Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2025**; 30(2): 26268
https://doi.org/10.31083/FBL26268

Original Research

Stellate Ganglionectomy Attenuates Pressure Overload-Induced Cardiac Hypertrophy and Dysfunction

Hui Yan[1,†], Xiujun Li[2,†], Beilei Liu[2], Bin Wu[2], Changgui Chen[1], Liqun He[1,*], Gang Wu[3,*]

[1]Department of Pharmacy, Wuhan No.1 Hospital, 430022 Wuhan, Hubei, China
[2]Department of Cardiology, Hubei Provincial Hospital of Traditional Chinese Medicine, Affiliated Hospital of Hubei University of Chinese Medicine, 431799 Wuhan, Hubei, China
[3]Department of Cardiology, Hubei Key Laboratory of Cardiology, Renmin Hospital of Wuhan University, Cardiovascular Research Institute, Wuhan University, 430060 Wuhan, Hubei, China
*Correspondence: liqunhe0902@163.com (Liqun He); gangwu@whu.edu.cn (Gang Wu)
[†]These authors contributed equally.
Academic Editor: Ioanna-Katerina Aggeli
Submitted: 25 August 2024 Revised: 28 October 2024 Accepted: 10 December 2024 Published: 19 February 2025

Abstract

Background: Enhanced cardiac sympathetic activity contributes to chronic heart failure (CHF). Interventions targeting the stellate ganglion (SG) can reduce this activity, potentially slowing the progression of cardiovascular diseases. This study examined the effects and mechanisms of stellate ganglionectomy on myocardial hypertrophy and cardiac dysfunction caused by pressure overload. **Methods**: A rat model of pressure overload was created using abdominal aortic constriction. Four groups were studied: the sham surgery, abdominal aortic coarctation (AB), aortic constriction plus left stellate ganglionectomy (LSG), and aortic constriction plus right stellate ganglionectomy (RSG) groups. Cardiac function was assessed via echocardiography, and myocardial hypertrophy and fibrosis were evaluated using hematoxylin-eosin staining (H&E) and Masson staining. Serum atrial natriuretic peptides (ANP) and norepinephrine (NE) levels were measured using enzyme linked immunosorbent assay (ELISA), and the levels of the molecular markers tyrosine hydroxylase (TH) and growth-associated protein-43 (GAP43) were analyzed using Western blotting and PCR. Calcium calmodulin dependent protein kinase II (CaMKII) and phosphorylated Ryanodine Receptor 2 (p-RyR2) expression were also investigated. **Results**: Stellate ganglionectomy significantly reduced myocardial hypertrophy and improved cardiac function, as indicated by decreased left ventricular posterior wall thickness (LVPWD) ($p < 0.01$), left ventricular end-diastolic diameter (LVEDD) and volume ($p < 0.001$), left ventricular end-diastolic volume (LVEDV) ($p < 0.001$), increased left ventricular ejection fraction (LVEF) ($p < 0.001$) and left ventricular fractional shortening (LVFS) ($p < 0.001$). Histological analysis confirmed reduced myocardial dilation. Molecular analysis revealed decreased CaMKII/RyR2 signaling ($p < 0.001$) and lower NE levels ($p < 0.01$), suggesting reduced neurohormonal stress. **Conclusions**: Stellate ganglionectomy alleviates hypertrophy and cardiac dysfunction caused by pressure overload, likely through inhibition of the CaMKII/RyR2 pathway, underscoring its potential as a therapeutic approach.

Keywords: stellate ganglionectomy; cardiac hypertrophy; CaMKII; p-RYR2

1. Introduction

Myocardial hypertrophy is caused by increased cardiac afterload, such as hypertension, aortic stenosis, and heart valve disease [1,2]. Long-term excessive cardiac afterload causes irreversible cardiac hypertrophy and dysfunction, even heart failure and cardiac death [3]. The pathophysiological mechanism of myocardial hypertrophy caused by pressure overload is very complex, among which dysfunction of the autonomic nervous system, especially overactivation of the sympathetic nervous system, is an important factor [4]. Although appropriate sympathetic activation can enhance myocardial contractility, it can increase heart rate and cardiac ejection function by promoting the release of norepinephrine (NE) to improve cardiac function over a period of time; moreover, it can lead to severe myocardial hypertrophy and cardiac dysfunction, ultimately leading to heart failure [5,6].

The stellate ganglion (SG), also known as the cervical thoracic sympathetic ganglion, is an important component of the distal sympathetic nervous system of the heart [7]. The sympathetic ganglia can innervate the ipsilateral eyelids, dilated pupils, and sweat glands while regulating the activity of the heart and blood vessels. Interventions such as resection, block, and ablation of the stellate ganglion can regulate cardiac sympathetic excitability and effectively prevent cardiovascular diseases [8]. Previous studies have shown that bilateral stellate ganglion blockade significantly reduces the burden of ventricular tachycardia or ventricular fibrillation in patients with refractory ventricular tachycardia or ventricular fibrillation [9]; moreover, it has similar therapeutic effects on ventricular arrhythmia subtypes (monomorphic and polymorphic ventricular arrhythmias) and the etiology of cardiomyopathy [10]. Another study revealed that left stellate ganglion ab-

lation can inhibit the occurrence of ventricular arrhythmias after acute stroke by downregulating catecholamine levels in plasma and preventing macrophage activation in the myocardium [11]. Similarly, research has shown that stellate ganglion stimulation facilitates atrial fibrillation (AF) induction and aggravates electrical remodeling in the atrium and pulmonary vein. Unilateral stellate ganglionectomy reduces the incidence of atrial fibrillation by inhibiting sympathetic nerve activation [12]. However, there is no relevant research revealing the impact of stellate ganglionectomy on cardiac sympathetic nerve activation or on pressure overload-related myocardial hypertrophy and cardiac dysfunction.

As an important calcium-binding protein, calmodulin (CaM) is composed of four EF-hand calcium (Ca)-binding motifs and can regulate various cellular functions. In cardiomyocytes, CaM plays a crucial role as a regulator of ryanodine Receptor 2 (RyR2) to control the flow of Ca between intracellular stores. RyR2, a member of the homologous tetramer Ca^{2+} release channel family, is a Ca^{2+} release channel on the cardiac sarcoplasmic reticulum membrane and is expressed mainly in the myocardium [13]. Studies have demonstrated that CaM-RyR2 interactions play a key role in various heart disorders [14]. For example, Søndergaard MT *et al*. [15] revealed that the aberrant regulation of RyR2 is a common reason that CaM mutations cause catecholaminergic polymorphic ventricular tachycardia (CPVT) and long QT syndrome (LQTS) arrhythmias, and Lv T *et al*. [16] demonstrated that CaM mutations are also an underlying mechanism for CPVT.

Additionally, the impaired binding of CaM and RyR2 has been observed in various heart failure models. However, it is unclear whether stellate ganglion intervention can reduce the expression of calcium calmodulin dependent protein kinase II (CaMKII) and the phosphorylation of RyR2 in heart failure. Based on the above issues, this study provides a detailed understanding of the effects of stellate ganglionectomy on pressure overload-induced myocardial hypertrophy and its possible molecular mechanisms.

2.Method

2.1 Animal Preparation

Male Sprague-Dawley rats (weighing 200–230 g, 6-week-old) were provided by the Animal Center of the People's Hospital of Wuhan University (animal certificate number: 00270753), and they were housed at the Animal Experiment Center of Renmin Hospital of Wuhan University with a controlled room temperature and free access to food and water under a natural day/night cycle. This study strictly follows the "Guidelines for Animal Protection and Use" formulated by Wuhan University. All animal experiments were approved by the Experimental Animal Ethics Committee of the Renmin Hospital of Wuhan University (Number: 20230901B), and performed in accordance with the Guidelines for the Ethical Review of Laboratory Animal Welfare and was granted on September 4, 2023. The rats were randomly assigned to one of four experimental groups using a random number table: a sham surgery control group (Sham), an abdominal aortic coarctation group (AB), a left stellate ganglionectomy group (LSG), and a right stellate ganglionectomy group (RSG). The AB group underwent isolated abdominal aortic constriction. The LSG group consisted of rats that received a left stellate ganglionectomy combined with abdominal aortic constriction. Similarly, the RSG group included rats that underwent a right stellate ganglionectomy along with the abdominal aortic constriction. There were 5 rats in each group, a total of 20 rats. The discrepancy between the initial number of rats and those ultimately included in the statistical analysis stems from technical difficulties encountered during surgical procedures. To ensure the robust establishment of the experimental model, we supplemented the rats. During the experiment, there were no abnormal deaths of rats, and all rats survived normally until the end of the experiment. At the termination of the experiment, the rats were humanely euthanized using Carbon dioxide (CO_2) inhalation (the CO_2 concentration elevated by 10% to 30% of the chamber volume per minute, continuing this incremental rise until the rodents lose consciousness and ultimately reach a state of euthanized repose).

