Cardiology Research and Practice

Minimally Invasive Surgical Treatment for Atrial Fibrillation

Lead Guest Editor: Ju Mei
Guest Editors: Zhe Zheng, Mark La Meir, and Tong Liu

Minimally Invasive Surgical Treatment for Atrial Fibrillation

Cardiology Research and Practice

Minimally Invasive Surgical Treatment for Atrial Fibrillation

Lead Guest Editor: Ju Mei
Guest Editors: Zhe Zheng, Mark La Meir, and Tong Liu

Contents

Hindawi
Cardiology Research and Practice
Volume 2021, Article ID 6633948, 9 pages
https://doi.org/10.1155/2021/6633948

Research Article

Association between Serum Adiponectin and Atrial Fibrillation: A Case-Control Study Stratified by Age and Gender

Tongjian Zhu, Zhuo Wang, Songyun Wang, Wei Hu, Hui Chen, Jing Xie, Meng Wang, Kezhong Ma, and Hong Jiang

Department of Cardiology, Renmin Hospital of Wuhan University, Cardiovascular Research Institute, Wuhan University, Hubei Key Laboratory of Cardiology, Wuhan, Hubei, China

Correspondence should be addressed to Hong Jiang; whujianghong@163.com

Received 22 December 2020; Revised 20 January 2021; Accepted 1 February 2021; Published 10 February 2021

Academic Editor: Tong Liu

Background. Circulating adiponectin has been suggested to be associated with atrial fibrillation (AF). However, whether the association differs by age and gender remains unknown. We performed a case-control study to evaluate the above association. *Methods*. AF patients who underwent 24-hour long-range 12-channel electrocardiogram examination at our center were included in this study, and people with normal sinus rhythm (NSR) were included as controls. All participants underwent echocardiography and heart rate variability tests. Biochemical parameters and adiponectin levels were also evaluated. Receiver operating characteristic (ROC) analyses were used to determine the predictive efficacy of adiponectin for AF, and multivariate logistic regression analysis was performed to evaluate the potential independent predictors of AF. *Results*. Overall, 84 patients with AF and 84 people with NSR were included. Serum adiponectin was significantly higher in AF patients compared to that in controls ($P < 0.001$). ROC analysis showed that higher serum adiponectin (>6.098 μg/mL) had predictive efficacy for AF, with an area under the curve of 0.660 (95% confidence interval [CI]: 577–0.742). The results of multivariate logistic regression analysis showed that higher adiponectin was an independent predictor of AF in the overall participants (odds ratio [OR] 1.224, 95% CI 1.018–1.471, $P = 0.032$). Subgroup analysis showed that higher adiponectin was independently associated with AF in women (OR 1.893, 95% CI 1.160–3.089, $P = 0.011$) and in patients aged < 65 years (OR 1.453, 95% CI 1.023–2.064, $P = 0.037$), but not in men or those aged ≥ 65 years. *Conclusions*. Higher serum adiponectin level was independently associated with higher odds for AF in women and in participants <65 years old, but not in men or those aged ≥65 years.

1. Introduction

Atrial fibrillation (AF) is a common arrhythmia in the elderly population and has been associated with higher risks of morbidity, mortality, and disability [1, 2]. Accumulating evidence from epidemiological studies has confirmed that obesity is an important risk factor for AF [3], but the key pathophysiological mechanisms underlying this association remain unknown. Adiponectin, one of the most abundant adipokines in human plasma, has been implicated in the pathogenesis of many chronic diseases due to its insulin-sensitizing, anti-inflammatory, and antioxidant effects [4–6]. Recent studies have related adiponectin with the risk of cardiovascular disease (CVD), and adiponectin is considered a potential biomarker for the risk of many CVDs [7–9], including AF. Previous prospective studies suggested that higher adiponectin could predict AF recurrence after catheter ablation in paroxysmal AF patients <65 years old [10]. However, lower plasma adiponectin was associated with a higher risk of major cardiovascular events after anticoagulation in women with AF, but not in men [11]. In view of the inconsistent results in previous studies, it could be hypothesized that the association between adiponectin and AF may be age- and gender-dependent. Additionally, atrial remodeling, autonomic imbalance, and inflammation have been recognized as important pathogenetic factors in AF [12–14]. However, the relationships between adiponectin and these pathogenetic factors in AF were rarely reported in

the previous studies. Therefore, in this study, we aimed to evaluate the age- and gender-specific associations between adiponectin and AF in a case-control study. Moreover, the correlations between serum adiponectin and markers of atrial remodeling, autonomic imbalance, and inflammation were explored.

