Correlative study on the expression of adipokine CTRP9 in a rat model of right ventricular outflow tract obstruction

Yanming Shen[1], Shaoqin Chen[2], Guanhua Fang[3,4], Hongmiao Huang[1], Liangwan Chen[3,4], Dongshan Liao[3,4]*

[1]Fujian Medical University, Fuzhou, Fujian, China
[2]Department of Intensive Care Unit, Xiamen Cardiovascular Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, Fujian Province, China
[3]Department of Cardiovascular Surgery, Union Hospital, Fujian Medical University, Fuzhou, Fujian, China
[4]Fujian Key Laboratory of Cardio-Thoracic Surgery (Fujian Medical University), Fuzhou, Fujian, China

Submitted: 25 September 2024; **Accepted:** 8 January 2025
Online publication: 3 April 2025

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/199929

***Corresponding author**
Dongshan Liao
Department of Cardiovascular Surgery
Union Hospital
Fujian Medical University
Fuzhou, Fujian, China
Fujian Key Laboratory of Cardio-Thoracic Surgery
Fujian Medical University, Fuzhou
Fujian, China
E-mail: liao89612@163.com, lds89612@fjmu.edu.cn

Abstract

Introduction: Right ventricular outflow tract obstruction (RVOTO) is linked to right ventricular hypertrophy and fibrosis, which can lead to significant cardiovascular complications. C1q-tumor necrosis factor-related protein-9 (CTRP9) may serve as a biomarker for cardiac remodeling. This study examined CTRP9 expression in a rat model of RVOTO and its association with hypertrophy and fibrosis.

Material and methods: Thirty male Sprague Dawley rats were divided into three groups: operation, sham operation, and control (10 rats each). The operation group underwent pulmonary arterial constriction, while the sham group had thoracotomy without pulmonary arterial constriction. After 4 weeks, heart specimens were collected for plasma CTRP9 quantification with ELISA, myocardial thickness measurement, and collagen fiber volume assessment. CTRP9 expression was analyzed using immunohistochemistry and Western blot. Statistical evaluations included *t*-tests and Pearson correlation analysis.

Results: The operation group showed a significantly ($p < 0.001$) higher collagen fiber volume ratio in right ventricular hypertrophy than the sham and control groups, indicating notable myocardial fibrosis. CTRP9 levels in plasma were significantly lower in the operation group ($p < 0.001$) as compared to the sham and control groups. Moreover, plasma CTRP9 showed a negative correlation with hypertrophy ($r = -0.910$, $p = 0.029$). Western blotting and immunohistochemical analysis confirmed significantly higher myocardial CTRP9 concentrations in the operation group compared to the sham ($p = 0.032$) and control ($p = 0.029$) groups, correlating strongly with hypertrophy ($r = 0.948$, $p = 0.036$) and fibrosis ($r = 0.947$, $p = 0.027$) respectively.

Conclusions: In this RVOTO model, decreased circulating plasma CTRP9 levels were observed alongside increased myocardial expression, suggesting a vital role for CTRP9 in the pathological processes of right ventricular hypertrophy during the remodeling process.

Key words: right ventricular outflow tract obstruction, myocardial hypertrophy, myocardial fibrosis, C1q-tumor necrosis factor-related protein-9.

Introduction

Congenital heart diseases involving obstruction of the right ventricular outflow tract are among the most prevalent forms of congenital anomalies, with conditions such as pulmonary stenosis, pulmonary atresia, and tetralogy of Fallot (TOF) being particularly common [1]. These conditions lead to significant right ventricular (RV) myocardial remodeling, adversely impacting cardiac function and often resulting in right ventricular failure. Studies indicate that children with obstructive right ventricular outflow tract (RVOT) lesions face increased postoperative complications, including heart failure and mortality, underscoring the urgent need for a deeper understanding of the underlying pathological mechanisms [2, 3]. Despite the clinical significance of RVOT obstruction, there is a notable lack of research focused on the specific pathological changes associated with cardiac hypertrophy in these conditions. The expression of cytokines and other molecular factors involved in the progression of right ventricular hypertrophy is critical to elucidating the mechanisms behind this condition and could reveal new therapeutic targets for delaying or alleviating hypertrophy and fibrosis [4, 5].

C1q-tumor necrosis factor-related protein-9 (CTRP9) has emerged as a promising biomarker for cardiac remodeling. Studies have shown that CTRP9 plays a protective role in cardiac hypertrophy and heart failure by modulating inflammation and fibrosis [6]. Elevated CTRP9 levels have been associated with improved cardiac function in patients with heart failure, suggesting its potential as a therapeutic target [7, 8]. Given its role in modulating cardiac remodeling, CTRP9 is a key candidate for this study, particularly in the context of right ventricular outflow tract obstruction (RVOTO), where understanding its expression and regulatory mechanisms may offer insights into hypertrophy and fibrosis associated with the condition.

Furthermore, clinical observations reveal that children with these congenital conditions often exhibit obesity, indicating a potential link to metabolic dysregulation [9]. This observation underscores the need to consider metabolic factors when studying cardiac conditions. Research has shown that obesity can exacerbate cardiovascular issues through mechanisms such as inflammation, oxidative stress, and altered adipokine secretion, which can further contribute to cardiac remodeling [10, 11]. Understanding how altered fat metabolism influences cardiac remodeling could illuminate the interplay between obesity and cardiac pathology. Additionally, recognizing the role of obesity suggests that interventions aimed at weight management or metabolic regulation could also impact CTRP9 expression and, consequently, cardiac remodeling, thereby unveiling new therapeutic strategies for improving outcomes in this vulnerable population [12, 13].

