovasculares al estimular la producción de autoprotección endógena. La activación de los canales de potasio en las células del músculo liso vascular puede causar vasodilatación y aumentar el flujo sanguíneo, reduciendo la presión arterial. Existe una sensibilidad a la concentración intracelular de ATP y ADP entre la variedad de canales de potasio distribuidos en las células del músculo liso vascular, que varían principalmente durante la actividad física aeróbica. Objetivo: Explorar el efecto del ejercicio aeróbico sobre la reactividad vascular de la aorta torácica en pacientes con obesidad e hiperlipidemia. Métodos: Ensayo controlado aleatorio en veinte ratas Wistar macho de 250 g y 2 meses de edad. El grupo de control permaneció en reposo mientras que el grupo experimental realizó ejercicios aeróbicos en una cinta de correr a velocidad creciente durante 8 semanas. Las ratas fueron disecadas y sus vasos sanguíneos fueron estimulados con fármacos vasoconstrictores y dilatadores en solución amortiguada. La observación de los cambios vasculares se midió bajo tensión controlada. Resultados: El bloqueo de los canales KATP en el músculo liso vascular provocó una contracción tónica de las células del músculo

liso vascular y un aumento de la presión arterial. Conclusión: El ejercicio aeróbico regular a largo plazo puede inducir cambios en la función vascular de la aorta torácica y en la reactividad del músculo liso vascular en ratas. El ejercicio aeróbico también puede mejorar significativamente la actividad del canal KATP. ***Nivel de evidencia II; Estudios terapéuticos - Investigación de resultados.***

Descriptores: *Canales KATP; Ejercicio Aeróbico; Vasodilatación; Obesidad.*

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INTRODUCTION

The life pressure of modern people is increasing, and cardiovascular diseases such as high blood pressure are gradually becoming younger. This poses a serious threat to human life and health. Many studies have shown that the effect of strengthening physical exercise on the prevention and treatment of cardiovascular diseases cannot be ignored.[1] Exercise can reduce the morbidity and mortality of cardiovascular diseases by improving the function of the cardiovascular circulatory system. This effect of exercise is achieved by inducing the body to produce endogenous self-protection, and vascular smooth muscle cell potassium channels play a vital role in it. A variety of potassium channels are distributed on vascular smooth muscle cells (VSMC). ATP-sensitive potassium channel (K_{ATP}) is one of the four types of potassium channels that exist on VSMC. The intracellular ATP concentration mainly regulates them. Hence the name ATP-sensitive potassium channel.[2] The gating kinetics of the K_{ATP} channel is ATP and voltage-dependent. The main factors that determine whether the channel is open or not are the concentration of intracellular ATP and ADP. This study started with the K_{ATP} channel of arterial smooth muscle cells through the in vivo blood pressure monitoring method combined with the experiment of removing the endothelial thoracic aortic vascular ring in vitro. To explore the possible smooth muscle K_{ATP} channel mechanism of aerobic exercise in improving the responsiveness of thoracic aortic smooth muscle.

METHOD

Experimental animals and grouping

Twenty male Wistar rats weighing 250 g at the age of 2 months. The rats were randomly divided into 2 groups, a quiet control group and an anaerobic exercise group, with 10 rats in each group.[3] Eat and drink freely. We are fed with national standard rodent conventional feed.

Exercise plan

The aerobic exercise group performed treadmill exercise with increasing speed for 8 weeks. We follow the adaptive training for 1 week and then exercise at 5d/week. The total time is 9 weeks. The initial speed is 15m/min, and the time is 20min. The increasing speed is 3m/min every 5min. Until 20m/min, the total time is 60min.

Preparation of experimental reagents and solutions

NE, glibenclamide, and pinacidil were all purchased from Sigma. Heparin sodium was purchased from Beijing Dongsheng Taibo Technology Co., Ltd.; penicillin was purchased from Shandong Quanlin Animal Pharmaceutical Company. ACh was purchased from Beijing Chemical Reagent Company.

Determination of the cardiovascular responsiveness of rats in vivo

We performed femoral arteriovenous cannulation in rats. The rats were awake 24h after the operation. After the physiological state returns to normal, we connect the intubation tube with the instrument catheter.[4] After a stable basal blood pressure can be recorded, the KATP channel-specific blocker glibenclamide (20mg/kg) is injected, and the blood pressure is recorded.