2. Materials and Methods

2.1. Study Population. We enrolled 84 consecutive patients with AF who underwent radiofrequency ablation at the Renmin Hospital of Wuhan University from March 2019 to October 2019. Age- and sex-matched individuals with normal sinus rhythm (NSR) were included as controls. Since plasma adiponectin levels can be affected by various comorbidities, patients with coronary artery disease, structural heart diseases, stroke, cardiac dysfunction (left ventricular ejection fraction [LVEF] < 50%), other arrhythmias (such as bradycardia, sick sinus syndrome, or ventricular arrhythmias), cancer, autoimmune diseases, hematological diseases, hepatorenal dysfunction (alanine aminotransferase [ALT] > 60 U/L, serum creatinine [SCr] > 120 umol/L), thyroid insufficiency, systemic acute diseases, and chronic infectious diseases were excluded. Data regarding demographic factors, clinical characteristics, CVD risk factors, blood biochemical parameters, echocardiography, and 24-hour dynamic electrocardiogram (ECG) results were collected.

2.2. Blood Sampling and Laboratory Analyses. Venous blood samples were collected from all participants, who were in a fasting state, the morning after admission. After centrifugation, the serum samples were stored at −80 centigrade until used for measurements. Fasting blood glucose, serum lipid, uric acid, and creatinine were determined with standard laboratory techniques using an automatic biochemical analyzer at the Central Laboratory of the Renmin Hospital of Wuhan University (Siemens Healthcare Diagnostics, Munich, Germany). Plasma adiponectin levels were determined with ELISA (Millipore, Billerica, Massachusetts, USA). High-sensitivity C-reactive protein (hs-CRP) was measured by nephelometry with a threshold of 0.01 mg/L. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured with an electrochemical luminescence immunoassay analyzer (Roche, Basel, Switzerland) according to the manufacturer's instructions.

2.3. Echocardiography. All participants received transthoracic echocardiography with Color Doppler Echocardiography performed by the same skilled ultrasound physician. The left ventricular end-diastolic diameter (LVEDD) and left atrial anteroposterior diameter (LAD) were measured using standard M-mode echocardiography. LVEF was calculated with the modified Simpson method.

2.4. Holter Monitoring and Heart Rate Variability (HRV) Analysis. All participants completed 24-hour long-range 12-lead ECG recordings within 3 days of admission, and the corrected data were analyzed manually. The 24-hour mean heart rate and HRV were recorded. HRV analysis, which reflects the cardiac autonomic function, was performed using commercial software (H-Scribe Analysis system of American Mortara Company). The HRV indexes included both the time-domain parameters (the standard deviation of all normal sinus RR intervals [SDNN] and the root mean square successive difference [RMSSD]) and the frequency-domain parameters (high-frequency power [HF, 0.15–0.4 Hz], low-frequency power [LF, 0.04–0.15 Hz], and high-frequency/low-frequency [HF/LF] ratio). RMSSD and HF generally reflect cardiac parasympathetic nerve activity, while LF is related to cardiac sympathetic nerve activity. Accordingly, the LF/HF ratio reflects the balance between sympathetic and parasympathetic activities, with higher LF/HF values indicating increased sympathetic nerve excitability [15]. During analysis, only normal pulsations were measured, and patients with sinoatrial node dysfunction and a large number of abnormal rhythms (abnormal rhythm ≥ 5% effective rhythm) were excluded. In addition, the data segments for AF and out-of-period pulsation were excluded.