Consistently, this study aims to investigate the expression of CTRP9 in a rat model of RVOTO and its correlation with right ventricular hypertrophy and fibrosis. By examining these relationships, we seek to clarify the role of CTRP9 in the pathological changes associated with RVOTO, ultimately identifying potential intervention targets that may help mitigate cardiac remodeling and improve clinical outcomes for affected children.

Material and methods

Chemicals and reagents

The following materials were utilized; Masson trichromatic staining solution (G1340, Solarbio, Beijing, China), TKR-200C small animal respirator (Jiangsu Teli Anaesthetic Respiratory Equipment Co., Ltd., Jiangsu, China), self-made U-shaped aluminum clips (width: 0.8 mm), 10% chloral hydrate (Qingdao Yulong Seaweed Co., Ltd., Qingdao, China), BCA protein quantification kit (Kangwei Century CW0014S, Nanjing, China), C1QTNF9 (CTRP9) (RPR877Hu01, Cloud-Clone Corp, Wuhan, China), and rabbit polymerized HRP-labeled anti-rabbit IgG (SV0002, PhD, Shanghai, China).

Study design, grouping and RVOTO model establishment

This study employed a randomized controlled animal experimental design involving a RVOTO rat model. Thirty male Sprague Dawley (SD) rats, weighing between 100 g and 150 g, were obtained from the Shanghai Experimental Animal Center. The sample size was determined based on a previous study [14], taking into consideration power testing and ethical considerations. The sample size was calculated to achieve 80% power ($\beta = 0.2$) and a significance level of 0.05 (α), assuming a medium to large effect size (0.8). Variability estimates were based on pilot data, and a 10% dropout rate was assumed. A minimum of 8 SD rats per group was determined to be sufficient, and the sample size was increased to 10 SD rats per group for robustness, totaling 30 SD rats across the operation, sham, and control groups. The RVOTO model was established by constricting the main pulmonary artery to a transverse diameter of 0.8 mm using a self-made aluminum clip. In the sham operation group, the chest was opened without arterial constriction. The control group underwent no surgical intervention. All animals were maintained under identical environmental conditions for 4 weeks. The study was approved by the animal ethics committee of Fujian Medical University, Fuzhou, Fujian, China under approval number FMU/AS/620.

Anesthesia and surgical procedure

Anesthesia was induced with 0.1 ml/100 g of chloral hydrate. Rats were fixed on the surgical table using a standard surgical setup, and a longitudinal incision was made in the neck to access the trachea. A 6G venous cannula (for tracheal puncture) was used to establish a connection for respiratory assistance, and a TKR-200C small animal respirator (Jiangsu Teli Anaesthetic Respiratory Equipment Co., Ltd., Jiangsu, China) was connected to assist with breathing at a rate of 30 breaths/min with a 1 : 3 inhalation-to-exhalation ratio. This respirator ensured controlled ventilation throughout the procedure.

Following thoracic disinfection, a left thoracotomy was performed at the third intercostal space using standard surgical instruments. After entering the pleural cavity, a cotton strip was inserted to compress the left lung. The pericardium was punctured, and a U-clip was placed under the main pulmonary artery using a nerve hook. After removing the cotton strip and ensuring lung re-expansion, the chest was closed, and the neck incision was sutured. Post-operative anti-infection treatment was administered using intraperitoneal cefazolin sodium for 3 days.

Measurement of right ventricular thickness

Right ventricular myocardium fixed in paraformaldehyde was sectioned and analyzed using the 9-point method. Myocardial thickness was measured across nine designated areas, including the right ventricular outflow tract and the anterior and lateral walls. The mean myocardial thickness and outflow tract thickness among the groups were statistically analyzed.

Calculation of right ventricular hypertrophy index (RVMI)

The right ventricle (RV), left ventricle, and ventricular septum (LV + S) were separated, excess moisture was absorbed, and RVMI was calculated using the formula: RVMI = RV/(LV + S + RV).

Collagen fiber volume measurement

Masson staining was performed on paraffin-embedded sections of the right ventricular myocardium. Myocardial cells were stained dark red, while collagen fibers appeared blue. Images were captured under a light microscope at 200× magnification. The collagen fiber volume ratio was calculated using Image-Pro-Plus 6.0 software (Media Cybernetics, Rockville, MD, USA).

Measurement of CTRP9 in plasma by ELISA

The concentration of CTRP9 in rat plasma was quantified using a double-antibody sandwich ELISA. The procedure was conducted according to the manufacturer's instructions (Cloud-Clone Corp, Wuhan, China). Briefly, plasma samples were diluted and added to the wells of a 96-well plate pre-coated with CTRP9 antibodies. After incubation, a secondary antibody conjugated to an enzyme was added. Following another incubation and washing step, a substrate solution was added, and the reaction was stopped with a stop solution. The absorbance was measured at 450 nm using a microplate reader. The concentration of CTRP9 in the samples was calculated by comparing the absorbance values to a standard curve generated from known concentrations of CTRP9.

