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Research article

Evaluation of cardiac index and right ventricular hypertrophy index in rats under a chronic hypoxic environment at high altitude

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ABSTRACT

High-altitude areas are characterized by low pressure and hypoxia, which have a significant impact on various body systems. This study aimed to investigate the alterations in cardiac index and right ventricular hypertrophy index(RVHI) in rats at different altitudes.Twenty-one male Sprague-Dawley (SD) rats aged 4 weeks were randomly divided into three groups based on altitude. The rats were raised for 28 weeks and then transferred to Qinghai University Plateau Medicine Laboratory. Body weight was measured, heart organs were isolated and weighed, and cardiac index and right ventricular hypertrophy index were determined. Statistical analysis was performed on the data from the three groups. Compared with the plain group, the body weight of the middle-altitude group was significantly decreased ($P < 0.05$), and cardiac index, RVHI-1, RVHI-2 increased significantly (($P < 0.05$). The body weight, whole heart mass, right ventricular mass were significantly decreased in high-altitude group ($P < 0.05$), RVHI-1 and RVHI-2 were significantly increased ($P < 0.05$). Compared with the middle-altitude group, the body weight, whole heart mass and right ventricular mass of the high-altitude group were significantly decreased ($P < 0.05$), and RVHI-1 and RVHI-2 were significantly increased ($P < 0.05$). Increasing altitude led to a decrease in body weight, whole heart mass, and right ventricular mass in rats, indicating structural changes in the right heart. Additionally, the proportion of right heart to body weight and whole heart increased with altitude.

1. Introduction

The plateau area is characterized by low pressure and hypoxia, which can have a significant impact on various systems of the human body [1,2]. Of particular concern is the cardiovascular system, which is highly sensitive to hypoxia and can lead to abnormal cardiac structure and function, ultimately resulting in acute and chronic altitude sickness, as well as high-altitude heart disease [3,4]. However, the precise pathogenesis of these conditions remains unclear [5,6]. Furthermore, previous animal studies on altitude

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sickness have mostly relied on simulated environments such as low-pressure and hypoxic chambers, which may not accurately reflect the physiological and pathological changes experienced by subjects in a real high-altitude environment [7,8]. Thus, to address this research gap, our study aimed to assess the effects of the natural plateau environment on body weight, cardiac index, and right ventricular hypertrophy index(RVHI) in rats.

2. Materials and methods

Male SPF Sprague-Dawley (SD) rats (n = 21, 4 weeks old) were obtained from Chengdu Dashuo Laboratory Animal Company, The production license number was SCXK (Chuan) 2020-030, and the use license number was SYXK (Chuan) 2018-119. This study was approved by the Medical Ethics Committee of Qinghai Provincial People's Hospital. The animals were handled in accordance with the "Guiding Opinions on Treating Laboratory Animals Kindly" issued by the Ministry of Science and Technology in 2006.

2.1. Grouping of experimental animals

Referring to the altitude classification criteria outlined in the book "Altitude Medicine" edited by Ge Rili [9], the SD rats were randomly divided into three groups. One group was transported to the Chengdu area (approximately 450 m above sea level, Oxygen content 20.15 %, 7 rats), designated as the plain group. Another group was transported to the Xining area (approximately 2200 m above sea level, Oxygen content 17.30 %, 7 rats), designated as the middle-altitude group. The remaining group was transported to the Maduo area (approximately 4300 m above sea level, Oxygen content 12.10 %, 7 rats), designated as the high-altitude group. The experimental animals were housed in separate animal facilities located in both plateau and plain areas. The temperature of the animal housing room was maintained at 18–25 °C, with a humidity range of 40–60 %. The rats were provided with an ample supply of feed on a daily basis. All three groups of SD rats were raised until they reached 28 weeks of age.

Measurement of cardiac index and left and right cardiac hypertrophy index.

The rats were transferred to the Highland Medical Laboratory at Qinghai University for measurements. Prior to measurement, the rats were weighed and then euthanized by intravenous injection of pentobarbital sodium. Dissecting and isolating the heart. The mass of the heart was recorded, and the cardiac index (=whole heart mass/body weight × 100 %) was calculated. Additionally, the right ventricular hypertrophy index-1(RVHI-1) = right ventricular mass/body weight × 100 % and right ventricular hypertrophy index-2 (RVHI-2) = right ventricular mass/whole heart mass × 100 % were determined.