2.5. Statistical Analysis. The variance homogeneity test (Leven test) and normality test (F test) were performed to evaluate the distribution of each dataset. Continuous variables that conformed to the normal distribution were presented as the means and standard deviations; otherwise, medians (interquartile ranges) were applied. The two-sample t-test was used to compare the normal distribution variables between two groups, and the Mann–Whitney U test was used to compare the nonnormal distribution variables between two groups. For categorized variables, frequencies and rates were used, and a chi-square test was used for comparisons between two groups. Spearman correlation analysis was performed to evaluate the correlations between adiponectin and other factors. Binary logistic regression analysis was used to determine the factors associated with AF. Univariate logistic regression analysis was first used to evaluate the associations between clinical characteristics and AF. Variables with a correlation trend ($P < 0.05$) were included in the multivariate logistic regression model. A $P < 0.05$ was considered statistically significant. SPSS 22.0 software was used for statistical analysis.

3. Results

3.1. Characteristics of AF Patients and NSR Controls. Overall, 84 patients with AF and 84 people with NSR were included. The characteristics of the included participants are shown in Table 1. The levels of NT-proBNP and cardiac troponin I (cTnI) in the AF group were significantly higher than those in the NSR group (both $P < 0.05$). Among the echocardiographic parameters, there were significant differences in LAD ($P < 0.001$) and LVEF ($P < 0.001$) between the two groups. Differences in other characteristics were not significant between AF patients and NSR controls.

Table 1: Clinical characteristics of patients with AF and controls with NSR.

Clinical characteristics	AF ($n = 84$)	NSR ($n = 84$)	P value
Age (years)	61.3 ± 10.3	60.7 ± 10.8	0.705
Men (n/%)	56 (67)	56 (67)	1.000
Body mass index (kg/m^2)	24.8 ± 3.3	24.2 ± 3.2	0.400
Hypertension (n/%)	40 (48)	44 (52)	0.537
Diabetes mellitus (n/%)	10 (12)	7 (8)	0.443
Smoking (n/%)	19 (23)	28 (33)	0.314
Drinking (n/%)	16 (19)	11 (13)	0.294
ACEI/ARB (n/%)	26 (31)	22 (26)	0.738
TZDs (n/%)	2 (2.4)	3 (3.6)	0.652
Paroxysmal AF (n/%)	57 (68)	—	—
Persistent AF (n/%)	27 (32)	—	—
NT-proBNP (pg/ml)	321.2 (113.1–716.7)	55.5 (25.6–110.2)	**<0.001**
cTnI (ng/ml)	0.006 (0.006–0.125)	0.006 (0.006–0.006)	**0.001**
Hs-CRP (mg/L)	0.68 (0.50–1.24)	0.81 (0.50–1.89)	0.643
Fasting glucose (mmol/L)	4.96 (4.57–5.78)	4.88 (4.44–5.87)	0.951
Uric acid (μmol/L)	384.3 ± 92.1	400.5 ± 123.7	0.339
Total cholesterol (mmol/L)	4.19 ± 0.81	4.52 ± 0.89	**0.015**
Triglycerides (mmol/L)	1.53 (1.10–2.28)	1.88 (1.16–2.69)	0.090
HDL-cholesterol (mmol/L)	1.17 ± 0.45	1.13 ± 0.33	0.499
LDL-cholesterol (mmol/L)	2.36 ± 0.68	2.59 ± 0.82	**0.048**
eGFR (mL/min)	93.7 ± 19.4	95.8 ± 19.5	0.496
Left atrium diameter (mm)	40.2 ± 5.6	34.4 ± 4.1	**<0.001**
LVEDD (mm)	44.9 ± 5.5	44.0 ± 3.6	0.199
LVEF (%)	57.7 ± 3.1	59.9 ± 1.9	**<0.001**

Continuous variables are presented as mean ± SD or median and IQR. Categorized variables are presented as number (percentage). P values < 0.05 are indicated in bold. AF, atrial fibrillation; NSR, normal sinus rhythm; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type II receptor blockers; TZD, thiazolidinedione; NT-proBNP, N-terminal probrain natriuretic peptide; cTnI, cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricle ejection fraction.