2.2 Construction Cardiac Pressure Overload Model of Rats Using Abdominal Aortic Coarctation Group (AB) Method

The surgical procedures were performed based on previously published methodologies [17]. Specifically, the rats were anesthetized following a standardized protocol via an intraperitoneal (IP) injection of 3% sodium pentobarbital at a dose of 50 mg/kg [18]. After skin preparation and disinfection, cut the skin, fascia, muscles, and parietal peritoneum longitudinally along the midline of the abdomen to expose the internal organs. Find the abdominal aorta, abdominal artery, and right renal artery from the abdominal vein upwards, and then passively separate the abdominal aorta between the abdominal artery and right renal artery. Place the 22-G needle parallel to the separated segment of the abdominal aorta, and ligate them. Then, carefully remove the needle to cause partial stenosis of the abdominal aorta, and restore the intestinal canal to its normal position, suturing the muscles, fascia, and skin. After surgery, 10,000 units of penicillin were administered to resist infection.

On the 2nd day after surgery, the rats gradually developed symptoms such as accelerated breathing and heartbeat, fear of cold fatigue, decreased appetite, cyanosis, and subcutaneous edema, indicating that the model was constructed successfully.

2.3 Record Rat Blood Pressure and Heart Rate

A physiological recorder was used to record the electrocardiogram of the rats after successful ligation of the ab-

dominal aorta. Preparing and disinfecting the middle of the neck, and blunt separation of subcutaneous tissue, fascia, and muscle on one side. Find the common carotid artery next to the trachea, and separate the surrounding nerves and blood vessels using a glass dividing needle carefully to get about 2 cm common carotid artery. Cross two 7-0 sutures below the common carotid artery for backup. Before operation, inject 0.3% heparin saline injection into the catheter and pressure transducer until there are no bubbles. Then ligate the distal end of common carotid artery with sutures and clamp the proximal end with arterial clamps to temporarily block this segment of blood vessel. Use ophthalmic scissors to make a small oblique incision on the vascular wall near the ligation at the distal end. Then, insert the prepared catheter into the blood vessel along the incision, after releasing the arterial clamp, push the catheter about 1cm further towards the proximal end to see the blood pressure waveform of the artery. Finally, use the remaining suture to ligate and fix the catheter. After the animal stabilizes for about 5 minutes, data such as heart rate, blood pressure, and electrocardiogram can be recorded.

2.4 Stellate Ganglionectomy

The stellate ganglionectomy was performed 30 minutes after abdominal aortic constriction surgery. The rats were fixed in a supine position and passively separated subcutaneous tissue, fascia, and muscle at the midpoint incision of the neck. The common carotid artery located at the inner edge of the sternocleidomastoid muscle and near the trachea. The superior cervical ganglia located on the dorsal side of the bifurcation of the common carotid artery. The stellate ganglion was found along the common carotid artery towards the proximal end, and it was severed 3 mm below the superior cervical ganglion. When the rat shows symptoms of Horner's syndrome such as enophthalmos, pupil narrowing, and ptosis within 5 minutes, it indicates that the stellate ganglionectomy has been successfully completed. Due to the difficulty in survival of rats with both left and right simultaneous stellate ganglionectomy, this experiment will not study on bilateral stellate ganglionectomy.

2.5 Echocardiography

Echocardiography was performed before and 10 weeks after SG resection for detecting cardiac function using a Mylab30CV ultrasound system (Biosound Esaote, Genoa, Italy) with a 15-MHz transducer. Surgery was performed under isoflurane anesthesia (5% for induction and 1–2% during surgery) (R500, RWD, Shenzhen, China). The ventricular interventricular septal defect (IVSD, mm), left ventricular posterior wall thickness (LVPWD, mm), left ventricular end diastolic diameter and volume (LVEDD, mm), left ventricular end diastolic volume (LVEDV, mL), left ventricular ejection fraction (LVEF, %), and left ventricular short axis shortening fraction (LVFS, %) were measured using animal cardiac ultrasound in three groups of rats. Detect at least 3 or more cardiac cycles for all parameters. The results were analyzed with the Chart 5.0 software (Applied Biosystems, Danvers, MA, USA).

2.6 Western Blot Analysis

Obtain heart tissue and to homogenize the tissue. Before operation, add sufficient tissue protein extraction reagents and an appropriate amount of protease inhibitors in advance. The thoroughly lysed tissue was centrifuged at 2000 rpm for 5 minutes, carefully collect the centrifuge supernatant as a total protein solution. Firstly, prepare a sufficient amount of BCA working solution, and add a certain concentration of sample and 25 µL standard samples to the micropores respectively. Then add 200 µL BCA working solution in sequence, mix thoroughly, and incubate at 37 °C for 30 minutes. Next, calculate the protein concentration and calculate the total protein (each sample to be 40 µg). Add protein loading buffer to the protein sample and soak in boiling water for 5 minutes. After preparing separation gel and concentration gel, sample loading and electrophoresis are carried out in sequence. After electrophoresis, membrane transfer is carried out. Rinse the PVDF film and place it in a sealing solution. Shake the bed for 2 hours and remove it in TBST for 3 times × 5 minutes. Incubate overnight in a shaking bed at 4 °C. Then, the membranes were incubated with primary antibodies against atrial natriuretic peptides (ANP) (1:500, PL0403306, PL Laboratories, Beijing, China), growth-associated protein-43 (GAP43) (1:500, 16971-1-AP, proteintech, Rosemont, IL, USA), Tyrosine Hydroxylase (TH) (1:500, 250905, Abbiotec, Danvers, MA, USA), CaMKII (1:5000, BW6769, Abcam, Cambridge, MA, USA), Ryanodine Receptor 2 (RyR2, 1:500, orb794741, Biorbyt, UK), phosphorylated (p) -RyR2 (1:500, BS4358, Bioworld, Danvers, MA ,USA). GAPDH (1:500; ab181602; Abcam, UK) was utilized as an internal reference control. After the completion of the first antibody incubation, wash the membrane 3 times with TBST × 5 minutes, HRP-linked anti-mouse (1:2000; Applygen, Danvers, MA, USA) or anti-rabbit IgG (1:2000; Applygen, Danvers, MA, USA) was used as the secondary antibody, incubate at room temperature for 1 hour, and perform chemiluminescence detection. Finally, the AlphaEaseFC 3.0 (https://www.genomeweb.com/arrays/alphaeasefc) was used to analyze and calculate the optical density of the target band.

2.7 Quantitative Reverse Transcription–polymerase Chain Reaction Analysis (RT-qPCR)

The expression of ANP, growth-associated protein-43 (GAP43), TH, CaMKII, PYR2 in myocardium was measured by RT-qPCR. Total RNA was isolated from ventricular samples with Tripure Extraction Reagent (orb782896, Biorbyt, Danvers, MA, USA) according to the manufacturer's protocol. cDNA was synthesized using EntiLink™ 1st Strand cDNA Synthesis Kit (EQ003, Yeasen, Shanghai, China). Real-time fluorescent quantitative PCR was performed on the StepOne real-time PCR instrument

(4376374, Thermo Fisher, Waltham, MA, USA), and each sample was made into three duplications using EnTurbo™ SYBR Green PCR SuperMix kit (EQ001, Biorbyt, Danvers, MA, USA). *GAPDH* was used as the internal control (Table 1), and all reactions were performed in triplicate. Relative RNA expression was calculated using the $2^{-\Delta\Delta Ct}$ method [15].

Table 1. RT-qPCR primer sequences.

Gene	Primer sequence
Anp (rat)	F: 5′- CTCCGATAGATCTGCCCTCTTGAA -3′
	R: 5′- GTACCGGAAGCTGTTGCAGCCTA -3′
CamkII (rat)	F: 5′- TGGCATAGTTCACAGGGACC -3′
	R: 5′- TGCCAGCAAAACCAAACCAC -3′
RyR2 (rat)	F: 5′- GTGAAGCAGCCCAAGGGTAT -3′
	R: 5′- TGGACTGTTCTCCGCTGTTC -3′
Gapdh (rat)	F: 5′- CTCAGTTGCTGAGGAGTCCC -3′
	R: 5′- ATTCGAGAGAAGGGAGGGCT -3′

Note: F: Forward; R: Reverse; Anp, atrial natriuretic peptide; CamkII, calcium/calmodulin-dependent kinase II; RyR2, ryanodine receptor type 2.