Immunohistochemical analysis

For immunohistochemical analysis, myocardial tissue sections were prepared and mounted on slides. Antigen retrieval was performed by incubating the slides in a citrate buffer (pH 6.0) and heating in a microwave. Following cooling, the slides were treated with 3% hydrogen peroxide to block endogenous peroxidase activity for 10 min. After washing with PBS, the sections were incubated with 5% BSA for 30 min to block non-specific binding. The primary antibody against CTRP9 (diluted 1 : 40, Cloud-Clone Corp, Wuhan, China) was added and incubated overnight at 4°C. After washing, a polymerized HRP-labeled anti-rabbit IgG secondary antibody was applied for 30 min at room temperature. The sections were then developed using a diaminobenzidine (DAB) substrate to visualize the antibody binding. Finally, the slides were counterstained with hematoxylin, dehydrated, and mounted for observation under a light microscope. Quantitative analysis of CTRP9 expression was performed using Image-Pro-Plus 6.0 software (Media Cybernetics, Rockville, MD, USA).

Western blotting

The right ventricular myocardial tissue was quickly frozen in liquid nitrogen and homogenized in RIPA lysis buffer supplemented with PMSF (1 mM) for protein extraction. The homogenate was incubated on ice for 30 min and then centrifuged at 12,000 rpm for 15 min at 4°C to isolate soluble proteins. Protein concentrations were measured using a BCA protein assay kit (Kangwei Century, CW0014S, China). Equal amounts of protein (30 µg) were loaded onto a 10% SDS-PAGE gel for electrophoresis. After separation, proteins were transferred to a PVDF membrane using a wet transfer method. The membrane was blocked for 1 h at room temperature with 5% non-fat dry milk in PBS-Tween 20 to reduce non-specific binding. It was then incubated overnight at 4°C with a primary antibody against CTRP9 (1 : 1000 dilu-

tion, Cloud-Clone Corp, Wuhan, China). Following washing, a HRP-conjugated secondary antibody (1 : 2000 dilution, PhD, China) was applied for 1 h at room temperature. Protein detection was achieved using a chemiluminescent substrate (Chemi Doc XRS+, Bole Life Medical Products, Shanghai, China). Band intensities were analyzed with Image J software (National Institutes of Health, Bethesda, MD, USA) to quantify CTRP9 expression relative to a loading control, GAPDH.

Statistical analysis

All data are presented as mean ± standard deviation (SD). The Shapiro-Wilk test was used to assess the normality of data distribution. For normally distributed data, independent sample *t*-tests were employed to compare differences between groups, with $p < 0.05$ indicating statistical significance. Levene's test was used to check for homogeneity of variances before applying parametric tests. For non-normally distributed data, appropriate non-parametric tests were applied. Pearson correlation analysis and linear fitting were utilized to evaluate relationships between variables using least-squares regression. All statistical analyses were conducted using SPSS 21.0 software (IBM Corp., Armonk, NY, USA).

Results

Right ventricular hypertrophy thickness

Gross examination revealed significant thickening of the right ventricle in the operation group, as shown in Figure 1 A and Table I. The average thickness measurements shown in Table II highlighted significant differences between the operation group and both the sham operation and control groups ($p < 0.001$). Specifically, the thickening of the right ventricular outflow tract was particularly pronounced in the operation group compared to the sham and control groups, as illustrated in Figure 1 B. Statistical analysis confirmed significant differences across all groups ($p < 0.001$), reinforcing the impact of pulmonary arterial constriction on right ventricular hypertrophy.

Right ventricular hypertrophy index

The operation group exhibited significantly ($p = 0.001$) higher values of right ventricular mass and hypertrophy index compared to both the sham and control groups, indicating that pulmonary arterial constriction effectively induced hypertrophy. Specifically, the right ventricular mass was 0.349 g, and the hypertrophy index was 0.293, both significantly higher than the values in the sham (0.192 g and 0.228 g) and control groups (0.198 g and 0.229 g). In contrast, no significant differences were found between the sham operation and control groups ($p = 0.925$), suggesting that the surgical procedure without pulmonary arterial constriction did not lead to structural changes. Detailed comparisons in Table II underscore the pronounced hypertrophy observed in the operation group, reinforcing the impact of pulmonary arterial constriction on the right ventricle.

Myocardial cell fiber volume ratio

Masson staining effectively visualized the myocardial tissue, revealing clear structural details, with collagen fibers stained blue and myocardial cells appearing red (Figure 2 A). The analysis showed that the myocardial collagen fiber volume ratio was significantly higher in the operation group compared to both the sham operation ($p < 0.001$) and control groups ($p < 0.001$) (Figure 2 B). There was no significant difference between the sham operation and control groups ($p = 0.380$),