Determination of the vascular reactivity of the isolated thoracic aorta in rats

After the rat was anesthetized, the thoracic cavity was opened, the thoracic aorta was removed, and the connective tissue and endothelium around the aorta were removed. We made it into a blood vessel ring of about 4cm. We used two stainless steel wires to pass through the blood vessel horizontally and suspended them in 5 mL of Na-HEPES buffer at 37°C without the blood vessel being stretched. The lower-end steel wire is fixed, and the upper-end steel wire is connected with the tension transducer through the iron wire. Rest load 1g and balance for 1h. We use 10^{-5}M norepinephrine (NE) to induce vasoconstriction and add 10^{-3}M ACh to relax the blood vessels.[5] If it does not exceed 10%, it is considered that the integrity of the vascular endothelium has been destroyed. Afterward, KATP channel blocker glibenclamide was added to record changes in tension caused by vasoconstriction. Flush blood vessels three times. After the vascular tension is restored, the blood vessels are contracted with 10^{-5}M NE, and then the KATP channel-specific opener pinacidil (10^{-9}-3×10^{-5}M) is added. We record the vasodilation caused by it.

Modeling and Simulation of Coronary Circulation of Heart

This article uses state variable analysis to analyze and establish a mathematical model of the left heart circulatory system. We use the state variable analysis method to analyze the dynamic circuit mainly in three steps: select the state variable, list the state equation, solve the state equation according to the initial conditions.[6] The article uses the MATLAB/Simulink tool to solve the state equation and simulate the model. According to the dynamic characteristics of system circulation and coronary circulation, we select the following 5 state variables:

V_{1v} represents the blood volume of the left ventricle. q_{ao} represents aortic blood flow. P_{aa} represents the pressure across the blood volume C_{aa} of the ascending aorta. V_{da} represents the blood volume of the descending aorta. P_{pc} represents the blood pressure across the peripheral blood vessel C_{pc} at both ends of the blood volume. List the following equation of state to represent

$$\dot{V}_{1v} = \frac{P_{1a} - e_{1v}V_{1v}}{\frac{1}{g_{mv}}} - \frac{e_{1v}V_{1v} - P_{aa}R_{aa}C_{aa}\dot{P}_{aa}}{R_{1v} + \frac{1}{g_{av}}} \quad (1)$$

$$\dot{P}_{aa} = \frac{\frac{g_{av}}{g_{av} + R_{1v}}(e_{1v}V_{1v} - P_{aa}) - q_{ao} - q_{co}}{C_{aa} + C_{aa}R_{aa}\frac{1}{g_{av} + R_{1v}}} \quad (2)$$

$$\dot{q}_{ao} = \frac{P_{aa} + R_{aa}C_{aa}\dot{P}_{aa} - (e_{da}V_{da} + R_{da}\dot{V}_{da}) - R_{ao}q_{ao}}{L_{ao}} \quad (3)$$

$$\dot{V}_{da} = \frac{q_{ao} - (R_{bp} + \frac{1}{R_{ca}})e_{da}V_{da} + R_{ba}(P_{pc} + R_{pc}C_{pc}\dot{P}_{pc})}{1 + R_{da}(R_{bp} + \frac{1}{R_{ca}})} \quad (4)$$

$$\dot{P}_{pc} = \frac{\dot{V}_{da}R_{da} + e_{da}V_{da} - \frac{P_{pc}}{R_{pr}R_{bp}} - P_{pc}}{\frac{C_{pc}}{R_{bp}} + \frac{R_{pc}C_{pc}}{R_{bp}R_{pr}} + R_{pc}C_{pc}} \quad (5)$$

The coronary blood flow q_{co} in the equation of state is determined by the following two equations:

$$\begin{aligned} q_{co} &= q_{ep} + q_{en} \\ P_{aa} + R_{aa}C_{aa}\dot{P}_{aa} - P_{dc} &= Rq_{co} + Sq_{co}^2 \end{aligned} \quad (6)$$

Due to the backpressure effect of endocardial pressure P_{en} and epicardial pressure P_{ep} on myocardial blood flow, therefore:

When $P_{de} > P_{en}$, then $q_{en} = \frac{P_{dc} - P_{en}}{R_{en}}$, otherwise $q_{en} = 0$.

When $P_{dc} > P_{ep}$, then $q_{ep} = \frac{P_{dc} - P_{ep}}{R_{ep}}$, otherwise $q_{ep} = 0$.

Statistical processing

Statistical data are expressed as mean ± standard deviation. Use SPSS13.0 statistical software, SigmaPlot10.0 for statistical data analysis. One-way analysis of variance and independent-sample t-test were used. When the significance level is P<0.05, the results are statistically significant.