2.8 Enzyme Linked Immunosorbent Assay (ELISA)

The concentration of brain natriuretic peptide (BNP) and norepinephrine (NE) generated from rat serum was detected by ELISA. The BNP concentration in the rat serum (n = 3) in validation cohort was determined by the ELISA BNP Immunoassay (RAB0386-1KT, Sigma, MO, USA) according to the manufacturer's instructions. The NE levels from rat serum (n = 3) were determined using NA/NE (Noradrenaline/Norepinephrine) ELISA Kit (E-EL-0047, Elabscience, Beijing, China) following the manufacturer's instructions.

2.9 Histological Assay

10 weeks after stellate ganglionectomy, rats were first anesthetized with 1.5–2% isoflurane by inhalation firstly, and then were euthanized by cervical dislocation. Take the hearts of rats for pathological examination to observe the degree of myocardial hypertrophy and ventricular remodeling. The heart was fixed in 4% paraformaldehyde buffer (P6148, Sigma, MO, USA) overnight and then transferred to 70% ethanol. Following this, the tissues were embedded in paraffin, sectioned at 30 µm and subjected to hematoxylin-eosin staining (H&E) (PH0516-100, PHYGENE, Fujian, China), Phygene Masson staining (G1340, Solarbio, Beijing, China). H&E staining was performed according to a routine standard operating procedure using a Leica Multistainer (ST5020, Leica, Vizna, Germany). Slides were dewaxed and rehydrated with successive applications of xylene, alcohol 100%, alcohol 70% and tap water. Haematoxylin (Mayer's, Klinipath, Benelux, USA) was applied for 4 minutes followed by a 20 second differentiation in ammonia after which eosin (Eosin Y A+B, Klinipath, Benelux, USA) was applied for 20 seconds. Masson staining was used to examine the myocardial fibrosis of the heart based on the proportion of myocardial collagen fibers.

2.10 Statistical Analysis

Statistical analyses were performed using GraphPad PRISM software v8.4.2 (GraphPad Software Inc, San Diego, CA, USA). As indicated, statistical analysis was performed by calculating mean SEM. Student's *t*-test was used when only two groups were analyzed. For comparisons between multiple groups, homo geneity variance was first tested, and the one-way ANOVA (Tukey's multiple comparisons test) was applied when variance was homogeneous, or non-parametric independent sample *t*-test (the Mann–Whitney test) was used for inhomogeneity. Paired Student's *t*-test or one-way ANOVA was used to analyze the quantitative Western blot as indicated in figure legends. Two-tailed test was used for all *t*-tests, and $p < 0.05$ was considered statistically significant.

3. Results

3.1 Effective Alleviation of Cardiac Symptoms in Chronic Heart Failure Patients Through Stellate Ganglionectomy

Previous study had demonstrated that inhibiting the activity of the stellate ganglia can effectively treat chronic heart failure [8]. Based on this knowledge, we aimed to further investigate the impact of stellate ganglion activity on cardiac function. To test this hypothesis, we developed a rat model of chronic heart failure (Fig. 1A). The successful establishment of the model was confirmed by comparing the mean arterial pressure and heart rate between the rats in the sham surgery group (Sham) and abdominal aortic coarctation group (AB) (Fig. 1B,C). Next, we surgically removed the left (LSG) or right stellate ganglion (RSG) to further investigate their roles in cardiac hypertrophy and chronic heart failure. Surprisingly, we found that resection of either the left (LSG) or right stellate ganglion (RSG) significantly reduced the mean arterial pressure and heart rate in rats compared with those in the AB group (Fig. 1D,E). These findings suggest that surgical removal of the stellate ganglia can effectively alleviate the elevated mean arterial pressure and tachycardia associated with chronic heart failure.

3.2 Stellate Ganglionectomy Significantly Mitigates Cardiac Dysfunction in Chronic Heart Failure Patients

The results of our preliminary experiments demonstrated that stellate ganglionectomy significantly improved abnormal vital signs, such as the mean arterial pressure and heart rate, in rats with chronic heart failure. Chronic overload of mean arterial blood flow and elevated heart rate are known contributors to cardiac overload, leading to heart failure [19]. To investigate the therapeutic potential of stellate ganglionectomy on cardiac function in chronic heart failure patients, we conducted echocardiographic measure-

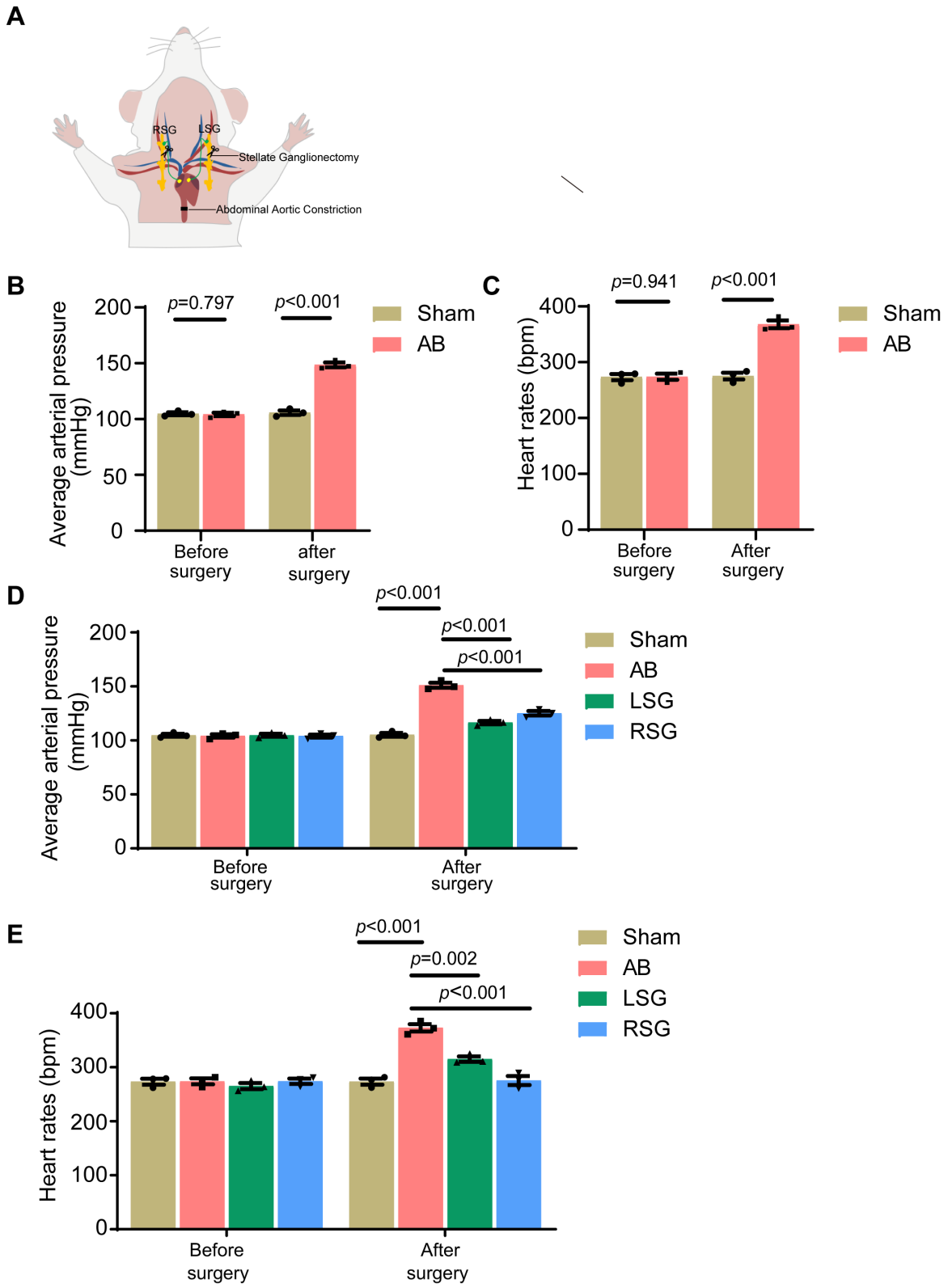

Fig. 1. Effective alleviation of cardiac symptoms in chronic heart failure patients through stellate ganglionectomy. (A) Schematic representation of stellate ganglionectomy. (B) The average arterial pressure of each group was tested before and 10 weeks after stellate ganglionectomy. (C) Heart rates of each group were tested before and 10 weeks after stellate ganglionectomy. (D) The average arterial pressure of each group was tested before and 10 weeks after stellate ganglionectomy. (E) Heart rates of each group were tested before and 10 weeks after stellate ganglionectomy. Sham, sham surgery group; AB, abdominal aortic coarctation group; LSG, left ganglionectomy group; RSG, right ganglionectomy group. Error bars, means ± SEMs (n = 3, each group). *p* values were determined by one-way ANOVA.