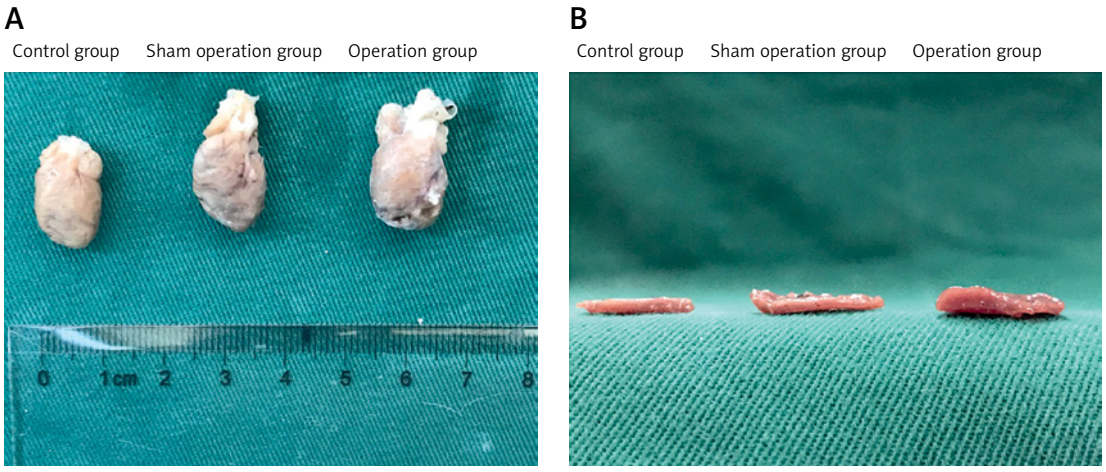

Figure 1. Right ventricular hypertrophy thickness. **A** – Gross examination showing thickness of the right ventricle in different study groups. **B** – Thickening of the right ventricular outflow tract in different study groups ($n = 10$ for each group)

Table I. Average thickness of each part of right ventricle (mm ± SD) in different study groups (n =10)

Group	Mean value	Outflow passage	Anterior wall	Lateral wall
Control group	0.249 ±0.587	0.250 ±0.082	0.249 ±0.059	0.248 ±0.064
Sham operation group	0.260 ±0.436	0.242 ±0.052	0.270 ±0.042	0.268 ±0.222
Operation group	0.938 ±0.054	1.147 ±0.233	0.853 ±0. 134	0.795 ±0.093

Table II. Body weight, whole heart mass, right ventricular mass and right ventricular hypertrophy index in different study groups (g ± SD, n = 10)

Group	Weight [g]	Whole heart mass [g]	Right ventricular mass [g]	RVM1
Control group	277.500 ±16.029	0.860 ±0.049	0. 198 ±0.029	0.229 ±0.026
Sham operation group	274.100 ±17.553	0.852 ±0.054	0. 192 ±0.024	0.228 ±0.019
Operation group	268.200 ±21.238	1.183 ±0.092	0.349 ±0.065	0.293 ±0.039

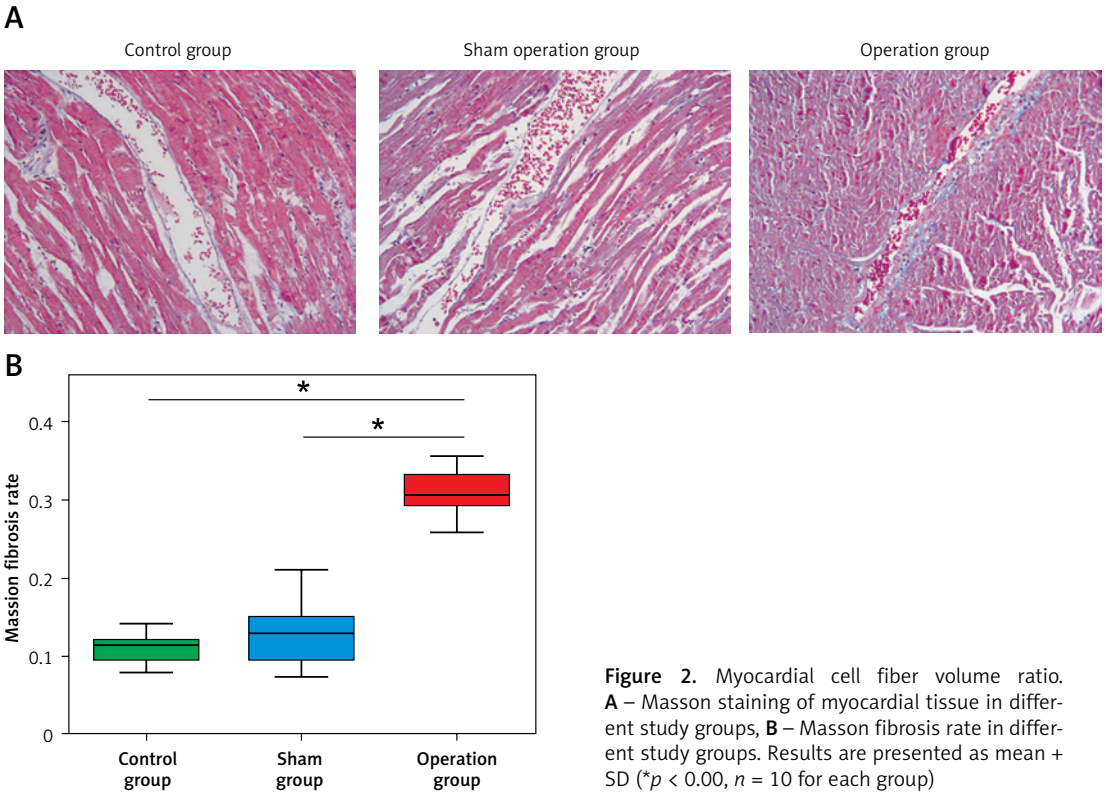

Figure 2. Myocardial cell fiber volume ratio. **A** – Masson staining of myocardial tissue in different study groups, **B** – Masson fibrosis rate in different study groups. Results are presented as mean + SD (*p < 0.00, n = 10 for each group)

supporting the validity of the animal model employed in this study.