3.2. Association between Adiponectin and AF. The serum levels of adiponectin were significantly higher in AF patients than in NSR controls ($P < 0.001$, Figure 1(a)). Consistent results were found in subgroup analyses according to the age and sex of the participants, as well as the type of AF (Figures 1(b)–1(d)).

3.3. Association between Serum Adiponectin and AF Risk Factors. The results of Spearman correlation analysis showed that serum adiponectin was significantly correlated with NT-proBNP ($P < 0.001$, Figure 2(a)), hs-CRP ($P = 0.029$, Figure 2(b)), LAD ($P = 0.009$, Figure 2(c)), and LVEF ($P = 0.003$, Figure 2(d)). Further, adiponectin showed positive correlations with RMSSD ($P = 0.014$, Figure 2(e)) and HF ($P = 0.011$, Figure 2(f)). Adiponectin levels were also significantly associated with gender, age, and body mass index (BMI), but not with LF and the LF/HF ratio (Table 2).

3.4. Association between Serum Adiponectin and AF Stratified by Age, Gender, and Type of AF. Univariate logistic regression analysis showed that NT-proBNP, LAD, LVEF, and adiponectin were related to the odds of AF ($P < 0.05$). Subsequent multivariate analysis showed that higher adiponectin was independently associated with AF in the overall participants (odds ratio [OR] 1.224, 95% confidence interval [CI]: 1.018–1.471, $P = 0.032$; Table 3). Further subgroup analysis confirmed the independent association in women (OR 1.893, 95% CI: 1.160–3.089, $P = 0.011$; Table 4), patients aged <65 years (OR 1.453, 95% CI 1.023–2.064, $P = 0.037$; Table 5), and patients with paroxysmal AF (OR 1.229, 95% CI 1.005–1.503, $P = 0.045$; Table 6), but not in men, those aged ≥65 years, or patients with persistent AF. The results of receiver operating characteristic (ROC) analysis showed a promising predictive efficacy of higher adiponectin for AF (Figure 3). With an optimal cut-off value of 6.098 μg/mL, the sensitivity and specificity of serum adiponectin for predicting AF were 78.6% and 54.8%, with an area under the curve (AUC) of 0.660 (95% CI: 577–0.742).

4. Discussion

In this case-control study with AF patients and NSR controls, we found that the serum adiponectin levels in AF patients were significantly higher than those in NSR patients. This finding was consistent in subgroup analysis according to the age, gender, and AF type of the participants. Moreover, serum adiponectin was found to be correlated with markers of cardiac remodeling, inflammation, and cardiac autonomic function. Subsequent multivariate analysis showed a significant independent association between higher adiponectin levels and AF in the overall participants. Subgroup analysis showed a similar association in women, participants <65 years old, and patients with paroxysmal AF, but not in men, those aged ≥65 years, or patients with persistent AF. Taken together, our results showed that