2.2. Statistical analysis

Data analysis was conducted using SPSS 26.0 statistical software. Measurement data were presented as mean ± standard deviation ($\overline{x}$ ±s). Independent samples *t*-test was employed to determine statistical significance, with a threshold of $P \leq 0.05$.

3. Result

1. Compared to the plain group, the middle-altitude group exhibited a significant decrease in body weight ($P < 0.05$). Although there was no statistically significant difference in whole heart mass ($P > 0.05$), it showed a decreasing trend. The right ventricular mass also increased, although not significantly. Notably, there was a significant increase in cardiac index, RVHI-1, and RVHI-2 ($P < 0.05$). In the high-altitude group, body weight, whole heart mass, and right ventricular mass were significantly decreased ($P < 0.05$), while the cardiac index increased, albeit without statistical significance ($P > 0.05$). Similar to the middle-altitude group, the high-altitude group exhibited a significant increase in RVHI-1 and RVHI-2 ($P < 0.05$).
2. When comparing the high-altitude group with the middle-altitude group, significant decreases were observed in body weight, whole heart mass, and right ventricular mass ($P < 0.05$). The cardiac index decreased as well, but the difference was not statistically significant ($P > 0.05$). However, similar to the previous comparison, there was a significant increase in RVHI-1 and RVHI-2 ($P < 0.05$). Table 1 presents the body weight, cardiac index, right cardiac hypertrophy index-1, and right cardiac hypertrophy index-2 of the plain group, middle-altitude group, and high-altitude group.

Table 1
The body weight, cardiac index and right ventricular hypertrophy index in plain group, middle-altitude group and high-altitude group.

index	Plain group (n = 7)	Middle-altitude group (n = 7)	High-altitude group (n = 7)
Body weight (g)	650.00 ± 59.72	536.86 ± 21.68$^{\Delta}$	371.57 ± 34.80$^{\Delta ¥}$
Whole heart mass (g)	1.53 ± 0.16	1.47 ± 0.14	0.97 ± 0.09$^{\Delta ¥}$
Cardiac index (%)	0.24 ± 0.02	0.27 ± 0.03$^{\Delta}$	0.26 ± 0.04
Right ventricular mass (g)	0.31 ± 0.03	0.34 ± 0.04	0.27 ± 0.03$^{\Delta ¥}$
Right ventricular hypertrophy index-1 (%)	0.05 ± 0.01	0.06 ± 0.01$^{\Delta}$	0.07 ± 0.01$^{\Delta}$
Right ventricular hypertrophy index-2 (%)	20.44 ± 1.06	22.90 ± 1.80$^{\Delta}$	27.77 ± 2.19$^{\Delta ¥}$

Note: Compared with the plain group, $^{\Delta}$means $P < 0.05$; compared with the moderate altitude group, $^{¥}$ means $P < 0.05$.

4. Discussion

The characteristics of high-altitude areas, such as low pressure, low oxygen, cold, drought, wind, strong radiation, and large temperature differences, can have a significant impact on heart structure and function. This can lead to the development of acute and chronic altitude sickness as well as high-altitude heart disease. However, the underlying mechanisms of these conditions are not yet fully understood. It is estimated that over 140 million people live in plateau areas above 2500 m above sea level, highlighting the importance of studying the health implications of living at high altitudes [10]. Previous experimental studies on animals at high altitudes have mostly been conducted in simulated environments using low pressure and hypoxia chambers [11,12]. These studies fail to accurately reflect the physiological and pathological changes that occur in subjects exposed to the natural high-altitude environment. To address this limitation, our research was conducted in a real natural high-altitude environment, allowing for more reliable and accurate data collection.