RESULTS

Changes in cardiovascular responsiveness after intravenous injection of KATP channel-specific blocker glibenclamide

The blood pressure of rats increased significantly after intravenous injection of glibenclamide (20mg/kg). (Figure 1) The increase in the exercise group was significantly greater than that in the quiet group, and the difference was statistically significant. The heart rate of the exercise group decreased significantly, with a decrease rate of (16.75±2.14) times/min (P<0.05). Figures 1, A, and B respectively represent the measured graphs of the increase in blood pressure of rats in the quiet group and exercise group after injection of glibenclamide. C represents the blood pressure statistics of rats in the quiet group and exercise group after injection of glibenclamide. D represents the heart rate changes of rats in the quiet group and exercise group after glibenclamide injection.

Vasoconstriction response caused by KATP channel blocker glibenclamide

Experiments have found that the KATP channel blocker glibenclamide can block the KATP channel on the rat aortic vascular smooth muscle cells.[7] It is statistically significant (P<0.05). (Figure 2) Figures 2, A, and B represent the measured graphs of vascular tension induced by glibenclamide in the quiet and exercise groups, respectively.

KATP channel-specific opener pinacidil induced vasodilation response

Pinacidil (10^{-9}-3×10^{-5}M) can induce vasodilation in a concentration--dependent manner after NE (10^{-5}M) induces vasoconstriction to the maximum. (Figure 3) There was a very significant difference between the exercise group and the quiet group under pinacidil (10^{-9}M) (P<0.01). (Table 1) Figures 3, A, and B represent the measured graphs of vascular tension induced by pinacidil in the quiet and exercise groups. Tension