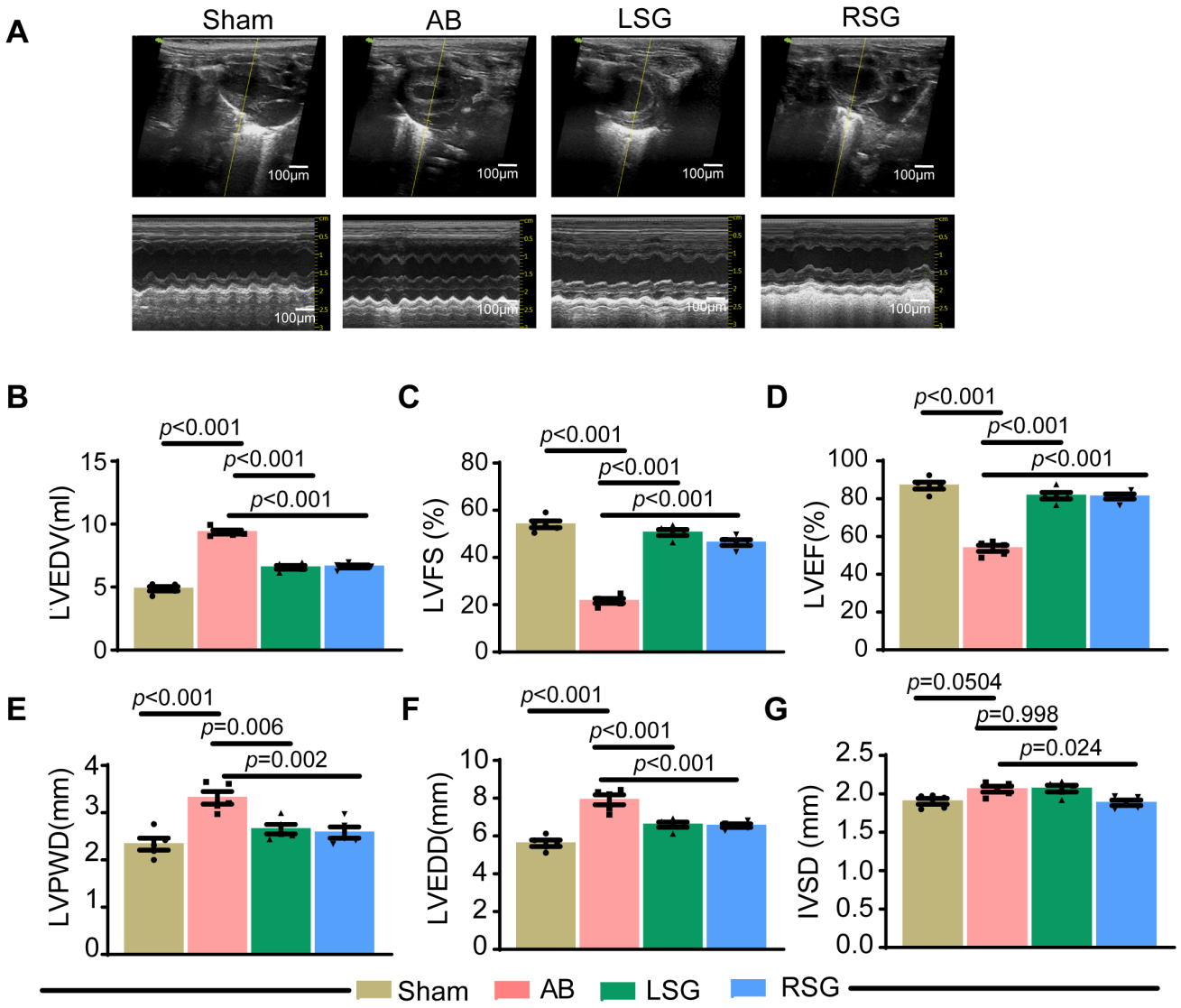

Fig. 2. Stellate ganglionectomy significantly mitigates cardiac dysfunction in chronic heart failure. (A) Representative images of echocardiograms from each group. The scale bars = 100 μm. (B–G) Statistical evaluation of echocardiography data from each group. Left ventricular end-diastolic volume (LVEDV, mL) (B), left ventricular short-axis shortening fraction (LVFS, %) (C), left ventricular ejection fraction (LVEF, %) (D), left ventricular posterior wall thickness (LVPWD, mm) (E), left ventricular end-diastolic diameter and volume (LVEDD, mm) (F), and ventricular interventricular septal defect (IVSD, mm) (G). Sham, sham surgery group; AB, abdominal aortic coarctation group; LSG, left ganglionectomy group; RSG, right ganglionectomy group. Error bars, means ± SEMs (n = 3, each group). *p* values were determined by one-way ANOVA.

ments. We assessed interventricular septal defect (IVSD, mm), left ventricular posterior wall thickness (LVPWD, mm), left ventricular end-diastolic diameter (LVEDD, mm), left ventricular end-diastolic volume (LVEDV, mL), left ventricular ejection fraction (LVEF, %), and left ventricular fractional shortening (LVFS, %), among other parameters, to evaluate postsurgical cardiac function across different groups of rats (Fig. 2A). Our findings indicate that stellate ganglionectomy significantly reduces the LVEDV (mL), LVPWD (mm) and LVEDD (mm) (Fig. 2B,E,F) while significantly increasing the LVFS (%) (Fig. 2C) and LVEF (%) (Fig. 2D). Notably, among the treatments considered, solely RSG exerts a significant influence on the interventricular septal diameter (IVSD) (mm) (Fig. 2G). These results suggest that stellate ganglionectomy effectively mitigates cardiac dysfunction associated with chronic heart failure.

3.3 Stellate Ganglionectomy Reduces Structural Cardiac Lesions and Mitigates Dysfunction in Chronic Heart Failure

In addition to investigating the impact of stellate ganglionectomy on cardiac function in chronic heart failure patients, we aimed to further explore whether this procedure can be used to treat structural lesions associated with chronic heart failure. Research has indicated that sustained mean arterial pressure overload and rapid heart

