

Sex-Specific Cardiac Adaptation to Chronic Hypoxia in High-Altitude Dwellers: Quantitative Insights from 3.0T Cardiovascular Magnetic Resonance

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How to cite this paper: Shen, Y., Zhang, J.J., Cai, C.Y. and Liu, H.P. (2025) Sex-Specific Cardiac Adaptation to Chronic Hypoxia in High-Altitude Dwellers: Quantitative Insights from 3.0T Cardiovascular Magnetic Resonance. *Open Journal of Medical Imaging*, 15, 79-88.

<https://doi.org/10.4236/ojmi.2025.152007>

Received: March 27, 2025

Accepted: May 3, 2025

Published: May 6, 2025

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Abstract

Purpose: The purpose of this study is to investigate gender differences in cardiac remodeling due to hypoxia, using cardiac magnetic resonance (CMR) in individuals living at high altitudes for extended periods. **Materials and Methods:** The study cohort consisted of 89 healthy high-altitude residents, categorized by sex: 49 males (55.1%) and 40 females (44.9%). We conducted comparative analyses of clinical demographics and CMR-derived structural indices within the study cohort. Single-variable logistic regression revealed significant associations, which were later confirmed using adjusted multivariable modeling to identify independent predictors. **Key Results:** Being female is associated with a 59.4% lower risk of cardiomegaly compared to males (OR = 0.538, 95% CI = 0.279 - 0.875, $p = 0.006$). BMI independently predicts the risk of cardiac enlargement (OR = 0.632, 95% CI = 1.088 - 1.536, $p = 0.003$). The diameter of the principal pulmonary artery showed the strongest association (OR = 0.988, 95% CI = 0.988 - 1.346, $p = 0.007$). **Conclusions:** Multivariate logistic regression analysis indicates that sex, body mass index (BMI), and primary pulmonary artery diameter are independent risk factors contributing to cardiac enlargement in high-altitude regions. Given the observed cardioprotective role of female sex in high-altitude populations, we hypothesize that female gender status, BMI range, and main pulmonary artery diameter synergistically influence susceptibility to hypoxia-induced cardiac remodeling in prolonged high-altitude residents. These findings not only provide a solid foundation for preventing chronic heart disease but also support the implementation of tailored treatment interventions in high-altitude areas.

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Keywords

High-Altitude Hypoxia, Cardiac Remodeling, Sex Differences, Magnetic Resonance Imaging

1. Introduction

High-altitude areas have a unique environment with low pressure and low oxygen levels, where the oxygen partial pressure is approximately 60% - 65% of that at sea level. These areas also experience strong ultraviolet radiation and dry conditions, which significantly affect the human cardiovascular system. Acute exposure to high altitude can cause symptoms such as headaches and reduced exercise endurance [1]. In contrast, long-term exposure to low oxygen can lead to excessive red blood cell production, pulmonary hypertension, and right ventricular remodeling due to the activation of the HIF-1 α pathway [2] [3]. In severe cases, it can lead to high-altitude heart disease (HAHD) [4] [5]. Chronic cardiac remodeling caused by hypoxia is a significant public health issue for residents living at high elevations. While magnetic resonance imaging (MRI) is a valuable tool for cardiac assessment due to its high spatial resolution and precise quantification capabilities, research on cardiovascular magnetic resonance (CMR) in healthy individuals living above 3500 meters remains limited. This study employs 3.0T CMR to quantitatively analyze gender differences in cardiac remodeling among residents in high-altitude areas, aiming to provide new insights for the prevention and treatment of altitude-related heart disease in a personalized manner.

2. Subjects and Methods

2.1. Research Subjects

The study involved 89 healthy individuals from high-altitude areas, comprising 49 males (55.1%) with an average age of 39.2 (\pm 11.5) years and 40 females (44.9%) with an average age of 38.5 (\pm 12.3) years. These individuals lived at an average altitude of approximately 3650 meters in Lhasa, Xizang. The inclusion criteria were as follows: participants were aged 19 to 58 years, born in low-altitude areas (altitude < 1000 meters), and migrated to the plateau as members of the Han ethnic group.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria include: 1) No history of cardiovascular disease or chronic conditions that affect heart function; 2) Long-term residence at an altitude of 3650m while performing low to moderate-intensity work for 5 to 6 days a week, totaling 6 to 8 hours per day; 3) Participants should have continuous residence at high altitude for more than 10 months each year; 4) Participants must provide complete clinical data and have voluntarily signed informed consent. Exclusion criteria are: 1) Long-term residents of high-altitude areas who are local Tibetans; 2)

Contraindications for MRI; 3) A history of congenital heart disease and/or myocardial infarction; 4) Severe coexisting internal diseases; 5) Positive findings from a general physical examination.

