

Association between the expression levels of miR-17-5p/IGFBP5 and exercise-induced physiological cardiac hypertrophy

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Abstract. Pathological cardiac hypertrophy (PaCH) leads to heart failure, whereas exercise-induced physiological cardiac hypertrophy (PhCH) represents a benign adaptive response, and counteracts PaCH. Here, we investigated the association of miR-17-5p and *IGFBP5* expressions with PhCH through a PhCH group (five mice with 21-days swimming exercise) and healthy controls ($n = 5$). The PhCH group showed higher body weight (BW), heart weight (HW), HW/BW ratio, ventricular septal thickness, left-ventricular end-diastolic diameter, and left-ventricular end-systolic diameter than control group ($p < 0.05$ for all). The *IGFBP5* expression was significantly reduced, whereas miR-17-5p expression was significantly elevated in PhCH group ($p < 0.05$). Dual-luciferase assays validated the direct binding of miR-17-5p with *IGFBP5*. Wheat germ agglutinin staining revealed enlarged cardiomyocytes of PhCH group, while Masson staining disclosed no increase of fibrosis. The reduction of *IGFBP5* and elevation of miR-17-5p are associated with PhCH, suggesting their potentials for further researches in myocardial hypertrophy.

Key words: miR-17-5p — *IGFBP5* — Cardiac hypertrophy — Heart failure

Highlights:

- The reduction of *IGFBP5* and elevation of miR-17-5p are associated with PhCH, suggesting their potentials for myocardial hypertrophy.

Abbreviations: BW, body weight; CVD, cardiovascular diseases; HF, heart failure; HW, heart weight; *IGFBP5*, insulin-like growth factor binding protein-5; IVS, interventricular septum; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic diameter; LVIDd, left ventricular end-diastolic diameter; LVIDs, left ventricular end-systolic diameter; LVPW, posterior wall thickness of the left ventricle; PaCH, pathological cardiac hypertrophy; PhCH, physiological cardiac hypertrophy; WGA, wheat germ agglutinin.

Introduction

Cardiovascular diseases (CVD) are the leading causes of death among the Chinese people, with an average hospitalization cost of 17,312.8 yuan *per* visit, seriously damaging

the health and wealth of family and country (Diseases et al. 2024). Conditions such as hypertrophic cardiomyopathy, coronary artery disease, and hypertension often lead to pathological cardiac hypertrophy (PaCH), a pivotal step toward heart failure (HF). Roughly 2% of the world's adults

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live with HF; once symptoms declare themselves; fewer than half survive five years (McDonagh et al. 2022). Despite annual, large-scale public investment in HF care, current PaCH management still hinges on drugs and devices. However, hypotension, renal impairment, or other comorbidities bar many patients from guideline-recommended pharmacotherapy. Exercise-based cardiac rehabilitation, though promising, remains embryonic in less-developed regions, and some patients are simply too frail to participate. The net result is a stubborn gap in PaCH prevention and treatment—one that demands fresh, broadly applicable solutions if the health of countless families and the nation itself is to be safeguarded.

Physiological myocardial hypertrophy (PhCH) serves as a countermeasure to PaCH. It is a benign, reversible adaptation in which the heart enlarges without myocyte loss or fibrosis, and without the marked elevation in pathological markers such as brain natriuretic peptide and transforming growth factor beta 1 in CVD (Bernardo et al. 2010; Martin et al. 2023). Exercise-induced PhCH drives cardiomyocytes proliferation, reduces oxidative stress, suppresses apoptosis, boosts energy availability, and enhances exercise tolerance; together, these effects blunt ischemia-reperfusion injury and modestly improve cardiac performance, offering a versatile shield against HF (Lin et al. 2021; Wang et al. 2021; Chen et al. 2022b; Jiang et al. 2023). Consequently, graded exercise is now embedded in international guidelines for the rehabilitation of coronary artery disease, cardiomyopathy, and valvular disorders (Taylor et al. 2023). However, the mechanism of PhCH is still insufficient.