Plasma CTRP9 concentration

ELISA results indicated a marked reduction in the plasma concentration of CTRP9 in the operation group compared to both the sham operation and control groups (p < 0.001). The sham operation and control groups did not exhibit significant differences (p = 0.956), highlighting a significant alteration in plasma CTRP9 expression during right ventricular remodeling (Figure 3). Additionally, Pearson correlation analysis demonstrated a negative correlation (r = –0.910, p = 0.29) between plasma CTRP9 concentration and the hypertrophy index (Figure 1 B).

CTRP9 expression in myocardial tissue

Western blot analysis demonstrated significantly elevated CTRP9 expression in the myocardium of the operation group compared to the sham (p = 0.032) and control (p = 0.029) groups (Figures 4 A, B). No significant differences were noted between the sham operation and control groups (p = 0.899). Furthermore, Pearson correlation analysis revealed a positive correlation between CTRP9 expression in myocardial tissues and hypertrophy (r = 0.948, p = 0.036) (Figure 4 C).

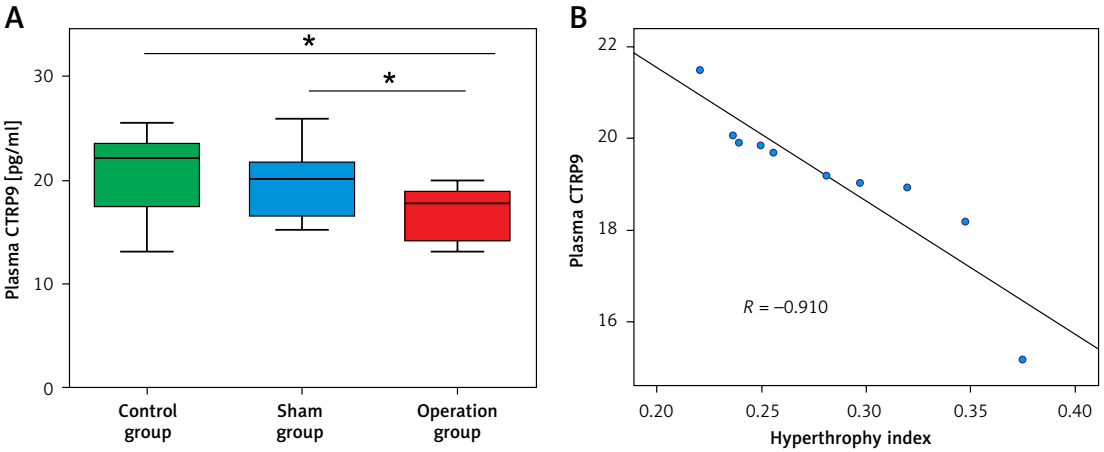

Figure 3. Plasma CTRP9 levels. **A** – Plasma CTRP9 levels in different study groups as determined by ELISA. **B** – Pearson correlation analysis between plasma CTRP9 levels and hypertrophy index. Results are presented as mean + SD (*p = 0.00, n = 10 for each group)