In this study, male Sprague-Dawley rats were divided into three groups based on altitude classification criteria. The plain group

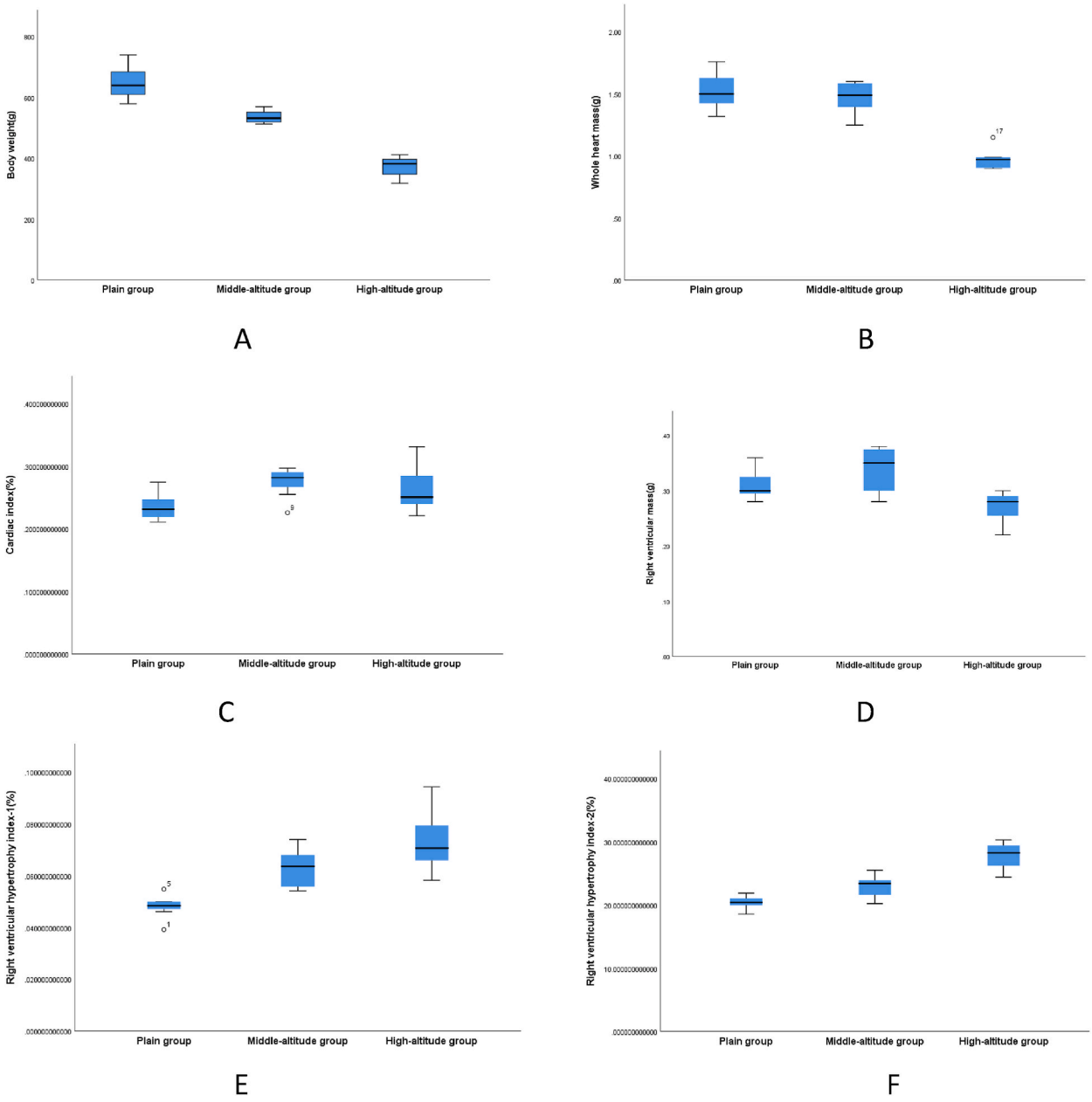

Fig. 1. A–F Boxplot of index of body weight, whole heart mass, Cardiac index, right ventricular mass, right ventricular hypertrophy index-1 and right ventricular hypertrophy index-2 in plain group, middle-altitude group and high-altitude group.

represented rats living at low altitude, the middle-altitude group represented rats living at moderate altitude, and the high-altitude group represented rats living at high altitude. Compared to the plain group, the middle-altitude group showed a significant decrease in body weight ($P < 0.05$), while the differences in whole heart mass and right ventricular mass were not statistically significant ($P > 0.05$). The cardiac index, RVHI-1, and RVHI-2 were significantly increased in the middle-altitude group ($P < 0.05$).