MicroRNAs have recently emerged as valuable tools for diagnosis and interference of certain diseases, such as CVD, cerebral infarction and cancer (Wang et al. 2024; Sadeghi et al. 2025; Tavares et al. 2025). In heart, miR-222 is elevated in both PaCH and PhCH; its suppression inhibits HIPK1 and halts exercise-driven cardiomyocytes growth, whereas forced expression protects mice from adverse post-ischemic remodeling and dysfunction (Liu et al. 2015; Liu et al. 2024). Serum levels of miR-17-5p are significantly increased in patients with hypertrophic cardiomyopathy and correlate directly with the extent of myocardial fibrosis; similarly, myocardial miR-17-5p levels rise in infarcted animals. Silencing this microRNA alleviates its inhibitory effect on STAT3, restores autophagy, and reduces fibrosis, scar burden, and cardiomyocytes death. One validated target of miR-17-5p is insulin-like growth factor-binding protein-5 (IGFBP5), which regulates the proliferation of neonatal cardiomyocytes and apoptosis induced by oxygen-glucose deprivation (Fang et al. 2015; Li et al. 2024). During the chronic remodeling stage, heart-specific regulation of *IGFBP5* improves pathological cardiac remodeling and dysfunction. Bioinformatics analysis revealed that *IGFBP5* is not only a common core regulatory gene for dilated cardiomyopathy but also for hypertrophic cardiomyopathy (Hoffmann et al. 2021; Zhu et al. 2024b).

Despite these findings, the association between miR-17-5p, *IGFBP5* and PhCH remains unclear, and the present study was designed to close this gap.

Materials and Methods

Animal handling and grouping

This study was approved by the Ethics Committee of The Second Affiliated Hospital of Guangxi Medical University (ID: KY-0128). Ten healthy male C57BL/6JNifdc mice (aged 8–10 weeks, weighing 20–25 g) were obtained from Charles River, Co., Ltd., Guangdong. Mice, that were unhealthy or previously had undergone intervention, were excluded. These mice were randomly (random number method) assigned to two groups: the PhCH group ($n = 5$) and the control group ($n = 5$). The mice were housed in an environment with controlled temperature ($25 \pm 2^\circ\text{C}$), humidity (50–60%), a 12-h light-dark cycle, and free access to water and standard chow.

Construction of PhCH animal model

As shown in Figure 1, mice were adapted to water for 3 consecutive days (10 min/day) before the training period as swimming in shallow water (10 cm deep), with the water temperature ranging from 25 to 30°C . At the same time, observe the grooming behavior and exploration behavior of the mice to ensure that there is no panic swimming. The PhCH group performed the 21-day swimming training: started with 2 daily sessions of 15 min, and sessions were separated by at least 6 h. The length of each session was then increased by 15 min every 2 days until they lasted 90 min; the program was conducted on 5 days/week, followed by 2 days for rest. The twice daily 90-min swimming sessions were continued for the next 7 days. The protocol thus lasted for a total of 21 days. During the swimming process, the temperature was controlled by a constant-temperature water ($25\text{--}30^\circ\text{C}$) tank, using semi-transparent resin buckets (with a diameter of 40–50 cm and a water depth of 30–35 cm) to avoid visual interference and spatial orientation stress caused by transparent materials. A dedicated person was assigned to watch over the mice every 10 to 15 seconds throughout to prevent them from drowning. Heart weight (HW) and body weight (BW) were recorded at baseline and after training, and HW/BW was also calculated.

Transthoracic echocardiography examination

All the mice were anesthetized for transthoracic echocardiography examination (TEE) at baseline and after 21 days' training, using the cardiac Doppler ultrasound with 10 MHz linear array probe (EPX-3500HD, Esaote S.p.A., Italy). The