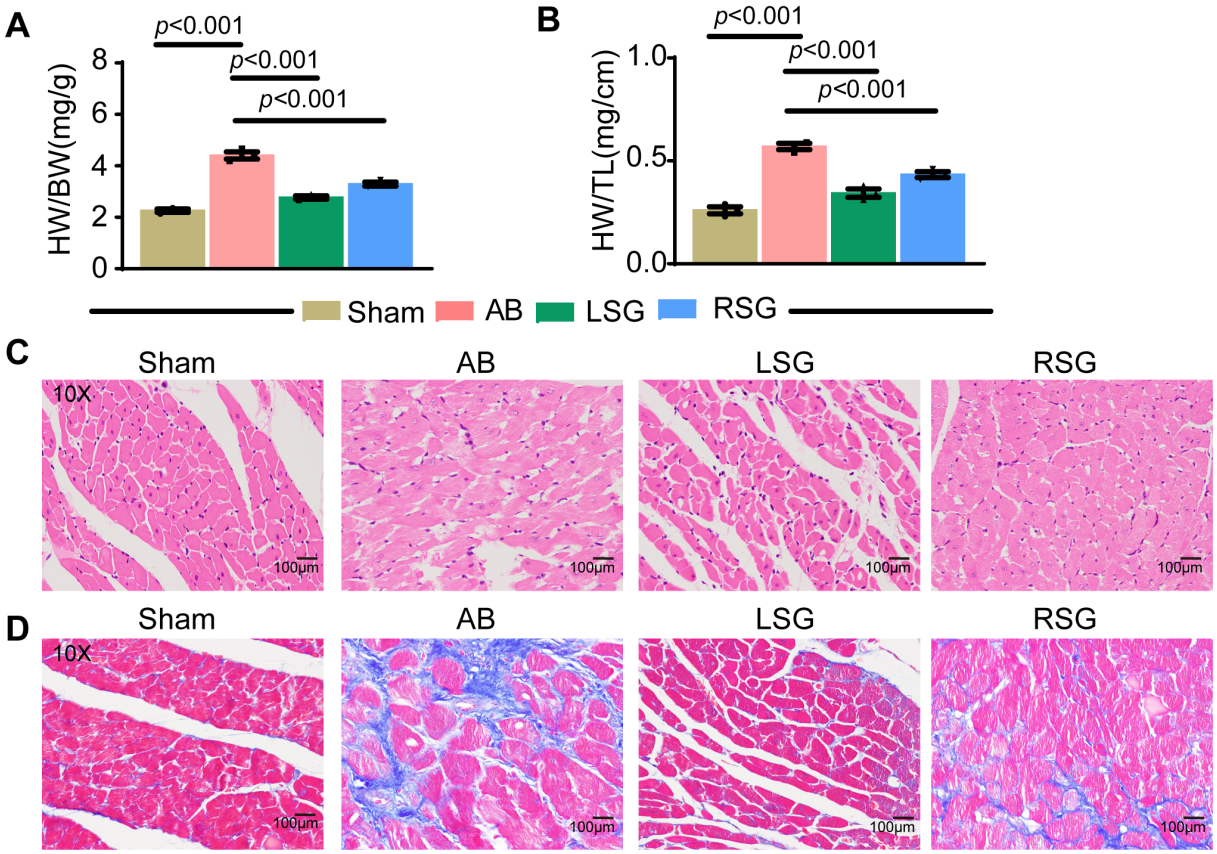

Fig. 3. Stellate ganglionectomy reduces structural cardiac lesions and mitigates dysfunction in chronic heart failure. (A) Statistical evaluation of heart weight-to-body weight (HW/BW) in each group. (B) Statistical evaluation of heart weight to tibia length (HW/TL) in each group. (C) H.&E. Analysis of myocardial fibers in the cardiac tissues of each group. (D) Masson strain analysis of myocardial fibers in the cardiac tissues of each group. Sham, sham surgery group; AB, abdominal aortic coarctation group; LSG, left ganglionectomy group; RSG, right ganglionectomy group. The scale bars = 100 μm for (C) and (D). Error bars, means ± SEMs (n = 3, each group). *p* values were determined by one-way ANOVA.

rate can lead to heart failure, resulting in compensatory cardiac hypertrophy and ultimately chronic heart failure [20]. Therefore, we utilized the heart-to-body weight ratio and heart size-to-calf length ratio as preliminary indicators of organic cardiac dilation. As anticipated, at 10 weeks post surgery, the rats in the AB group presented significant increases in both the heart-to-body weight ratio and heart size-to-calf length ratio compared with those in the sham group (Fig. 3A,B). Notably, stellate ganglionectomy markedly reduced these ratios (Fig. 3A,B). We further employed H&E staining and Masson staining to assess the pathological changes associated with postoperative cardiac hypertrophy. The results demonstrated that the rats in the AB group presented significant pathological dilation of myocardial fibers, whereas stellate ganglionectomy significantly ameliorated this pathological myocardial fiber dilation (Fig. 3C,D). In conclusion, inhibiting stellate ganglion activity not only effectively mitigates cardiac dysfunction caused by chronic heart failure but also fundamentally addresses the structural lesions associated with chronic heart failure.

3.4 Modulation of Neurohormonal Activity by Stellate Ganglionectomy in Chronic Heart Failure

In the early stages of heart failure, a decrease in cardiac output and blood pressure triggers the neurohormonal system, including the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (SNS), as a compensatory mechanism to maintain circulatory homeostasis [21]. The stellate ganglia, formed by the fusion of the 7th cervical and 1st thoracic sympathetic ganglia, serve as postganglionic nerves to regulate cardiac function. Prolonged elevation of mean arterial pressure, which leads to cardiac dysfunction, activates the stellate ganglia to secrete neurotransmitters such as norepinephrine, which in turn activate atrial natriuretic peptide (ANP) to provide stress-induced cardiac protection [22]. To further investigate the molecular mechanisms underlying stellate ganglion activity in the context of myocardial fiber dilation and chronic heart failure, we measured the protein expression levels of GAP43 and TH proteins, which are markers of stellate ganglion activity, using protein immunoblotting. Our results indicated that, compared with those in the

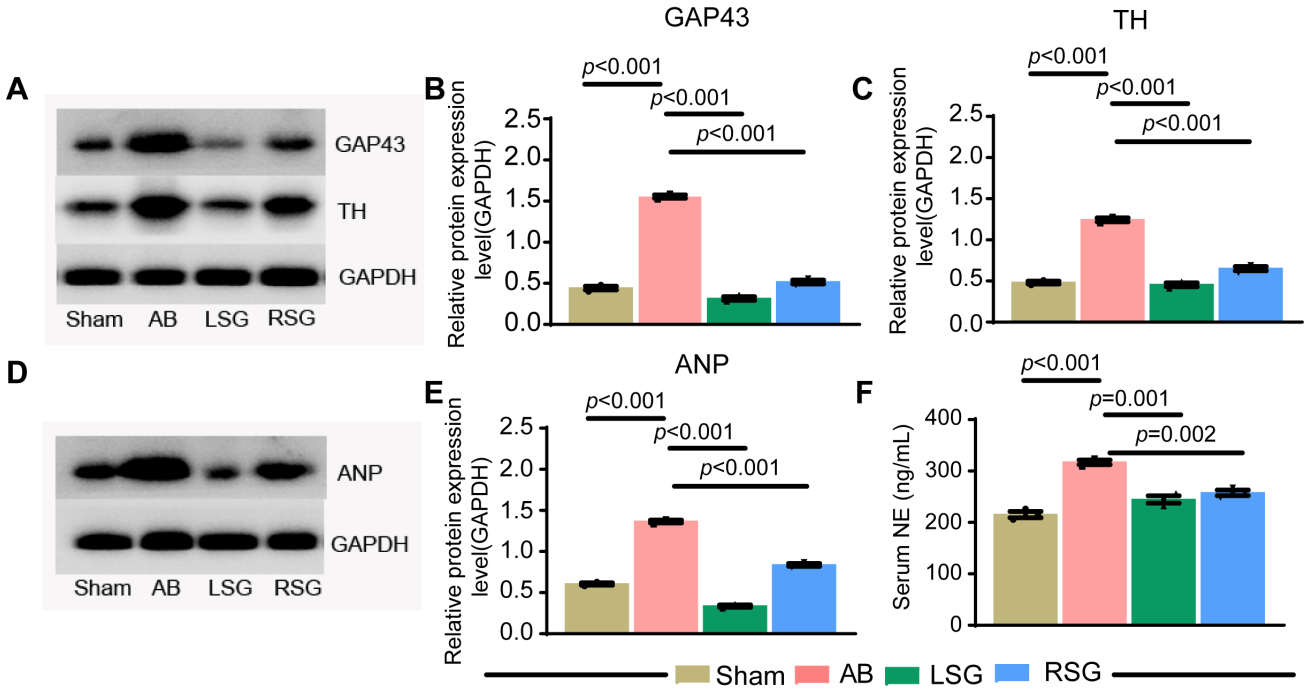

Fig. 4. Modulation of neurohormonal activity by stellate ganglionectomy in chronic heart failure. (A) Western blotting was used to detect the protein expression levels of tyrosine hydroxylase (TH) and growth-associated protein-43 (GAP43) in the cardiac tissues of each group. (B) Statistical analysis of GAP43 expression. (C) Statistical analysis of TH expression. (D) Western blotting was used to detect the protein expression levels of atrial natriuretic peptides (ANP) in the cardiac tissues of each group. (E) Statistical analysis of ANP expression. (F) The concentration of norepinephrine (NE) in serum. Sham, sham surgery group; AB, abdominal aortic coarctation group; LSG, left ganglionectomy group; RSG, right ganglionectomy group. Error bars, mean ± SEM (n = 3, each group). *p* values were determined by one-way ANOVA.

sham group, GAP43 and TH expression levels were significantly elevated in the AB group. Notably, these elevations were significantly reversed following stellate ganglion resection (Fig. 4A–C). Additionally, we quantified plasma norepinephrine levels using ELISA. Compared with that in the sham group (215.2 ± 10.64), norepinephrine secretion was significantly increased in the AB (317.0 ± 4.568) group, and this increase was markedly reduced after stellate ganglionectomy (LSG, 244.6 ± 7.110, RSG, 257.6 ± 5.460) (Fig. 4F). Consistent with these findings, protein immunoblotting revealed that ANP protein levels were significantly elevated in the AB group due to chronic heart failure, and stellate ganglion resection significantly decreased this increase (Fig. 4D,E). Therefore, our study demonstrated that inhibiting stellate ganglion activity effectively reduces norepinephrine secretion and mitigates the depletion of cardiac ANP, highlighting a potential therapeutic target for managing chronic heart failure.