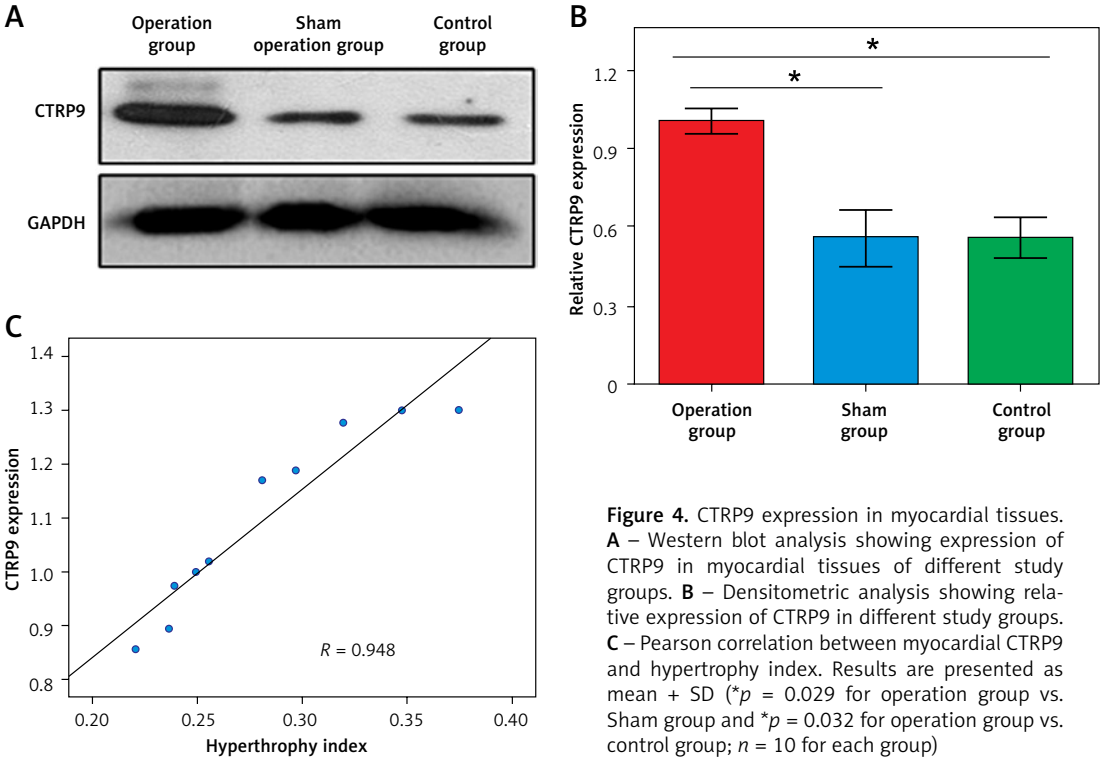

Figure 4. CTRP9 expression in myocardial tissues. **A** – Western blot analysis showing expression of CTRP9 in myocardial tissues of different study groups. **B** – Densitometric analysis showing relative expression of CTRP9 in different study groups. **C** – Pearson correlation between myocardial CTRP9 and hypertrophy index. Results are presented as mean + SD (*p = 0.029 for operation group vs. Sham group and *p = 0.032 for operation group vs. control group; n = 10 for each group)

CTRP9 detection in myocardial tissue

Immunohistochemical analysis revealed that the distribution of CTRP9 in the right ventricular myocardium was markedly elevated and uniform, particularly around blood vessels, suggesting its involvement in the remodeling processes associated with right ventricular hypertrophy (Figure 5 A). Moreover, average immuno-optical density of CTRP9 in cardiac tissue from the operation group was significantly ($p < 0.05$) higher than in both the sham operation and control groups (Figure 5 B). Interestingly, the immuno-optical density of CTRP9 positively correlated with fibrosis (r = 0.947, p = 0.027) (Figure 5 C).

Discussion

Congenital heart disease remains a significant concern in pediatric cardiology, particularly conditions leading to right ventricular hypertrophy such as TOF, pulmonary artery stenosis, and pulmonary artery atresia. These conditions not only present challenges during surgical interventions but also contribute to long-term complications, including right heart failure and impaired post-surgery recov-

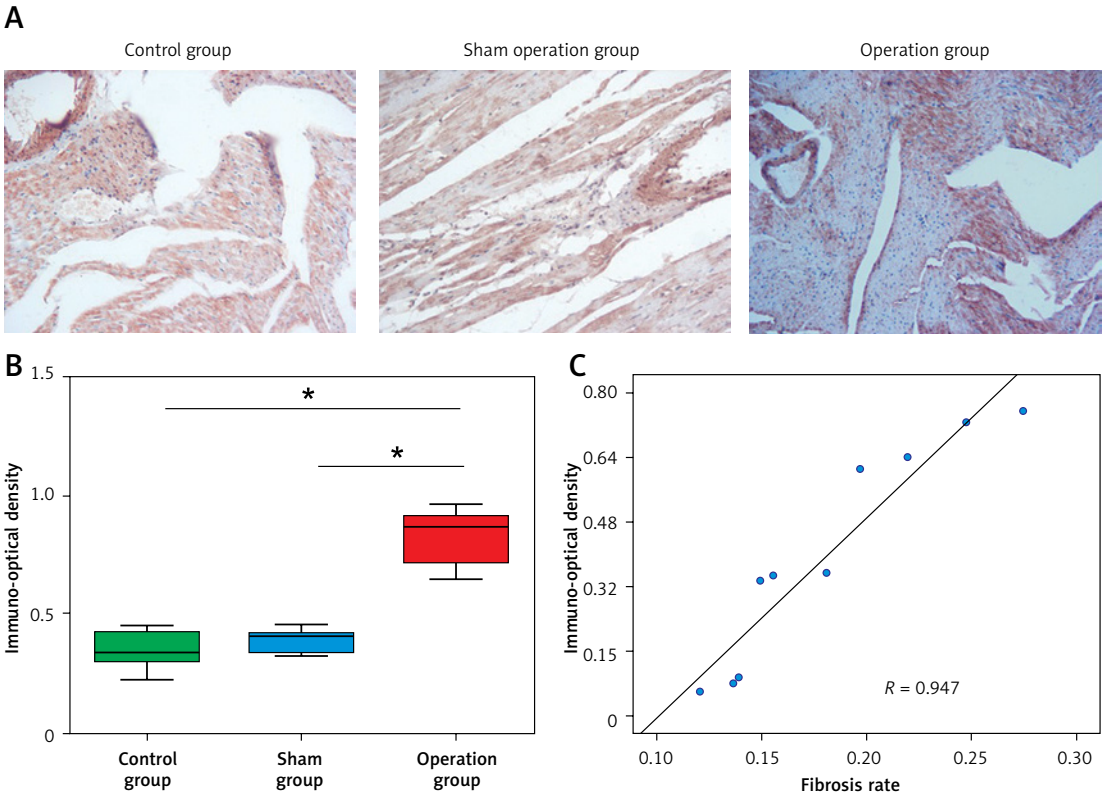

Figure 5. Immunohistochemical analysis (**A**). Expression of CTRP9 in myocardial tissues of different study groups as determined by immunohistochemistry (**B**). Immuno-optical density of myocardial tissues of different study groups (**C**). Pearson correlation analysis between immuno-optical density and fibrosis rate. Results are presented as mean + SD (*$p < 0.05$, $n = 10$ for each group)

ery. Mortality rates associated with congenital heart diseases often stem from right ventricular dysfunction, fibrosis, and inadequate recovery of right heart function, underscoring the need for effective monitoring and management strategies [15, 16].