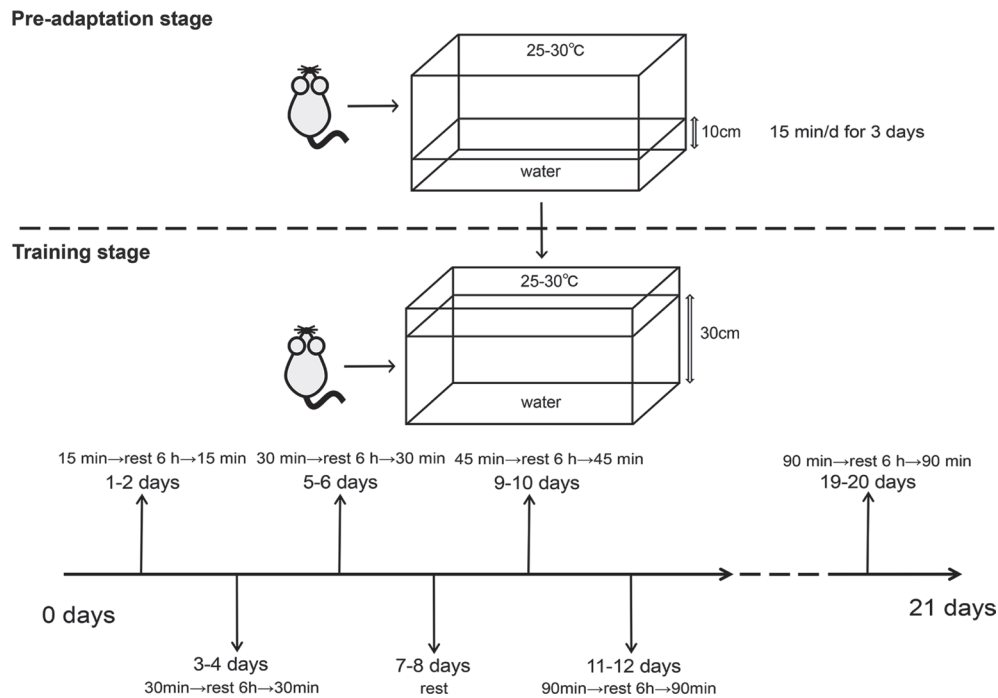


Figure 1. Construction of PhCH animal model. Mice were adapted to water for 3 consecutive days (10 min/day) before the training period as swimming in shallow water (10 cm deep), with the water temperature ranging from 25 to 30°C. At the same time, observe the grooming behavior and exploration behavior of the mice to ensure that there is no panic swimming. The PhCH group performed the 21-day swimming training: started with 2 daily sessions of 15 min, and sessions were separated by at least 6 h. The length of each session was then increased by 15 min every 2 days until they lasted 90 min; the program was conducted on 5 days/week, followed by 2 days for rest. The twice daily 90-min swimming sessions were continued for the next 7 days. The protocol thus lasted for a total of 21 days.

procedure of Isoflurane (R510-22-10, RWD, Guangdong, China) inhalation anesthesia was set as: 1.) Induction stage: 3.5% concentration, placed in the induction box for 1–2 min until the inversion reflex disappears; 2.) Maintenance stage: 2.0% concentration, continuous administration via nasal cone; 3.) Gas flow rate: 1 l/min (pure oxygen). The heart rate ranged from 400–500 bpm was considered as appropriate. M-mode images were recorded in the short axis view of the left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic diameter (LVESV), left ventricular ejection fraction (LVEF), interventricular septum (IVS), posterior wall thickness of the left ventricle (LVPW), left ventricular end-diastolic diameter (LVIDd), and left ventricular end-systolic diameter (LVIDs).

Histological examination

After 21 days' training, the mice were humanely sacrificed, and their hearts were harvested for subsequent analysis. The hearts were fixed in 10% formalin solution and processed for paraffin embedding according to standard histological procedures. The paraffin-embedded hearts were then sliced into 5-μm-thick transverse sections at the mid-ventricular

level and stained with hematoxylin, phloxine, and saffron. Additionally, MASSON staining and WGA staining were carried out to assess myocardial fibrosis and myocardial hypertrophy, respectively. These reagents were purchased from Zhuoyi Biotechnology Co., Ltd, Guangxi, China.

RNA isolation, quantification and qualification

After swimming exercise, cardiac tissues were harvested from mice in both the PhCH and control groups. For each sample, total RNA was extracted from the cardiac tissues using a total RNA isolation system (No. M5106, NCM Biotech Co., Ltd., Suzhou, China). The purity of the extracted RNA was evaluated using a NanoDrop™ 2000 spectrophotometer, which measured the absorbance at 260 and 280 nm. The 260/280 ratio was calculated to assess RNA quality, and only samples with a ratio ranging from 1.8 to 2.1 were included for further analysis.

Polymerase chain reaction (PCR)

The RNA was reverse-transcribed into cDNA using the reverse transcription kit (RR092A) from TaKaRa Biotech-

Table 1. Primer sequences of the target gene, miRNA and internal reference gene

mRNA/miRNA	F primer (5'→3')	R primer (5'→3')
IGFBP5	CCCTGCGACGAGAAAGCTC	GCTCTTTTCGTTGAGGCAAACC
miR-17-5p	GCGCAAAGTGCTTACAGTGC	AGTGCAGGGTCCGAGGTATT
18S	TTGACGGAAGGGCACCACCAG	GCACCACCACCCACGGAATCG
U6	CAAATTCGTGAAGCGTTCCAT	AGTGCAGGGTCCGAGGTATT

nology Co., Ltd., Japan. The expression levels of *IGFBP5* and -17-5p were measured by real-time PCR using the PCR analyzer (ABI) set. The specific primers for amplification are detailed in Table 1. A universal miRNA reverse primer system was used. The PCR protocol included an initial denaturation at 95°C for 30 s, followed by 40 cycles of denaturation at 95°C for 5 s and annealing/extension at 60°C for 30 s. A melting curve analysis was conducted over the range of 65–95°C. The expression levels were quantified using the

$2^{-\Delta\Delta C_q}$ method and normalized to 18S for mRNA and U6 for miRNA (Livak et al. 2001). The PCR kit (No. A304-05) and primers were obtained from GenStar Biosolutions Co., Ltd., Beijing, and Sangon Biotech Co., Ltd., Shanghai, China.