3.5 Stellate Ganglionectomy Reverses Abnormal Calcium Regulation in Chronic Heart Failure (CHF) Patients

Calcium ions play a crucial role in cardiac excitation, with excessive diastolic calcium ion (Ca^{2+}) leakage leading to arrhythmia and heart failure. Previous studies have demonstrated that calcium/calmodulin-dependent kinase II (CaMKII) enhances RyR2-mediated Ca^{2+} leakage through the phosphorylation of RyR2 at Ser2814 [23]. However, the precise mechanism by which hyperactivity of the stellate ganglia results in abnormal calcium loading in cardiomyocytes remains unclear. To address this, we assessed the expression levels of CaMKII and RyR2 in different experimental groups by immunoblotting and RT-qPCR. Our findings indicate that chronic heart failure significantly elevates in total CaMKII protein levels, but has no change in the total of RyR2 (Fig. 5A,B). Importantly, stellate ganglionectomy effectively mitigated these increases, reversing the elevated expression levels of total CaMKII protein and the RyR2 phosphorylation associated with chronic heart failure (Fig. 5C,D).

4. Discussion

Our research provides initial insights into the effectiveness of stellate ganglionectomy in treating chronic heart failure. We developed a model of chronic heart failure through abdominal artery ligation, which led to elevated expression of GAP43, a marker of stellate ganglion activity [24]. These findings suggest that chronic heart failure induces a robust response from the peripheral nervous system. We then surgically removed the left or right stellate ganglion and observed significant improvements in cardiac

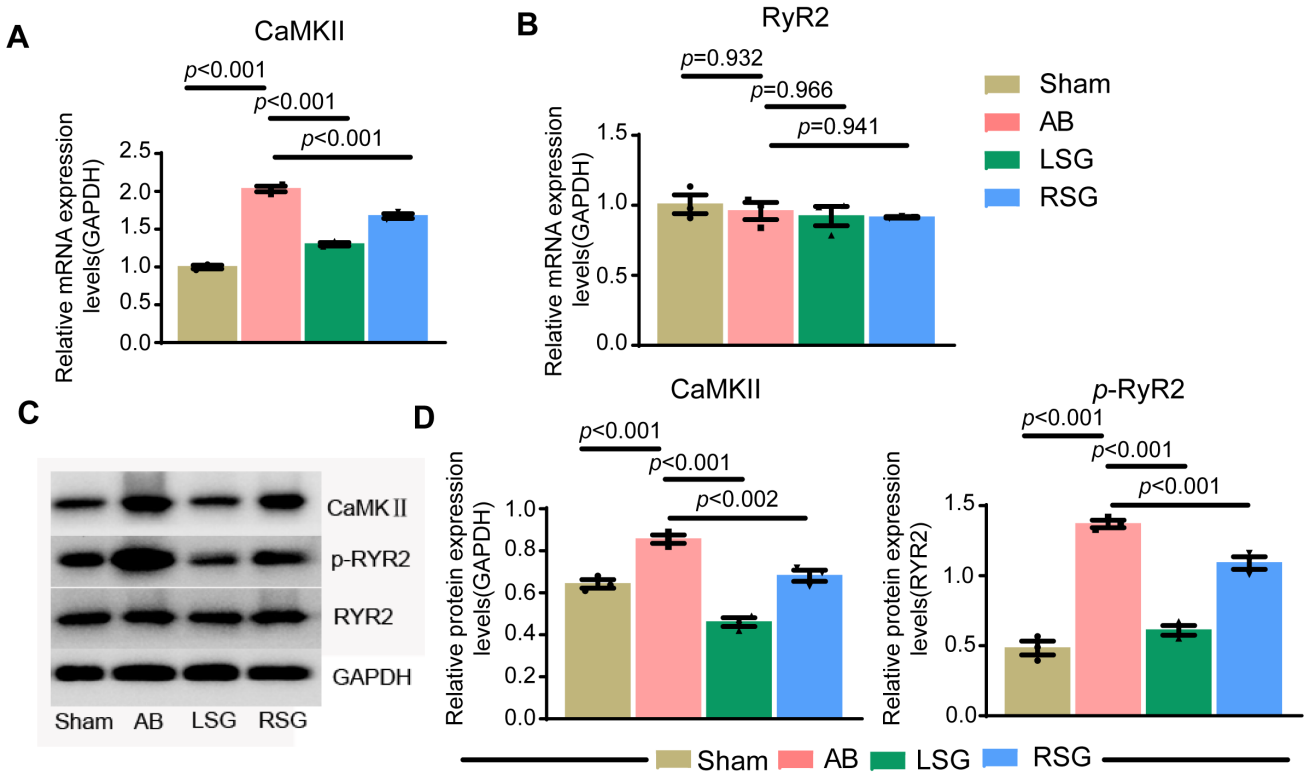

Fig. 5. Stellate ganglionectomy reverses abnormal calcium regulation in chronic heart failure. (A,B) RT-qPCR was used to measure the gene expression levels of calcium/calmodulin-dependent kinase II (CaMKII) and Ryanodine Receptor 2 (RyR2) in the cardiac tissues of each group. (C) Western blotting was used to detect the protein expression levels of CaMKII, phosphorylated RyR2 and total RyR2 in the cardiac tissues of each group. (D) Statistical analysis of CaMKII and phosphorylated RyR2 expression. Sham, sham surgery group; AB, abdominal aortic coarctation group; LSG, left ganglionectomy group; RSG, right ganglionectomy group. Error bars, mean ± SEM. (n = 3, each group). *p* values were determined by one-way ANOVA.

function and structural heart conditions, such as cardiac hypertrophy. Further investigations revealed that stellate ganglionectomy reduces epinephrine secretion, which in turn diminishes the activity of the CaMKII/RyR2 signaling pathway in cardiomyocytes. This alleviation of signaling pathway activity enhances cardiac ejection function and mitigates the symptoms of chronic heart failure. Thus, our study highlights the CaMKII/RyR2 pathway, which is regulated by the stellate ganglion, as a novel target for chronic heart failure therapy, marking a significant advancement in the field.

Cardiac sympathetic overactivation is a key feature of heart failure and primarily contributes to arrhythmias and sudden cardiac death. The stellate ganglion, located at the fusion of the 7th cervical and 1st thoracic sympathetic ganglia, predominantly governs the postganglionic nerves of the cardiac sympathetic nervous system [25]; it regulates heart ejection functions through the release of neurotransmitters such as norepinephrine and neuropeptide Y. Human adrenoceptors are broadly categorized into alpha and beta types, with each type further divided into subtypes: α1 and α2 and β1, β2, and β3 [26]. Predominantly, the regulation of heart functions involves β1 and β2 receptors, with β1 receptors located mainly in the cardiac ventricles, increasing heart rate, conduction speed, and myocardial contractility. The β2 receptor, which is found in smooth muscle and glandular cells as well as ventricular myocytes, shows heightened responsiveness to catecholamines in chronic heart failure conditions [27]. Norepinephrine, released from stellate ganglion nerve endings, binds to these β-adrenergic receptors, influencing cardiac electrophysiology and contractility, which affects heart rate, conduction, and myocardial contraction, thereby regulating cardiac output [28]. Surgical removal of the stellate ganglion can thus be an effective method to mitigate the excessive norepinephrine release that leads to increased cardiac blood volume in heart failure patients. For this reason, successful cases of the use of cardiac sympathetic denervation (CSD) to treat refractory ventricular tachycardia (VT) have been reported in clinical practice. The surgical results indicate that the above methods can significantly reduce VT recurrence and defibrillation shock in patients with ischemic and nonischemic cardiomyopathy [29]. These findings indicate that the stellate ganglion plays a very important regulatory role in the activation of the cardiac sympathetic nervous system. In addition, researchers have reported that clearing macrophages in ganglia can significantly alleviate CHF-induced cardiac sympathetic overactivation and ventricular

arrhythmia. Therefore, we found through our experiments that removing the stellate nerve can effectively reduce the release of adrenaline from the sympathetic nervous system, thereby reducing excessive activation of myocardial cells and alleviating the disease progression of chronic heart failure.