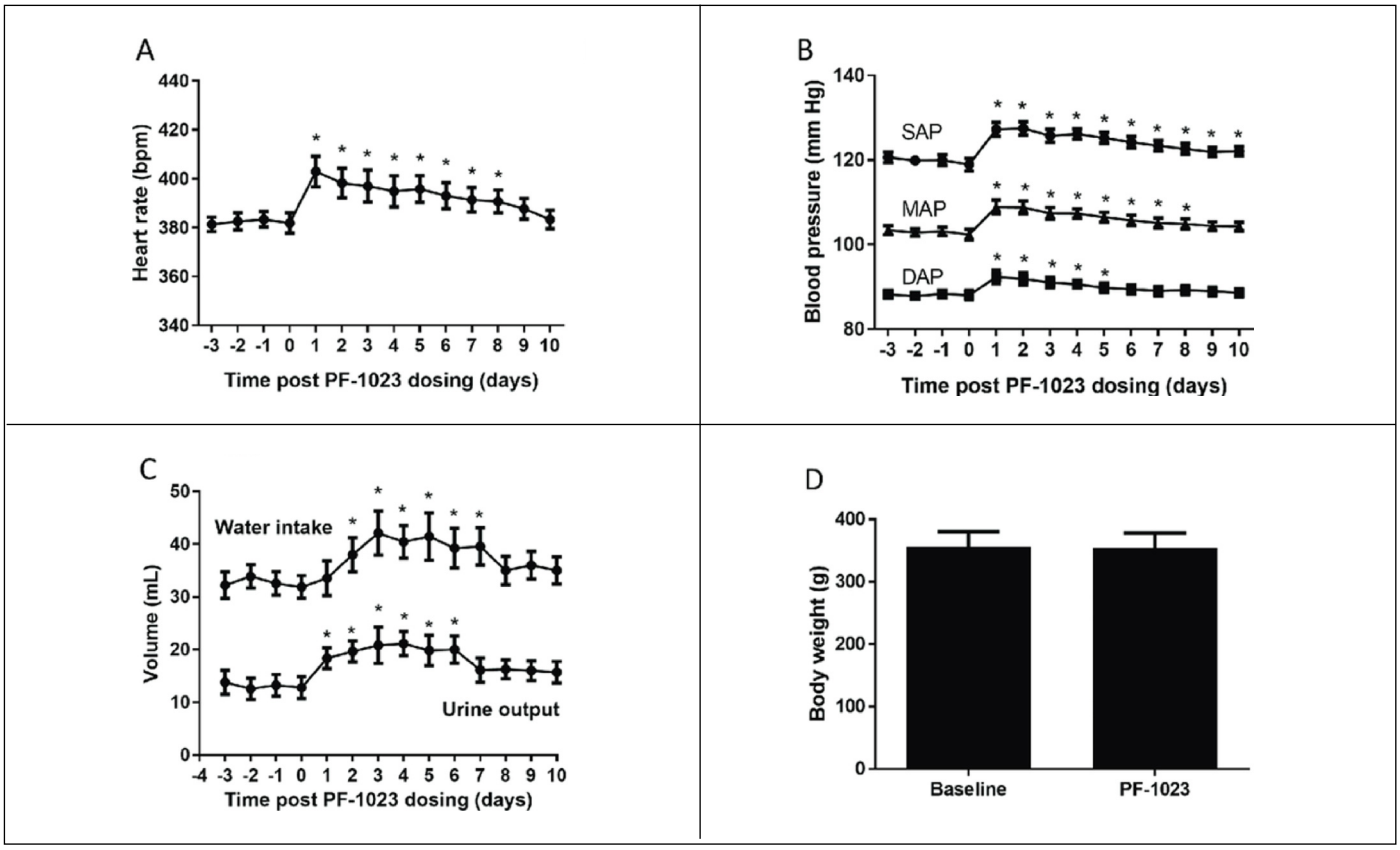

Figure 1. Blood pressure and heart rate changes in rats after glibenclamide injection.

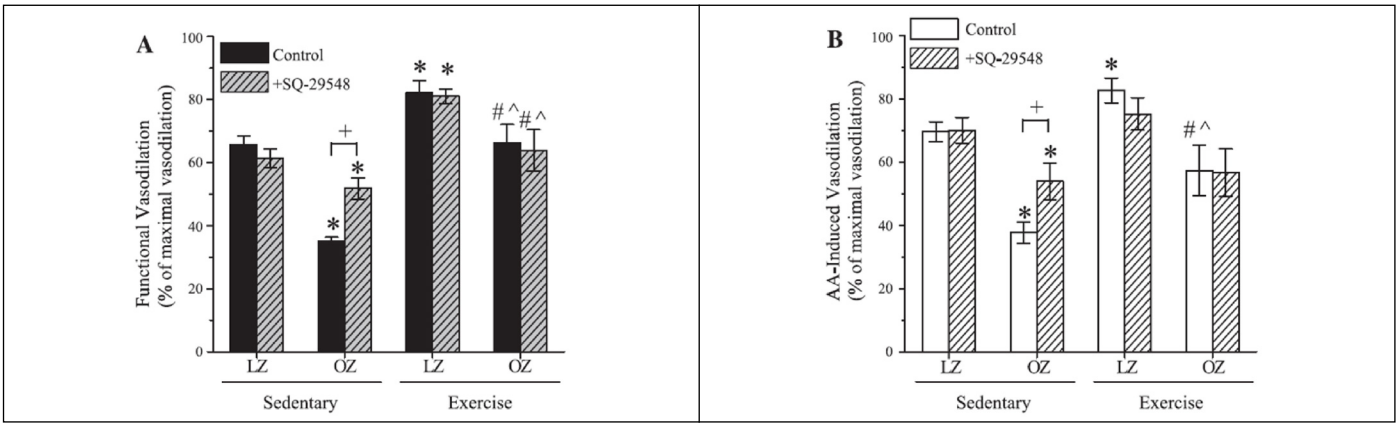

Figure 2. The effect of aerobic exercise on the vascular reactivity induced by glibenclamide.