Dual-luciferase report assay

In the experiment, the PmirGLO vector was used, and the target fragment was inserted at two restriction sites, *SacI*

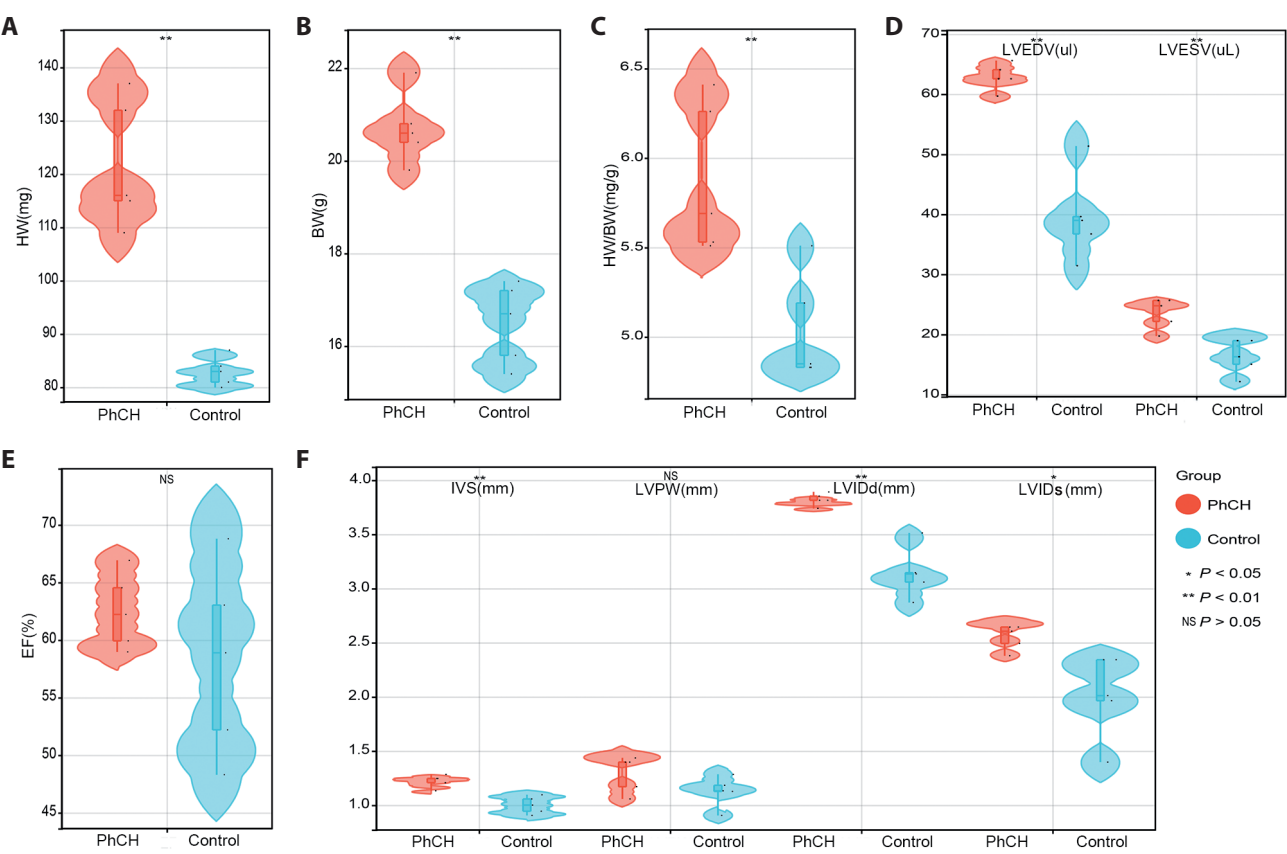


Figure 2. Comparison of weight: HW (A), BW (B), HW/BW (C) and echocardiography: left ventricular volume (D) left ventricular ejection fraction (E), the thicknesses of different parts of the heart (F) between Control group ($n = 5$) and PhCH group ($n = 5$). The horizontal lines in the box represent Mean, the weight of the violin represents the Standard deviation, and the dots represent the measured results of mice. HW, heart weight; BW, body weight; IVS, interventricular septum; LVPW, posterior wall thickness of the left ventricle; LVIDd, left ventricular end-diastolic diameter; LVIDs, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction. Two-side $p < 0.05$ of t -test indicates significance. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, NS $p > 0.05$.