The present study underscores the pathological remodeling of the right ventricle in response to outflow tract obstruction. Our findings reveal significantly increased right ventricular thickness in the operation group compared to both the sham and control groups. This observation is consistent with existing literature that documents right ventricular hypertrophy as a common adaptation to increased afterload conditions [17]. The right ventricle's response to pressure overload differs from that of the left ventricle, often failing to adhere to the classical Starling curve [18]. This divergence highlights the importance of understanding the unique physiological characteristics of the right heart, which are critical for guiding post-surgical treatment strategies.

In our analysis, we noted significantly higher values of both right ventricular mass and the hypertrophy index in the operation group. These findings corroborate studies linking elevated right ventricular mass to adverse clinical outcomes in pediatric populations with congenital heart defects [19]. Regular monitoring of right ventricular parameters, including mass and hypertrophy index, is essential to predict and mitigate potential complications following surgical interventions.

Our investigation into myocardial cell fiber volume ratios provided further insights into the structural changes associated with right ventricular hypertrophy. The presence of increased collagen deposition, indicated by Masson staining, reflects myocardial fibrosis – a well-documented predictor of poor cardiac outcomes [20]. Previous studies have established a strong correlation between myocardial fibrosis and the transition from hypertrophy to heart failure, where elevated collagen levels can disrupt normal cardiac function and lead to arrhythmias [21]. The data support the notion that the degree of myocardial fibrosis is a critical factor influencing prognosis in patients with congenital heart disease, emphasizing the necessity for accurate assessment tools to evaluate myocardial remodeling.

A key focus of our study was the examination of CTRP9 levels in plasma and myocardial tissue. The observation of lower plasma CTRP9 concentrations in the operation group was striking. CTRP9, known for its cardioprotective properties, is associated with improved endothelial function

and anti-inflammatory effects [22]. The reduction of CTRP9 in the context of RVOTO suggests its potential role as a biomarker for myocardial stress and remodeling. The disparity between systemic and local levels of CTRP9 raises intriguing questions about the underlying mechanisms driving these changes.

While plasma CTRP9 levels were significantly lower in the operation group, we found a corresponding elevation in CTRP9 expression within the myocardial tissue. This finding suggests that the myocardium may attempt to compensate for increased stress by upregulating protective factors locally, despite the systemic decline in CTRP9 levels. Previous research supports this notion, indicating that local upregulation of adipokines, including CTRP9, may act as an intrinsic response to myocardial injury [23]. However, this compensatory mechanism may not be sufficient to prevent the overall progression of heart failure, indicating a complex interplay between local and systemic factors influencing cardiac health.

Moreover, the immunohistochemical analysis demonstrated a significantly higher average optical density of CTRP9 in cardiac tissue from the operation group. This increased expression around blood vessels suggests a role for CTRP9 in promoting angiogenesis and enhancing myocardial perfusion during states of increased stress [24]. The findings align with studies that propose CTRP9 as a critical factor for vascular function and recovery following myocardial injury, reinforcing its potential importance in therapeutic strategies for cardiac conditions.

Correlational analyses revealed a negative relationship between plasma CTRP9 levels and the right ventricular hypertrophy index. At the same time, there is a strong correlation of myocardial CTRP9 with hypertrophy index and fibrosis. This suggests that CTRP9 may serve as a valuable biomarker for assessing the severity of right ventricular remodeling. The association between lower plasma CTRP9 and increased myocardial fibrosis aligns with literature that highlights the significance of myocardial stress markers in predicting adverse outcomes in patients with congenital heart disease [25]. Given the correlation between elevated myocardial fibrosis and the likelihood of heart failure, further investigation into the clinical utility of CTRP9 as a prognostic marker for right ventricular health is warranted.

The implications of our findings extend beyond merely identifying biomarkers; they underscore the need for a holistic approach to managing congenital heart disease. By integrating the assessment of biomarkers like CTRP9 with traditional measurements of cardiac function and structure, clinicians may enhance their ability to predict outcomes and tailor interventions for pediatric patients with congenital heart diseases. Understanding the relationship between right ventricular hypertrophy, myocardial fibrosis, and biomarkers such as CTRP9 can inform future research and clinical practice, ultimately improving the care of these vulnerable populations.

Although the results are interesting, there are some limitations that should be acknowledged. Firstly, the use of a rat model, while providing valuable insights, may not fully replicate the complex pathophysiology of congenital heart disease in humans. Translating these findings to clinical practice requires cautious interpretation. Secondly, the sample size, though statistically determined, was relatively small and may not capture the full spectrum of variability in biological responses. Lastly, the study design did not include long-term follow-up to assess the progression from right ventricular hypertrophy to heart failure, which limits our ability to draw conclusions about the chronic effects of RVOTO.