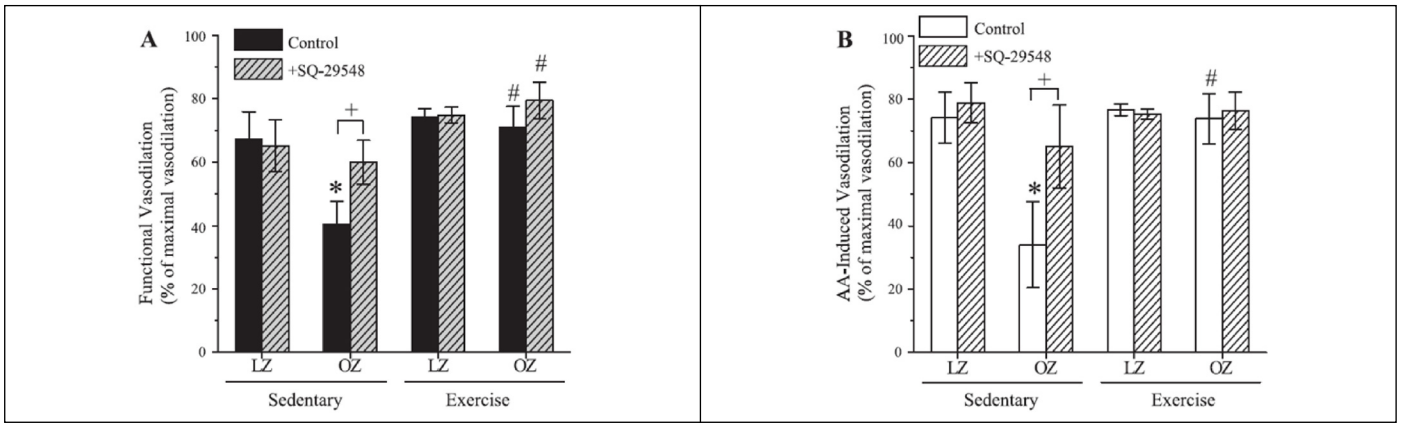

Figure 3. Dose-response curve of pinacidil induced vasodilation.

Table 1. Aerobic exercise on pinacidil (10^{-9}M) inhibits the vasoconstriction caused by NE.

	Quiet group	Sports group
Pinacidil + NE (%Kmax)	44.23±2.67	11.64±2.17
Inhibition of NE (%NEmax)	33.56±3.48	57.93±3.65

(%NEmax) represents the inhibition rate of the tension contraction caused by pinacidil when 10^{-5}MNE is used as the maximum contraction response (100%).

DISCUSSION

This study used awake, in-vivo ambulatory blood pressure monitoring methods combined with ex vivo endothelial thoracic aortic vascular loop experiments. We recorded the changes in blood pressure and the tension of the thoracic aortic vascular ring in rats by adding KATP channel blockers and openers. This can explore the role of the enhancement of KATP channel activity in aerobic exercise to improve the responsiveness of thoracic aortic vascular smooth muscle.

In vivo experiments found that the blood pressure of the two groups of rats increased significantly after intravenous glibenclamide injection, and the exercise group's increase was significantly greater than that of the quiet group. This preliminarily shows that KATP channels play a certain role in maintaining the membrane tension of vascular smooth muscle cells. After injection of the blocking agent glibenclamide, the KATP channel on the vascular smooth muscle was blocked, which caused the vascular smooth muscle cells to undergo tonic contraction. This will cause blood pressure to rise.[8] In our analysis, there may be two main reasons for this result.

On the one hand, the hallmark of the KATP channel is that its activity can be inhibited by ATP, which is regulated by the intracellular ATP and ADP concentration ratio. Exercise can lead to a decrease in ATP content in the body and an increase in ADP to activate KATP channels. Long-term aerobic exercise causes the KATP channel to adapt to this change, which leads to increased KATP channel activity.

On the other hand, exercise is a typical source of stress. It has a significant effect on cAMP concentration and induces an increase in cAMP concentration. As a second messenger, cAMP can activate PKA, and PKA can directly phosphorylate the three functional residues of the KATP channel to increase the opening probability of the channel.

In the heart rate record, it was found that the heart rate of the exercise group showed a downward trend after glibenclamide injection. This phenomenon was not found in the quiet group. This shows that exercise as a kind of stress causes a series of adaptive changes in rats. This significantly enhances the cardiovascular regulation mechanism of rats and improves the activity of autonomic nervous function. This can help strengthen the protective effect of external stimuli.

To further prove the influence of exercise on the activity of KATP channels, we experimented with isolated vascular rings. Adding the blocking agent glibenclamide in the experiment of the isolated vascular rings can cause the contraction reaction of the two groups of blood vessels. The change in tension of the exercise group was significantly greater than that of the quiet group. This further shows that KATP channels play an important role in regulating vascular tone. The greater the activity of potassium ion channels. The stronger the blocking effect of the potassium channel blocker at the same concentration, the stronger the vasoconstriction effect caused by it. In addition, we added the KATP channel-specific opener pinacidil to the maximum vasoconstriction. It can induce vasodilation in a concentration-dependent manner. This shows that under the same concentration of pinacidil, the open rate of KATP channels in the exercise group is significantly greater than that in the quiet group. It is also proved that exercise can enhance the activity of KATP channels.

CONCLUSION

Long-term regular aerobic exercise can induce changes in the vascular function of the thoracic aorta in rats. In addition to the improvement of endothelial function, the reactivity of vascular smooth muscle also changes. Mainly manifested as the enhancement of diastolic function. The enhancement of KATP channel activity may be one of the important mechanisms.

All authors declare no potential conflict of interest related to this article

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. Xi Peng and Yinuo Zhao: writing and performing surgeries; Qiang Gao: data analysis and performing surgeries; Wei Sun: article review and intellectual concept of the article.

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