Statistical analysis quantitative data are reported as mean $\pm$ standard deviation (SD). Comparisons of two groups were

HW, heart weight; BW, body weight; IVS, interventricular septum; LVPW, posterior wall thickness of the left ventricle; LVIDd, left ventricular end-diastolic diameter; LVIDs, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction. Two-side $p < 0.05$ of t -test indicates significance. Data are mean $\pm$ SD.

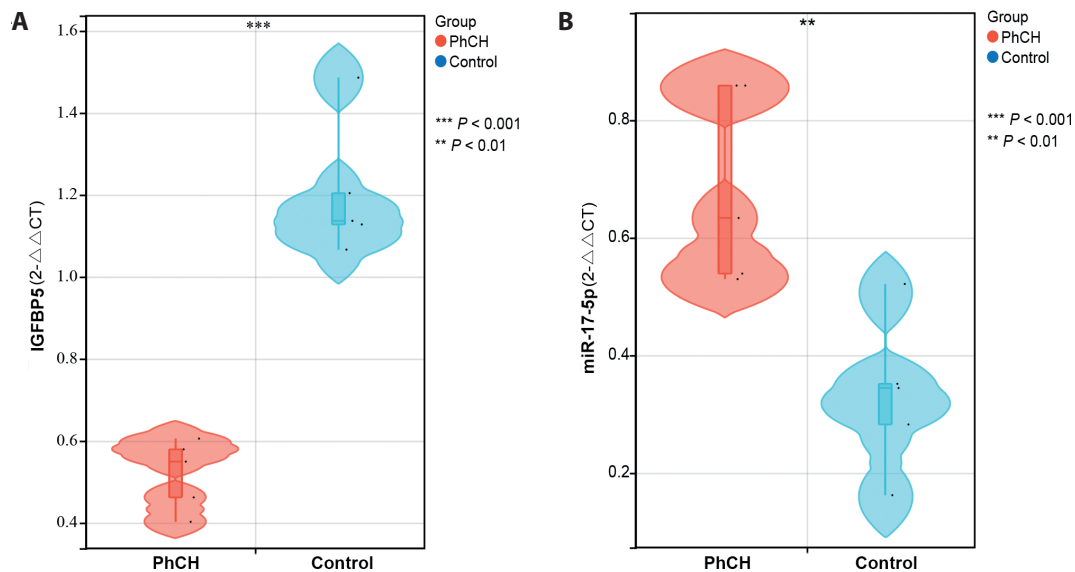


Figure 4. The relative expressions of *IGFBP5* (A) and miR-17-5p (B) in Control group ($n = 5$) and PhCH group ($n = 5$). The horizontal lines in the box represent Mean, the weight of the violin represents the Standard deviation, and the dots represent the measured results of mice. Two-side $p < 0.05$ of t -test indicates significance. ** $p < 0.01$, *** $p < 0.001$.

performed by two-tailed unpaired t -tests. Mann-Whitney U test and Kruskal-Wallis H test was used to compare the expression difference between the two different time-points, and expressions among all time-points in athletes. All analyses were performed with SPSS software (version 22.0, IBM Corporation, Armonk, NY, USA) and two-side $p < 0.05$ was considered as significant.

Results

General parameters and ultrasound changes of the cardiac structure

No animals died during the training period or routine husbandry. TEE showed that, compared with controls, the PhCH mice exhibited significant elevations in HW, BW, HW/BW ratio, IVS, LVIDd, LVIDs, LVEDV, and LVESV ($p < 0.05$ for all, Fig. 2A–E). But, LVPW and LVEF did not differ between the two groups ($p > 0.05$, details in Table 2). The M-type echocardiograms of two groups are shown in Figure 3. It can be observed that mice in the PhCH group got a significant thickening of IVS and an increase in cardiac cavity volume.

The expression levels of *IGFBP5* and miR-17-5p in mice, and their targeted binding

The *IGFBP5* mRNA was notably lower ($p < 0.001$, Fig. 4A), whereas miR-17-5p was higher in the PhCH group than in controls ($p < 0.001$, Fig. 4B).

After co-transfection of the reporter plasmid into 293T cells, the relative expression value of the *IGFBP5* wild-type luciferase reporter gene showed a significant difference compared with the NC group ($p < 0.05$), indicating that miR-17-5p could regulate *IGFBP5*-WT in this experiment. In addition, there was no significant difference between the *IGFBP5* mutant type and the NC group ($p > 0.05$, Fig. 5), indicating that miR-17-5p exerts regulatory effects by binding to the predictive sites of *IGFBP5*-WT.