While the current study has provided significant insights into the efficacy of stellate ganglionectomy in mitigating pressure overload-induced cardiac hypertrophy and dysfunction, several limitations warrant critical evaluation. Primarily, our experimental model was based on a rodent system, which may not fully replicate the complex pathophysiological nuances of human chronic heart failure. Therefore, future research should aim to validate these findings in more advanced animal models or, ideally, through clinical trials, to better assess the translational potential of this therapeutic intervention. Additionally, although the CRISPR-Cas9-based lineage tracking platform has proven effective in delineating cellular lineages, integrating this technology with *in vivo* imaging techniques could enhance real-time monitoring of cellular dynamics. This integration would provide a more comprehensive understanding of the underlying biological mechanisms, thereby enabling researchers to thoroughly examine both the immediate and long-term effects of stellate ganglionectomy on myocardial cells and their interactions within the cardiac microenvironment.

The CaMKII (calcium/calmodulin-dependent protein kinase II) and RyR2 (type 2 ryanodine receptor) signaling pathways have garnered significant attention for their roles in chronic heart failure. CaMKII is crucial in regulating calcium ion flow within cardiomyocytes, a fundamental process for myocardial contraction and relaxation. RyR2 serves as a vital calcium channel in cardiomyocytes, where its activation triggers calcium ion release from the sarcoplasmic reticulum, influencing myocardial contractility [30]. In chronic heart failure, aberrant activation of these proteins may disrupt calcium homeostasis in cardiomyocytes, potentially causing myocardial dysfunction and structural changes in the heart. Overactivation of CaMKII can hasten RyR2 opening, increasing myocardial calcium leakage and leading to hyperexcitability and arrhythmias in cardiomyocytes. Research indicates that inhibiting CaMKII activity can diminish RyR2 overactivation, helping to reestablish calcium balance in cardiomyocytes and enhance cardiac function [31]. Our experimental findings suggest that stellate ganglionectomy effectively reduces epinephrine secretion, subsequently suppressing CaMKII/RyR2 pathway activity in cardiomyocytes. Thus, therapeutic strategies targeting the CaMKII/RyR2 signaling pathway may offer promising options for treating chronic heart failure.

While this study underscores the beneficial effects of stellate ganglion resection on cardiac hypertrophy and function induced by pressure overload, several limitations merit attention. Primarily, the research was confined to rat models, limiting the direct applicability of the findings to human subjects; thus, clinical trials are essential for further validation. Additionally, the study did not examine the long-term effects of stellate ganglionectomy, leaving the sustained impact on cardiac function unclear. Potential physiological or psychological side effects resulting from the procedure have also not been thoroughly explored. Moreover, the stellate ganglion, strategically positioned at the confluence of the cervical and upper thoracic vertebrae, represents an indispensable element within the sympathetic nervous system. Although anatomically symmetrical, the left and right stellate ganglia exhibit divergent functional profiles due to their distinct innervation territories and neural connectivity patterns. Of particular significance is the greater influence exerted by the right stellate ganglion over cardiac and pulmonary functions, which can be attributed to its direct participation in the pericardial bronchial plexus—a network that assumes a critical role in modulating the tension within the heart's and lungs' vasculature. In contrast, while the left stellate ganglion also exerts effects on the cardiovascular system, its primary function seems to revolve around the regulation of vascular tone in the ipsilateral upper extremity. Recent studies had demonstrated that a blockade of the left stellate ganglion could markedly enhance left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) in normative subjects; however, analogous changes were not as evident when interventions targeted the right side [32]. These observations suggested that the differential physiological responses elicited by the resection or blockade of either stellate ganglion may fundamentally stem from intrinsic functional disparities between these bilateral entities. In conclusion, the significant variations in the physiological roles of the left and right stellate ganglia underscore the intricate nature of autonomic nervous system regulation. This complexity highlights the imperative need for considering lateralized differences in both clinical practice and experimental research paradigms. In addition, although we have preliminarily demonstrated through experiments that star-shaped ganglion resection can restore cardiac function by inhibiting the protein expression of the CaMKII/RyR2 signaling pathway to rebuild the myocardial cell calcium balance in a chronic heart failure model, we still need to activate the expression of CaMKII/RyR2 on the basis of star-shaped ganglion resection in the future to demonstrate the effectiveness of the above pathway in treating chronic heart failure function through salvage experiments. Future research should aim to overcome these limitations to assess the clinical viability of stellate ganglionectomy fully.

In conclusion, our investigation highlights the role of sympathetic nervous system hyperactivation in cardiac hypertrophy and dysfunction using *in vivo* animal experiments and probing its downstream molecular mechanisms. These findings provide new research avenues for clinical therapeutic development.

5. Conclusions

Our study revealed that stellate ganglionectomy has significant therapeutic potential in reducing myocardial hypertrophy and improving cardiac function in rats with pressure overload-induced heart conditions. This surgical intervention not only delayed the progression of heart failure but also elucidated a potential mechanism involving the inhibition of the CaMKII/RyR2 signaling pathway. These findings highlight the importance of modulating sympathetic nerve activity to treat cardiac dysfunction and suggest a promising avenue for future clinical applications in managing similar cardiac conditions in humans. Further studies are warranted to explore the long-term effects and potential clinical implementation of this procedure.

Abbreviations

CHF, chronic heart failure; SG, stellate ganglion; AB, abdominal aortic coarctation group; LSG, left stellate ganglionectomy; RSG, right stellate ganglionectomy; RyR2, ryanodine receptor type 2; IVSD, ventricular interventricular septal defect; LVPWD, left ventricular posterior wall thickness; LVEDD, left ventricular end diastolic diameter and volume; LVEF, left ventricular ejection fraction; LVFS, left ventricular short axis shortening fraction; ANP, atrial natriuretic peptides; BNP, brain natriuretic peptide; NE, norepinephrine; LVEDV, eft ventricular end diastolic volume; TH, tyrosine hydroxylase; GAP43, growth-associated protein-43; CaMKII, Calcium Calmodulin Dependent Protein Kinase II.

Availability of Data and Materials

All analyzed data supporting the study are included in this published article and its supplementary information files. And the raw data will be made available from the corresponding author on request.

Author Contributions

Conceptualization: GW, HY and XJL; methodology: BL; data curation: BW; formal analysis: CGC; investigation and project administration: GW and LQH; resources: LQH; software: HY and XJL; supervision: GW; writing—original draft: HY; writing—review and editing: GW and LQH. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All animal experiments were approved by the Experimental Animal Ethics Committee of the Renmin Hospital of Wuhan University (Number: 20230901B), and performed in accordance with the Guidelines for the Ethical Review of Laboratory Animal Welfare and was granted on September 4, 2023.

Acknowledgment

GW were supported by the Department of Cardiology, Hubei Key Laboratory of Cardiology, Renmin Hospital of Wuhan University, Cardiovascular Research Institute, Wuhan University, Wuhan, China. LQH were supported by the Department of Cardiology, Intervention Cardiology Center, Wuhan No.1 Hospital, Wuhan, Wuhan hospital of Traditional Chinese and western medicine, 430022, Wuhan, China.

Funding

This work was supported by grants from The National Natural Science Foundation of China (82270243).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Shafqat A, Shaik A, Koritala S, Mushtaq A, Sabbah BN, Nahid Elshaer A, *et al*. Contemporary review on pediatric hypertrophic cardiomyopathy: insights into detection and management. Frontiers in Cardiovascular Medicine. 2024; 10: 1277041. https://doi.org/10.3389/fcvm.2023.1277041.

[2] Nakamura M, Sadoshima J. Mechanisms of physiological and pathological cardiac hypertrophy. Nature Reviews. Cardiology. 2018; 15: 387–407. https://doi.org/10.1038/s41569-018-0007-y.

[3] Martin TG, Juarros MA, Leinwand LA. Regression of cardiac hypertrophy in health and disease: mechanisms and therapeutic potential. Nature Reviews. Cardiology. 2023; 20: 347–363. https://doi.org/10.1038/s41569-022-00806-6.