Similarly, compared to the plain group, the high-altitude group exhibited a significant decrease in body weight, whole heart mass, and right ventricular mass ($P < 0.05$). The cardiac index showed an increasing trend, although the difference was not statistically significant ($P > 0.05$). Additionally, the RVHI-1 and RVHI-2 were significantly increased in the high-altitude group ($P < 0.05$). Furthermore, when comparing the middle-altitude group to the high-altitude group, the high-altitude group displayed a significant decrease in body weight, whole heart mass, and right ventricular mass ($P < 0.05$). The cardiac index showed a decreasing trend, although the difference was not statistically significant ($P < 0.05$). Moreover, the RVHI-1 and RVHI-2 were significantly increased in the high-altitude group compared to the middle-altitude group ($P < 0.05$). These findings indicate that as altitude increases, rats experience a decrease in body weight, a tendency towards decreased whole heart mass and right ventricular mass, and structural changes in the right heart. Additionally, the proportion of the right heart to body weight and the proportion of the right heart to whole heart increase with altitude (Fig. 1A–F). Analysis of the findings suggests that the observed changes in heart indices and right ventricular hypertrophy in Sprague-Dawley rats at different altitudes are likely attributed to the altitude-induced decrease in atmospheric pressure. This reduction in atmospheric pressure subsequently leads to a decline in arterial oxygen content and saturation. Consequently, pulmonary arterioles constrict, resulting in an elevation of pulmonary circulatory resistance. This increase in resistance ultimately leads to the development of pulmonary hypertension and an augmented right ventricular pressure load [13]. Moreover, these alterations in hemodynamic parameters are also accompanied by significant structural modifications in the right heart. On the other hand, hypoxia induces the high expression of hypoxia inducible factor (HIF), which leads to the increase of erythropoietin [14], excessive proliferation of red blood cells, increased blood flow resistance, further increase of pulmonary hypertension, increased pressure load of the right ventricle, and structural changes of the right heart [15,16]. Moreover, in a hypoxic environment, the myocardial aerobic metabolism is hampered [17], leading to inadequate myocardial energy supply. This can subsequently result in myocardial degeneration, necrosis, and diminished contractility and compliance of the right ventricle, ultimately causing structural alterations in the right heart. Our investigation revealed that as altitude increased, there was a gradual reduction in body weight and total heart mass. Additionally, the cardiac index of the middle-altitude group was significantly higher compared to the plain group. Furthermore, we observed a significant increase in the RVHI-1 in both the middle-altitude and high-altitude groups, in comparison to the plain group. Notably, there were discernible differences in the RVHI-2 among the three groups, suggesting that the reduction in right heart dimensions was not as pronounced as the decrease in body weight and total heart mass, signifying a structural transformation within the right heart.

5. Limitations

This study has several limitations that need to be acknowledged. Firstly, the sample size included in our analysis was relatively small, which may affect the generalizability of our findings. However, it is important to note that efforts will be made to increase the sample size in future studies to enhance the statistical power and robustness of our results. Secondly, this study did not consider blood and pathological indicators, which are crucial for a comprehensive understanding of the topic. Future research endeavors will address this limitation by incorporating blood analyses, immunohistochemistry, and pathological indicators, enabling a more thorough investigation of the underlying mechanisms.

6. Conclusions

As altitude increased, a noticeable reduction in body weight of rats was observed, accompanied by a tendency for the whole heart mass to decrease. Moreover, there was a distinct decrease in the mass of the right heart, along with notable structural alterations. Consequently, the ratio of the right heart to body weight and the ratio of the right heart to the whole heart exhibited an upward trend. These findings contribute to our understanding of the etiology and potential preventive measures for chronic altitude sickness, while also offering novel insights and approaches towards the prevention and treatment of acute and chronic altitude-related conditions.

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Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Qinghai Provincial People’s Hospital (2018-SF-114).

Consent for publication

All the authors listed have approved the manuscript to be published.

Data availability statement

Data and other materials can be made available by the corresponding author upon a reasonable request.

CRediT authorship contribution statement

Yanqiu Sun: Supervision, Conceptualization. **Jinfeng Ma:** Writing – review & editing, Writing – original draft. **Tingjun Yan:** Writing – original draft, Formal analysis. **Dengfeng Tian:** Resources, Investigation, Data curation. **Chenhong Zhang:** Writing – review & editing, Formal analysis. **Fengjuan Zhang:** Resources, Methodology. **Yuchun Zhao:** Resources, Methodology. **Shihan Fu:** Resources, Investigation. **Chunlong Yan:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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