Histological changes

The naked eye observations of the hearts *in vitro* of PhCH group were significantly larger than those in control group (Fig. 6A). Under WGA staining, it was observed that the cardiomyocytes of mice in PhCH group were significantly enlarged (Fig. 6B,C), while MASSON staining showed that myocardial fibrosis did not increase in PhCH group compared with control group (Fig. 6D,E). This indicates that PhCH training successfully induces the formation of PhCH but not PaCH.

The expression levels of *IGFBP5* in athletes

The expression levels of *IGFBP5* during different time-sets are shown in Figure 7. During the first exercise, the expression level of *IGFBP5* is highest in T1, while it decreases at the time after ramp test to exhaustion, and then recovers to a higher level in T4. During the second exercise, the expression level of *IGFBP5* is higher in T6, and then recov-

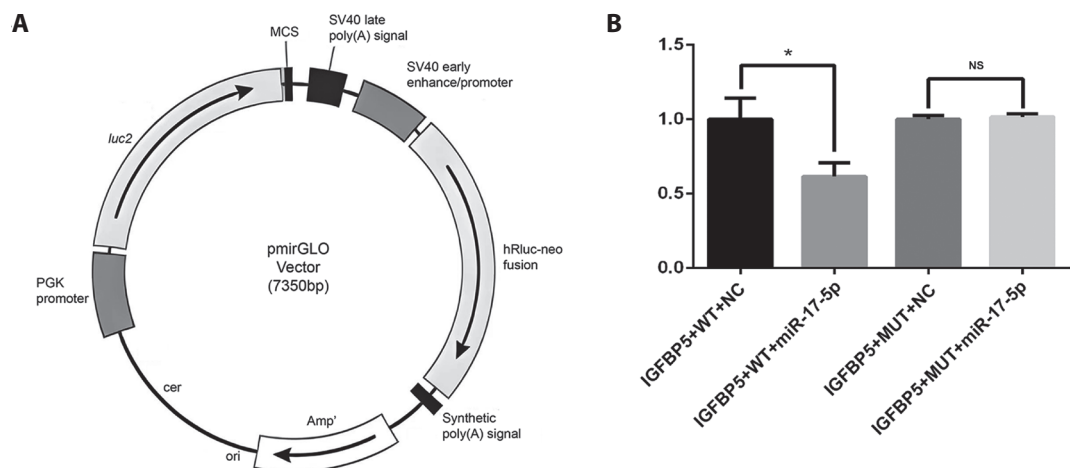


Figure 5. The dual-luciferase assay verified the targeted regulation of miR-17-5p and *IGFBP5*. **A.** PmirGLO vector. **B.** Dual-luciferase report. WT, wild type; MUT, mutant type. * $p < 0.001$, ^{NS} $p > 0.05$.

ers to a lowest level in T7. Though there are no significant differences among different time-sets, the expression level of *IGFBP5* would decrease during exercise.

Discussion

In this study, 21 days of swimming produced a PhCH model. WGA and Masson stains confirmed that the resulting hypertrophy was physiological, not pathological. Dual-luciferase assays then verified that miR-17-5p directly

regulates *IGFBP5*, pointing to both molecules as potential mediators of PhCH.

A recent systematic review found that long-term, exercise-based cardiac rehabilitation decreases all-cause re-hospitalization by 20% and HF admissions by 12%, while simultaneously improving exercise capacity and well-being (Yamamoto et al. 2024). In a randomized, controlled trial (RCT), older obese patients with HF and preserved ejection fraction who combined caloric restriction with aerobic training raised peak VO_2 and quality-of-life scores by nearly 30 ml/min (Brubaker et al. 2023). A multicenter RCT like-