[4] Borovac JA, D'Amario D, Bozic J, Glavas D. Sympathetic nervous system activation and heart failure: Current state of evidence and the pathophysiology in the light of novel biomarkers. World Journal of Cardiology. 2020; 12: 373–408. https://doi.org/10.4330/wjc.v12.i8.373.

[5] Olshansky B, Sabbah HN, Hauptman PJ, Colucci WS. Parasympathetic nervous system and heart failure: pathophysiology and potential implications for therapy. Circulation. 2008; 118: 863–871. https://doi.org/10.1161/CIRCULATIONAHA.107.760405.

[6] Grassi G, Quarti-Trevano F, Esler MD. Sympathetic activation in congestive heart failure: an updated overview. Heart Failure Reviews. 2021; 26: 173–182. https://doi.org/10.1007/s10741-019-09901-2.

[7] Li YL. Stellate Ganglia and Cardiac Sympathetic Overactivation in Heart Failure. International Journal of Molecular Sciences. 2022; 23: 13311. https://doi.org/10.3390/ijms232113311.

[8] Scott-Solomon E, Boehm E, Kuruvilla R. The sympathetic nervous system in development and disease. Nat Rev Neurosci. 2021; 22: 685–702.

[9] Fudim M, Qadri YJ, Waldron NH, Boortz-Marx RL, Ganesh A, Patel CB, *et al*. Stellate Ganglion Blockade for the Treatment of Refractory Ventricular Arrhythmias. JACC. Clinical Electrophysiology. 2020; 6: 562–571. https://doi.org/10.1016/j.jacep.2019.12.017.

[10] Chia KKM, Kanagaratnam L, Hellestrand K, Kowey P, Whalley D. Pharmacological therapy for ventricular arrhythmias: a state-of-the art review. Heart Lung Circ. 2019; 28: 49–56.

[11] Wang Y, He S, Xiong X, Liu J, Xie B, Yao Y, *et al*. Left Stellate Ganglion Ablation Inhibits Ventricular Arrhythmias through Macrophage Regulation in Canines with Acute Ischemic Stroke.

International Journal of Medical Sciences. 2021; 18: 891–901. https://doi.org/10.7150/ijms.50976.

[12] Zhou Q, Hu J, Guo Y, Zhang F, Yang X, Zhang L, *et al*. Effect of the stellate ganglion on atrial fibrillation and atrial electrophysiological properties and its left-right asymmetry in a canine model. Experimental and Clinical Cardiology. 2013; 18: 38–42.

[13] Okuda S, Sufu-Shimizu Y, Kato T, Fukuda M, Nishimura S, Oda T, *et al*. CaMKII-mediated phosphorylation of RyR2 plays a crucial role in aberrant Ca^{2+} release as an arrhythmogenic substrate in cardiac troponin T-related familial hypertrophic cardiomyopathy. Biochemical and Biophysical Research Communications. 2018; 496: 1250–1256. https://doi.org/10.1016/j.bbrc.2018.01.181.

[14] Greene D, Shiferaw Y. Mechanistic link between CaM-RyR2 interactions and the genesis of cardiac arrhythmia. Biophysical Journal. 2021; 120: 1469–1482. https://doi.org/10.1016/j.bpj.2021.02.016.

[15] Søndergaard MT, Tian X, Liu Y, Wang R, Chazin WJ, Chen SRW, *et al*. Arrhythmogenic Calmodulin Mutations Affect the Activation and Termination of Cardiac Ryanodine Receptor-mediated Ca2+ Release. The Journal of Biological Chemistry. 2015; 290: 26151–26162. https://doi.org/10.1074/jbc.M115.676627.

[16] Lv T, Li S, Li Q, Meng L, Yang J, Liu L, *et al*. The role of RyR2 mutations in congenital heart diseases: insights into cardiac electrophysiological mechanisms. Journal of Cardiovascular Electrophysiology. 2025. (online ahead of print) https://doi.org/10.1111/jce.16569.

[17] Ku HC, Lee SY, Wu YKA, Yang KC, Su MJ. A Model of Cardiac Remodeling Through Constriction of the Abdominal Aorta in Rats. Journal of Visualized Experiments: JoVE. 2016; 54818. https://doi.org/10.3791/54818.

[18] Lin J, Chen R, Liao H, Zhang Y, Zheng Z, Hong C. Mechanisms of cordycepin in the treatment of pulmonary arterial hypertension in rats based on metabonomics and transcriptomics. Scientific Reports. 2024; 14: 12431. https://doi.org/10.1038/s41598-024-62163-3.

[19] Palatini P. Role of elevated heart rate in the development of cardiovascular disease in hypertension. Hypertension (Dallas, Tex.: 1979). 2011; 58: 745–750. https://doi.org/10.1161/HYPERTENSIONAHA.111.173104.

[20] Wei FF, Wu Y, Xue R, Liu X, He X, Dong B, *et al*. Clinical Significance of Mean and Pulse Pressure in Patients With Heart Failure With Preserved Ejection Fraction. Hypertension (Dallas, Tex.: 1979). 2022; 79: 241–250. https://doi.org/10.1161/HYPERTENSIONAHA.121.17782.

[21] Maryam, Varghese TP, B T. Unraveling the complex pathophysiology of heart failure: insights into the role of renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS). Current Problems in Cardiology. 2024; 49: 102411. https://doi.org/10.1016/j.cpcardiol.2024.102411.

[22] Goetze JP, Bruneau BG, Ramos HR, Ogawa T, de Bold MK, de Bold AJ. Cardiac natriuretic peptides. Nature Reviews. Cardiology. 2020; 17: 698–717. https://doi.org/10.1038/s41569-020-0381-0.

[23] Uchinoumi H, Yang Y, Oda T, Li N, Alsina KM, Puglisi JL, *et al*. CaMKII-dependent phosphorylation of RyR2 promotes targetable pathological RyR2 conformational shift. Journal of Molecular and Cellular Cardiology. 2016; 98: 62–72. https://doi.org/10.1016/j.yjmcc.2016.06.007.

[24] Rosskothen-Kuhl N, Illing RB. Gap43 transcription modulation in the adult brain depends on sensory activity and synaptic cooperation. PloS One. 2014; 9: e92624. https://doi.org/10.1371/journal.pone.0092624.

[25] Mehrotra M, Reddy V, Singh P. Neuroanatomy, Stellate Ganglion. StatPearls: USA. 2023.

[26] Lymperopoulos A, Rengo G, Koch WJ. Adrenergic nervous system in heart failure: pathophysiology and therapy. Circulation Research. 2013; 113: 739–753. https://doi.org/10.1161/CIRCRESAHA.113.300308.

[27] Maslov LN, Naryzhnaya NV, Voronkov NS, Kurbatov BK, Derkachev IA, Ryabov VV, *et al*. The role of β-adrenergic receptors in the regulation of cardiac tolerance to ischemia/reperfusion. Why do β-adrenergic receptor agonists and antagonists protect the heart? Fundamental & Clinical Pharmacology. 2024; 38: 658–673. https://doi.org/10.1111/fcp.12988.

[28] Zhang DY, Anderson AS. The sympathetic nervous system and heart failure. Cardiology Clinics. 2014; 32: 33–45, vii. https://doi.org/10.1016/j.ccl.2013.09.010.

[29] Elliott IA, DeJesus M, Dobaria V, Vaseghi M, Ajijola OA, Shivkumar K, *et al*. Minimally Invasive Bilateral Stellate Ganglionectomy for Refractory Ventricular Tachycardia. JACC. Clinical Electrophysiology. 2021; 7: 533–535. https://doi.org/10.1016/j.jacep.2020.12.001.

[30] Bers DM, Grandi E. Calcium/calmodulin-dependent kinase II regulation of cardiac ion channels. Journal of Cardiovascular Pharmacology. 2009; 54: 180–187. https://doi.org/10.1097/FJC.0b013e3181a25078.

[31] Yao Y, Li F, Zhang M, Jin L, Xie P, Liu D, *et al*. Targeting CaMKII-δ9 Ameliorates Cardiac Ischemia/Reperfusion Injury by Inhibiting Myocardial Inflammation. Circulation Research. 2022; 130: 887–903. https://doi.org/10.1161/CIRCRESAHA.121.319478.

[32] Lobato EB, Kern KB, Paige GB, Brown M, Sulek CA. Differential effects of right versus left stellate ganglion block on left ventricular function in humans: an echocardiographic analysis. Journal of Clinical Anesthesia. 2000; 12: 315–318. https://doi.org/10.1016/s0952-8180(00)00158-6.