2.3. CMR Examination Method

We utilized the Siemens Magnetom Skyra 3.0 T MRI system with an 18-channel phased array coil, employing both respiratory and prospective ECG gating. The gradient field was set to 45 mT/m and switched at a rate of 200 mT/m per second. Before scanning, participants received repeated breath-holding training. They were instructed to lie on their backs on the exam table, with their heads positioned at the top and their arms resting at their sides. In the axial plane, we aligned the two-chamber view with the interventricular septum at the left ventricular apex. In the two-chamber view, we oriented the four-chamber view along the line extending from the left ventricular apex to the midpoint of the mitral valve. In the four-chamber view, we positioned the standard short-axis view perpendicular to the interventricular septum. Localizer images were acquired using a balanced steady-state free precession (bSSFP) sequence to obtain standard transverse, coronal, and sagittal anatomical planes. For axial T2-weighted imaging, a Half-Fourier Acquisition Single-shot Turbo Spin-Echo (HASTE) sequence was utilized to acquire multislice axial images encompassing the anatomical extent from the aortic arch to the cardiac base level. Cardiac cine imaging in the short-axis orientation was performed with an electrocardiogram-gated bSSFP sequence at contiguous 8 mm slice thickness without interslice gaps, covering the entire ventricles from the base to the apex.

2.4. Image Evaluation

Cardiac structure evaluation: Heart segments were categorized according to the American Heart Association's 2002 standard anatomical planes [6]. We measured the wall thickness of each segment and the dimensions at end-diastole using both black-blood and bright-blood sequences. The parameters assessed were: right atrial left-right diameter, right atrial anteroposterior diameter, right ventricular end-diastolic transverse diameter, left atrial anteroposterior diameter, left atrial left-right diameter, left ventricular end-diastolic diameter, and main pulmonary artery diameter. Two radiologists independently measured each parameter twice, and the mean value was recorded. Refer to **Figure 1** for additional details. Cardiac enlargement and chamber dimensions were defined according to consensus guidelines: Left ventricular enlargement was defined as LV end-diastolic diameter (LVEDD) ≥ 60 mm in males and ≥ 54 mm in females, while right ventricular dilatation required an end-diastolic transverse diameter >45 mm or RV/LV diameter ratio >1.0 based on axial cine imaging [7] Left atrial enlargement was identified by an anteroposterior diameter >40 mm in the long-axis view. The main pulmonary artery diameter threshold of >29 mm at the bifurcation level was applied to assess vascular remodeling [8].