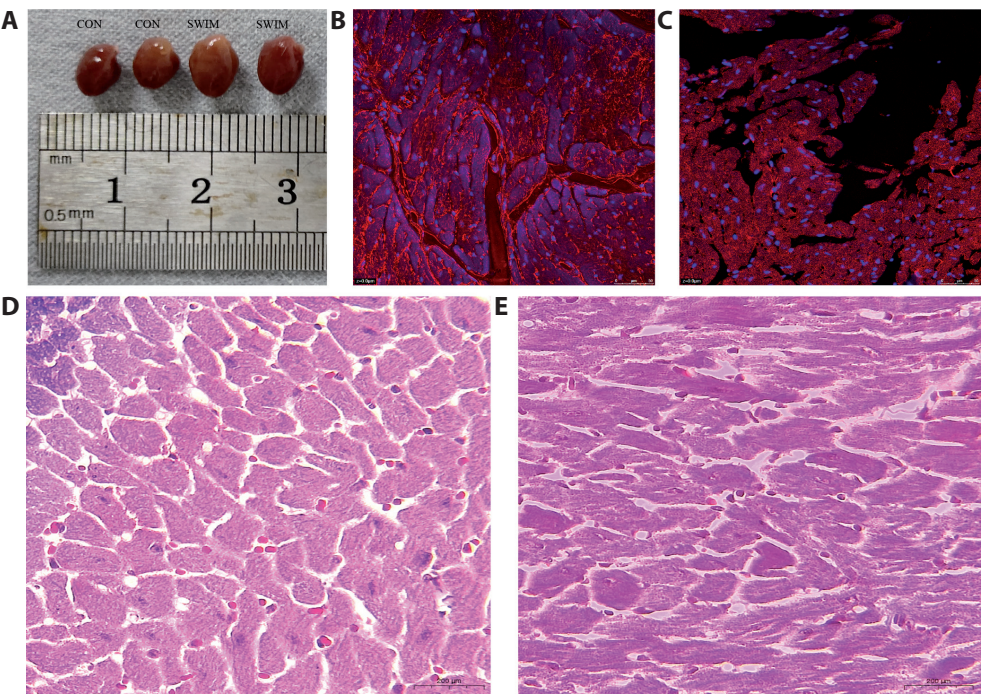


Figure 6. Comparison of myocardial changes between Control group and PhCH group. **A.** Gross cardiac view. WGA staining in PhCH group (**B**) and Control group (**C**) (scale 50 μm). MASSON staining in PhCH group (**D**) and Control group (**E**) (scale 200 μm).

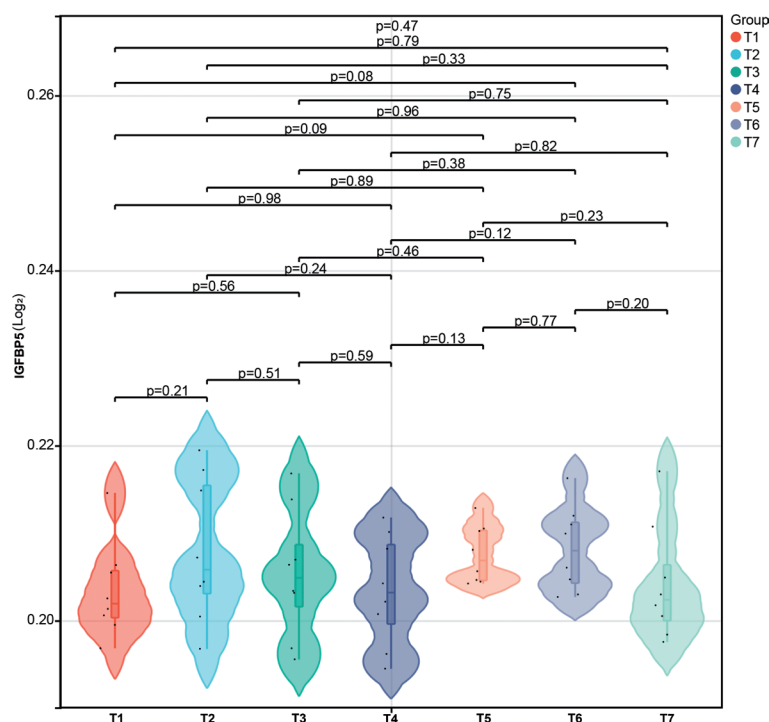


Figure 7. The expression levels of *IGFBP5* during different exercise-points in human athletes' blood samples in GEO dataset GSE46075. The original expression data is count form, and we normalized it through $\log_2$ Count for analysis. The dataset contains the sequence data of the blood samples from eight athletes, taken from the antecubital vein using indwelling catheter before (T1), immediately after ramp test to exhaustion (T2) and after 30 min of recovery (T3). Two weeks later, athletes participated in running at 80% VO_2 peak for 30 min on a treadmill. Blood samples were taken from the antecubital vein using indwelling catheter before (T4), immediately after running at 80% VO_2 peak for 30 min on a treadmill (T5), after 30 min (T6) and 60 min (T7) of recovery. The horizontal lines in the box represent Mean, the weight of the violin represents the Standard deviation, and the dots represent the measured results of expressions. Mann-Whitney U test and Kruskal-Wallis H test were used to compare the expression difference between the two different time-points, and expressions among all time-points in athletes.

wise reported that physical rehabilitation added 1.5 points to the short physical-performance battery and trimmed all-cause re-hospitalization risk by 7% (Kitzman et al. 2021). These results suggest that appropriate exercise has a good improvement on the prognosis of cardiovascular diseases. In our study, mice subjected to swimming showed marked rises in HW, IVS, LVEDV and LVESV, and unchanged LVEF with larger chambers can be compatible with physiological remodeling under the reported anesthesia and heart rate. Histology revealed no fibrosis, only hypertrophic cardiomyocytes, which is consistent with prior studies and confirm swimming as a reliable inducer of PhCH. This might be effective training that adaptively thickens the myocardium, enabling it to better adapt to stress and facilitating the improvement of cardiac compensatory function and resistance to pathological remodeling, such as reducing apoptosis, mitigating ischemia-reperfusion injury (Wang et al. 2022).