In conclusion, significant insights into the pathological remodeling of the right ventricle in response to pulmonary arterial constriction were provided in this study. Pronounced right ventricular hypertrophy and increased myocardial collagen fiber deposition were observed in the operation group, accompanied by notable structural and biochemical changes. Plasma CTRP9 levels were markedly reduced, while myocardial CTRP9 expression and immuno-optical density were elevated, suggesting a dual role in systemic and localized responses to myocardial stress. Significant correlations were identified between CTRP9 levels, the hypertrophy index, and myocardial fibrosis, highlighting its potential as a biomarker for assessing right ventricular remodeling. The findings highlight involvement of CTRP9 in the compensatory mechanisms of the myocardium and its relevance as a target for future therapeutic interventions in congenital heart disease.

Acknowledgments

Yanming Shen and Shaoqin Chen contributed equally to this study and share first authorship.

Funding

We would like to express our gratitude for the support provided by the Joint Funds for Medical Innovation project in Fujian Province (Grant Number: 2020CXB021). This funding has been instrumental in advancing our research and contributing to our findings.

Ethical approval

Approval number: FMU/AS/620.

Conflict of interest

The authors declare no conflict of interest

References

1. Chessa M, Plucchinotta FR. Congenital heart disease: a medical overview. In: Clinical Psychology and Congenital Heart Disease: Lifelong Psychological Aspects and Interventions 2014 Nov 2 (pp. 3-20). Milano: Springer Milan.
2. Leonardi B, Calvieri C, Perrone MA, et al. Risk factors of right ventricular dysfunction and adverse cardiac events in patients with repaired tetralogy of Fallot. Int J Environ Res Public Health 2021; 18: 10549.
3. Davey B, Sinha R, Lee JH, Gauthier M, Flores G. Social determinants of health and outcomes for children and adults with congenital heart disease: a systematic review. Pediatr Res 2021; 89: 275-94.
4. Hiram R. Cardiac cytokine therapy? Relevance of targeting inflammatory mediators to combat cardiac arrhythmogenic remodeling. Int J Cardiol Heart Vasc 2021; 37: 100918.
5. Cohn JN, Ferrari R, Sharpe N, an International Forum on Cardiac Remodeling. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. J Am Coll Cardiol 2000; 35: 569-82.
6. Liu M, Li W, Wang H, et al. CTRP9 ameliorates atrial inflammation, fibrosis, and vulnerability to atrial fibrillation in post-myocardial infarction rats. J Am Heart Assoc 2019; 8: e013133.
7. Zhu Z, Niu Q, Tang S, Jiang Y. Association between circulating CTRP9 levels and coronary artery disease: a systematic review and meta-analysis. PeerJ 2024; 12: e18488.
8. Lu J, Zhang Y, Wang Y, et al. The role of CTRP9 in cardiovascular health: a review. Cardiovasc Res 2016; 109: 23-33.
9. Kernan WN, Viscoli CM, Furie KL. Obesity and cardiovascular disease in children: a review. J Pediatr 2018; 198: 22-8.
10. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2011; 124: 20-7.
11. Herring SJ, Arslanian SA, Holubkov R. Impact of obesity on cardiovascular disease. J Clin Hypertens 2014; 16: 157-63.
12. Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med 1999; 340: 115-26.
13. Ghosh S, Karam J, Gabbay-Benziv R. Adipokines in obesity and metabolic syndrome: a review. J Diabetes Metab Disord 2014; 13: 45-52.
14. Sakai T, Li RK, Weisel RD, et al. The fate of a tissue-engineered cardiac graft in the right ventricular outflow tract of the rat. J Thorac Cardiovasc Surg 2001; 121: 932-42.
15. Edelson JB, Rossano JW, Griffis H, et al. Resource use and outcomes of pediatric congenital heart disease admissions: 2003 to 2016. J Am Heart Assoc 2021; 10: e018286.
16. Strzelecka I, Słodki M, Chrzanowski J, Rizzo G, Respondek-Liberska M. An investigation of the optimal inter-pregnancy interval following pregnancy with a fetus with congenital heart disease. Arch Med Sci 2022; 18: 388-94.
17. Chen J, Li Y, Xu Y. Mechanisms of right ventricular hypertrophy: insights from experimental models. Circ Res 2015; 116: 1296-312.
18. Banerjee D, Haddad F, Zamanian RT, Nagendran J. Right ventricular failure: a novel era of targeted therapy. Curr Heart Fail Rep 2010; 7: 202-11.
19. D'Alonzo GE, Barst RJ, Ayres SM. Long-term outcomes of patients with pulmonary hypertension. J Am Coll Cardiol 2007; 50: 597-604.
20. Vasan RS, Lyass A, Benjamin EJ. Myocardial fibrosis and cardiovascular outcomes. Circulation 2008; 117: 75-83.
21. Elias N, Tarasoutchi F, Spina GS, et al. Myocardial fibrosis and ventricular remodeling in severe chronic aortic regurgitation. Arq Brasil Cardiol 2009; 92: 63-7.
22. Kambara T, Yamaguchi S, Nishida M. CTRP9 and its cardioprotective effects. J Biol Chem 2012; 287: 18965-73.
23. Ouchi N, Parker J, Lugus JJ. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011; 11: 85-97.
24. Wong GW, Kusari AB, Kwon H. Identification and characterization of CTRP9. FASEB J 2009; 23: 241-58.
25. Zheng Q, Liu Y, Zhang Y. C1q/TNF-related proteins and their role in vascular function. Arterioscler Thromb Vasc Biol 2011; 31: 2616-23.