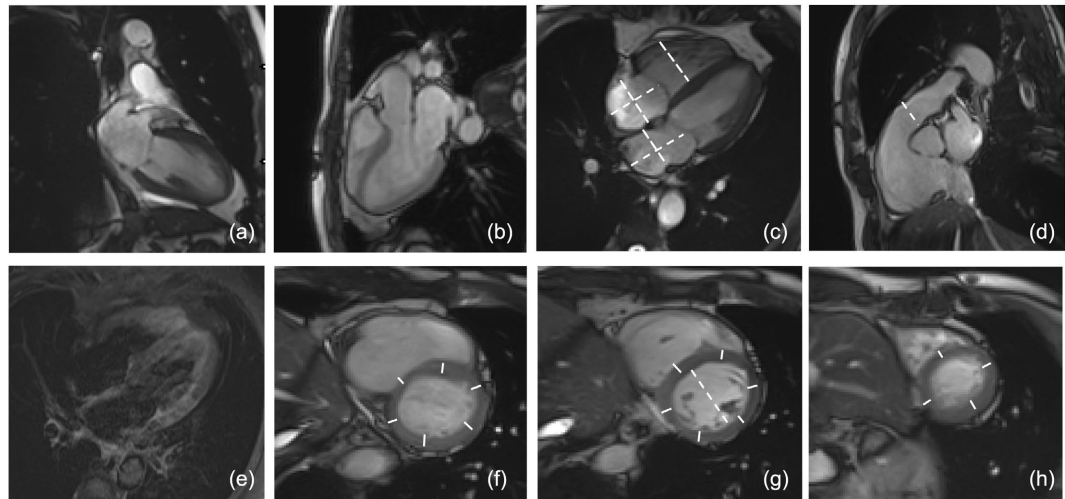


Figure 1. CMRI Structural Assessment Measurement Criteria Levels. (a)-(d) displays the CMR video sequence at end-diastole, comprising: (a) two-chamber heart; (b) three-chamber heart; (c) four-chamber heart, which measures the anteroposterior and lateral dimensions of the left and right atria, along with the end-diastolic diameter of the right ventricle; and (d) right ventricular outflow tract, measuring the inner diameter of the main pulmonary artery. (e) illustrates the FLAIR inversion recovery sequence, also known as the black blood sequence. (f)-(h) presents the short-axis two-chamber heart video sequence, which includes: (f) basal level; (g) papillary muscle level, measuring the left ventricular end-diastolic inner diameter; and (h) apical level, which assesses the wall thickness of each segment.

2.5. Statistical Analysis

Statistical analysis was performed using SPSS 22.0, with significance set at $p < 0.05$. We applied the Kolmogorov-Smirnov test to determine whether the quantitative data followed a normal distribution. Based on the results, we reported the data as mean \pm standard deviation (SD) or median (interquartile range). We compared the ventricular structural parameters between groups using one-way ANOVA and applied a post hoc Bonferroni correction. We utilized Pearson correlation coefficients for normally distributed data and Spearman correlation coefficients for non-normally distributed data to assess the relationship between clinical parameters and cardiac structure and function. We conducted a binary logistic regression analysis to identify risk factors for cardiac remodeling, defining statistical significance as a two-sided $p < 0.05$.

3. Results

3.1. Analysis of Clinical Characteristics of the Two Groups

There were no statistically significant differences between the two groups regarding age, blood oxygen saturation, heart rate, admission time, and hypertension status ($p > 0.05$), as detailed in **Figure 2**.

3.2. Analysis of CMR Cardiac Structure of the Two Groups

The analysis showed that males had slightly larger atria and ventricles than females, including thicker left ventricular walls. The two groups showed no signifi-

cant differences in RALRD, RAAPD, RVEDTD, LALRD, LAAPD, LVEDD, and MPAD. Furthermore, MPAD significantly differed between the two groups ($p = 0.016$). Among the 16 segmental myocardial thickness measurements, only the inferior wall thickness at the papillary muscle level showed a significant difference between the female and male groups ($p = 0.032$), while the other wall thicknesses were not statistically significant.

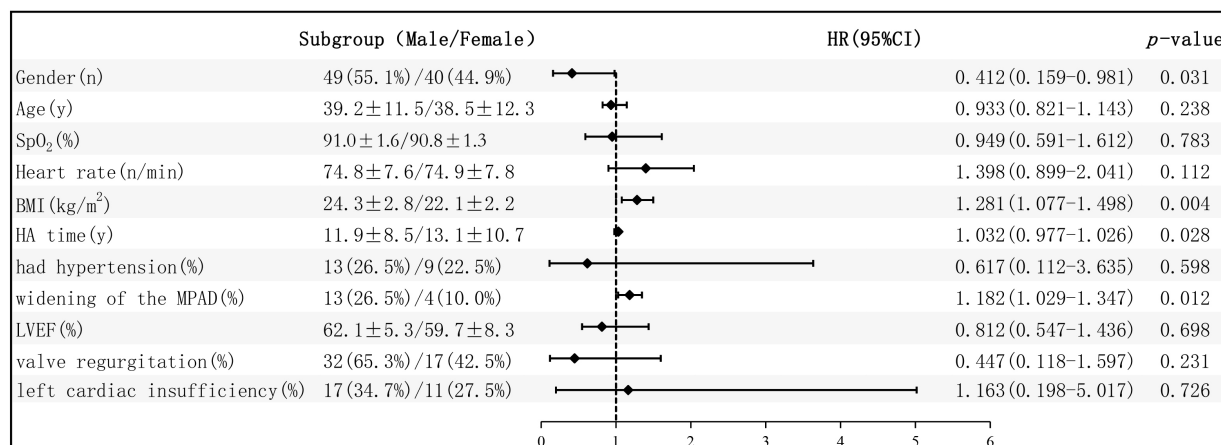


Figure 2. Clinical data and related multifactorial logistic regression analysis of two groups of populations.