In recent years, the important role of miR-17-5p has garnered increasing attention. Chen et al. (2021) showed that HOTAIR dampens miR-17-5p to activate STAT3 signaling, and that silencing HOTAIR blunts the anti-apoptotic benefit of Propofol in ischemia-reperfused cardiomyocytes. Other studies indicate that miR-17-5p itself suppresses autophagy by targeting STAT3, thereby limiting post-infarct remodeling (Chen et al. 2022a). Elevated miR-17-5p also aggravates ischemic injury after acute myocardial infarction via Tsg101, an effect reversed by anti-miR-17-5p treatment (Zhao et al. 2021). Xu et al. (2021) found that miR-17-5p can inhibit

Mfn2 expression, activates the PI3K/AKT/mTOR pathway and suppresses autophagy to promote cardiac hypertrophy (Xu et al. 2021). In addition, a meta-analysis reported that miR-17-5p showed slight association with HF incidence [HR = 0.84 (0.72–0.98)], and there is racial difference of the miR-17-5p expression (Wakabayashi et al. 2020; Parvan et al. 2025). These observations indicate a multifaceted role for miR-17-5p in pathological myocardial hypertrophy and prognosis, but its behavior in physiological hypertrophy remains unexamined. Our swimming model revealed a clear increasing in miR-17-5p, implying that the elevated miR-17-5p may be non-specific for myocardial hypertrophy, that is, its expression trend in PaCH and PhCH may be in the same direction, but whether the hypertrophy is physiological or pathological is not directly regulated by miR-17-5p.

Previous studies depict *IGFBP5* as a driver of mitochondrial injury, calcium imbalance, fibroblast-to-myofibroblast transition, cardiomyocyte apoptosis and, ultimately, systolic failure-placing it at the center of pathological cardiac remodeling (Tuersuntuoheti et al. 2024; Zhao et al. 2024; Zhu et al. 2024b). Serum *IGFBP5* is also elevated in coronary artery disease, where it partners with *NKX2.5* to inhibit transcriptional activity and serves as a predictor of major adverse cardiac events (Lai et al. 2020; Zhu et al. 2024a). These observations suggest a potential association between high *IGFBP5* levels and PaCH. However, our swimming model shows the opposite pattern: increased miR-17-5p coincides with decreased *IGFBP5*, and the dual-luciferase

assay confirms direct targeting of the *IGFBP5* 3'-UTR by miR-17-5p. Thus, the specific microRNA-target pair appears to operate in opposite directions during physiological versus pathological hypertrophy, underscoring a context-dependent switch in their regulatory relationship. Thus, it might suggest that the regulation of *IGFBP5* by miR-17-5p may mediate the myocardial hypertrophy towards physiological rather than pathological hypertrophy.

There are several limitations of our study. First, we did not manipulate miR-17-5p levels to detect the direct effect on *IGFBP5* expression. Second, we did not explore whether the same regulatory mechanism is present in a PaCH model. Finally, due to budget constraints, our research did not include validation with a larger sample size, which diminishes the credibility of our findings. Nevertheless, investigations using PCR, histological analysis, dual-luciferase assays, and public databases have provided new insights into the study of PhCH. We intend to explore the underlying mechanisms in both PaCH and PhCH in future studies, supported by robust findings.

Conclusions

The reduction of *IGFBP5* while elevation of miR-17-5p is associated with exercise-induced PhCH, showing a targeted regulatory relationship, and suggesting their potential value in the intervention of exercise-induced PhCH for PaCH and heart failure.

Ethics approval statement. This study was approved by the Ethics Committee of The Second Affiliated Hospital of Guangxi Medical University (ID: KY-0128).

Data availability statement. The data of this study can be obtained from the corresponding author.

Conflict of interests. The authors declare no conflict of interest.

Acknowledgments. We express our gratitude to all study participants of the Experimental Animal Center of Guangxi Medical University.

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Received: September 21, 2025

Final version accepted: January 9, 2026