3.3. Analysis of Cardiac Remodeling in Two Groups

In the male group, there were 34 cases of right atrial enlargement (69.4%), 11 cases of right ventricular enlargement (22.4%), 24 cases of left atrial enlargement (49.0%), 32 cases of valve regurgitation (65.3%), and 13 cases of widening of the main pulmonary artery (26.5%). In the female group, there were a total of 18 cases of right atrial enlargement (45.0%), 3 cases of right ventricular enlargement (7.5%), 14 cases of left atrial enlargement (35.0%), 17 cases of valve regurgitation (42.5%), and 4 cases of widening of the main pulmonary artery (10.0%). Higher occurrence rates in males compared to females were noted, with significant differences for valve regurgitation, right atrial enlargement, and widening of the main pulmonary artery ($p = 0.032$, $p = 0.028$, $p = 0.035$). This indicates that gender could significantly influence these cardiac structural changes. This suggests that gender may be a key factor influencing these cardiac structural changes. Functional abnormalities, including excessive cardiac load and left heart failure, were more prevalent in males than in females; however, this difference was not statistically significant ($p > 0.05$).

3.4. Analysis of Factors Related to Cardiac Enlargement

We conducted Spearman's bivariate correlation analysis to investigate the relationship between basic data, magnetic resonance-related parameters, and cardiac enlargement in populations living at high altitudes. Our analysis revealed that gender, BMI, time at high altitude (HA time), and main pulmonary artery diameter (MPAD) were significantly correlated with cardiac enlargement ($p < 0.05$).

We included the correlated parameters in a binary logistic regression analysis to assess the factors related to cardiac enlargement. The univariate regression analysis indicated significant associations between gender, BMI, length of stay, main pulmonary artery diameter, and cardiac enlargement. Women had a 54.8% lower risk of developing cardiac enlargement compared to men ($p < 0.05$). Additionally, each unit increase in BMI raised the risk by 27.5% ($p < 0.05$), each additional year of residence increased the risk by 3.2% ($p < 0.05$), and each 1 mm increase in main pulmonary artery diameter raised the risk by 17.6% ($p < 0.05$). The multivariate analysis confirmed that gender (OR = 0.538, 95% CI = 0.279 - 0.875, $p = 0.006$), BMI (OR = 1.632, 95% CI = 1.088 - 1.536, $p = 0.003$), and main pulmonary artery diameter (OR = 1.012, 95% CI = 0.988 - 1.346, $p = 0.007$) remained statistically significant predictors of cardiac enlargement, indicating that these relationships persisted after controlling for other confounding factors. Check out **Figure 2** for more details.

4. Discussion

Chronic hypoxia's impact on heart structure and function at high altitudes has emerged as a significant research focus in public health. People living at high altitudes are at risk for heart changes, especially in cardiac structure and function, which can lead to cardiovascular diseases [9]. Currently, diagnosing high-altitude heart disease mainly depends on imaging tests and biochemical markers, but these methods still have limitations in creating individualized treatment plans [10]. Thus, researching the effects of chronic hypoxia on the heart at high altitudes, particularly concerning gender differences, is clinically significant. It also has important implications for the efficient allocation of healthcare resources.

Cardiac Magnetic Resonance Imaging (CMRI) offers a comprehensive examination of the heart, including cardiac morphology, function, myocardial activity, and valve motion, all in a single test, making it highly valuable in clinical practice [11]. In 2010, the American College of Cardiology Foundation (ACCF) collaborated with the American College of Radiology (ACR), the American Hospital Association (AHA), and other organizations to create a consensus on cardiovascular magnetic resonance [12]. This consensus highlights the importance of cardiac magnetic resonance exams in clinical heart assessments. CMR provides high-resolution anatomical and functional imaging without ionizing radiation, enabling precise assessment of cardiac structures. Unique sequences like T1/T2 mapping and late gadolinium enhancement (LGE) allow detailed evaluation of myocardial pathology (e.g., infarction, inflammation, amyloidosis), which is unmatched by echocardiography or CT [13]. CMR integrates anatomical, functional, and hemodynamic data in a single exam, avoiding limitations of modality-specific workflows [14].

This study employs CMR multimodal technology to quantitatively evaluate how chronic high-altitude hypoxia affects cardiac remodeling, with a particular focus on gender differences. We analyzed 89 healthy individuals living at an alti-

tude of 3650 meters and found notable gender differences in cardiac remodeling. Specifically, we observed variations in valve regurgitation, right atrial enlargement, and main pulmonary artery dilation. This suggests that gender may significantly affect chronic cardiac remodeling at high altitudes [15]. We identified significant correlations between gender, body mass index (BMI), main pulmonary artery size, and cardiac enlargement, indicating that gender may influence how the heart adapts to low oxygen levels at high altitudes [16]. Notably, women in hypoxic environments face a much lower risk of cardiac enlargement compared to men. This finding could alter our approach to screening and managing heart disease in high-altitude regions. Doctors can develop more personalized prevention and treatment plans based on gender differences, which could enhance the prognosis for cardiac diseases related to altitude. Furthermore, the strong link between BMI and cardiac enlargement suggests that managing weight could be key in preventing and treating heart diseases in high-altitude areas [17] [18].

The differences in cardiac structure between men and women due to long-term hypoxic exposure are complex and may involve various physiological and biochemical mechanisms. Evidence suggests that gender influences differences in resting cardiac hemodynamic responses and vascular regulation during both acute and prolonged high-altitude exposure [19]. While both women and men experience similar increases in resting heart rate and blood pressure under acute hypoxic conditions, their resting blood flow and vascular conductance in the femoral and forearm vessels differ significantly. Recent studies show that premenopausal women respond differently to physiological stressors, such as hypoxic exposure, exhibiting less vasoconstriction and more vasodilation [18] [20]. Gender differences significantly affect local blood flow and how the body responds to hypoxic exercise through vasodilation. Gender differences also appear in microvascular function. Studies show that women's microvasculature responds more effectively to hormonal and physiological stimuli, enabling better blood flow regulation in low-oxygen conditions [21]. This may be due to higher estrogen levels in women, which enhance endothelial cell function and vasodilatory capacity. In contrast, men tend to have stronger vasoconstrictive responses under hypoxic conditions, making it more difficult for them to adapt blood flow to the heart [22]. This may explain the different changes in cardiac structure and function between men and women in hypoxic environments. The relationship between BMI and cardiac enlargement is complex and requires further confirmation, but it remains statistically significant. The diameter of the main pulmonary artery, as an independent risk factor, suggests it could play a role in how cardiac structure and function change. When assessing the risk of cardiac enlargement, gender, BMI, and main pulmonary artery diameter should be taken into account since they might affect how patients are managed and treated. This study has limitations, including being conducted at a single center with a small sample size from one geographical area.

In high-altitude regions, the study found that being female is associated with a significantly lower risk of cardiomegaly. BMI and the diameter of the principal

pulmonary artery are also independent risk factors. The conclusions suggest that sex, BMI, and main pulmonary artery diameter synergistically influence susceptibility to hypoxia-induced cardiac remodeling. These findings provide a basis for preventing chronic heart disease and support tailored treatment interventions. The practical significance of personalized medicine in high-altitude areas includes gender-specific screening, prevention, and treatment plans, such as annual cardiac MRI monitoring for men and dynamic estrogen monitoring for women during menopause. This approach is expected to reduce unnecessary invasive treatments.

In summary, this study reveals significant adaptive changes in cardiac structure due to long-term hypoxia in high-altitude environments, emphasizing the crucial role of sex in cardiac remodeling. The results indicate that men show more significant impairments in heart structure and function, whereas women exhibit a greater ability to compensate for heart function. These findings provide valuable evidence for future prevention and intervention strategies for cardiac remodeling at high altitudes. Thus, these findings suggest that sex differences should be taken into account in clinical practice when developing personalized treatment plans.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. The study is supported by the Key Project of the Natural Science Foundation of Xizang Autonomous Region (Project Approval Code: XZ202201ZR0029G).

Consent

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of FOKIND Hospital affiliated with Xizang University. Written informed consent was signed by each patient or their authorized person.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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