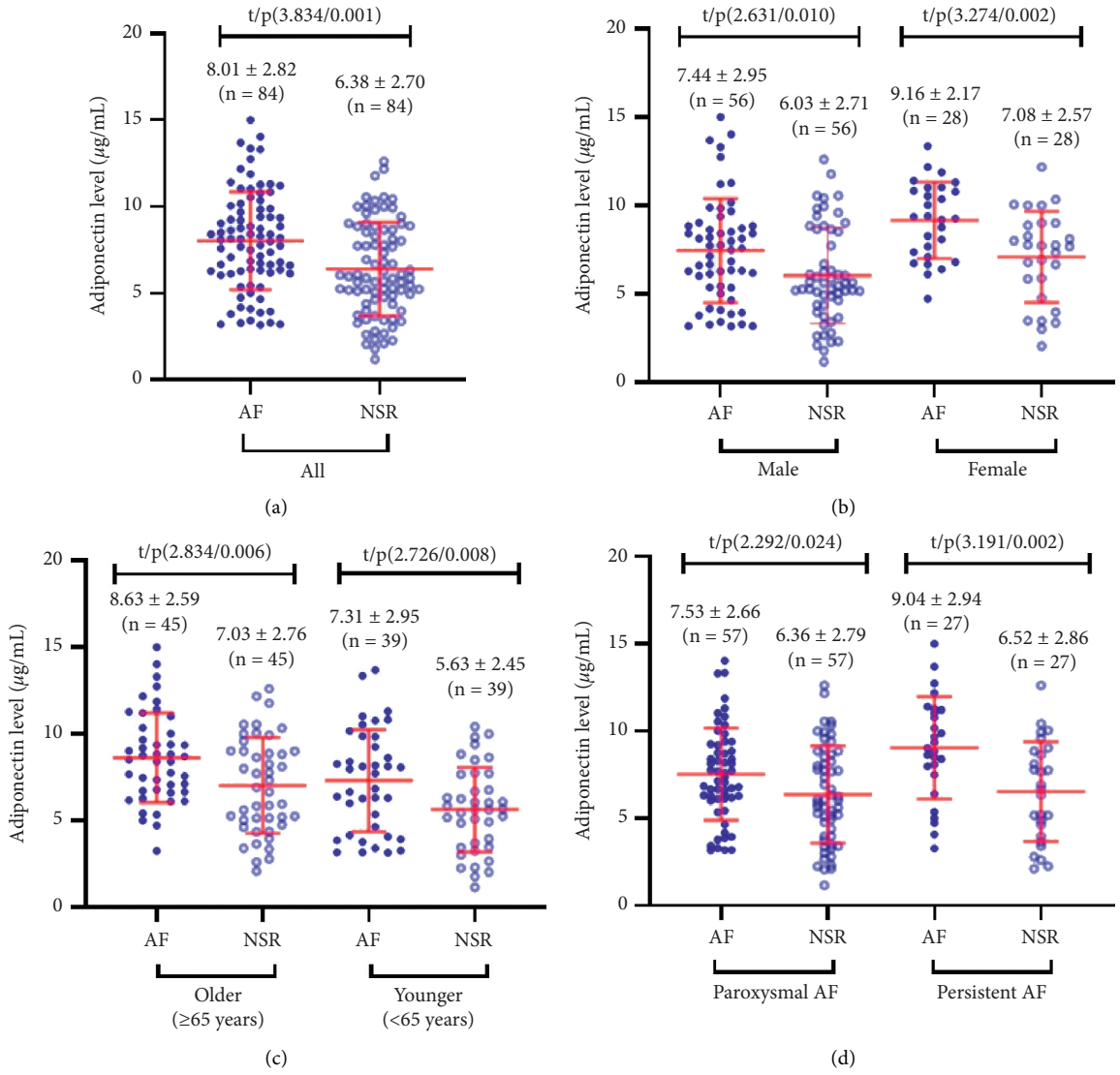


Figure 1: Serum adiponectin levels in patients with AF and controls with NSR: (a) scattergram comparing the serum adiponectin levels in the overall participants; (b) scattergram comparing the serum adiponectin levels according to the gender of the participants; (c) scattergram comparing the serum adiponectin levels according to the age of the participants; (d) scattergram comparing the serum adiponectin levels according to the type of AF.

adiponectin is correlated with cardiac remodeling, inflammation, and cardiac autonomic function in AF patients. Moreover, the potential independent association between adiponectin and AF may be age- and sex-specific.

Previous studies showed that the association between serum adiponectin and the progression of CVD may have a "U" shape [16]. Similarly, the association between adiponectin and AF risk remains inconsistent [17]. Two cross-sectional studies showed that, compared to the levels in people with sinus rhythm, serum adiponectin levels were significantly higher in persistent AF patients [18], but significantly lower in patients with paroxysmal AF [19]. These conflicting results may be explained by the potential influences of sex, age, BMI, or comorbidities in patients with these associations. One of the strengths of our study is that we included age- and sex-matched AF patients and NSR controls, and we strictly excluded patients with comorbidities that may affect the serum adiponectin. Our results showed that higher adiponectin was independently associated with AF, and the association remained in women, participants <65 years old, and patients with paroxysmal AF. Currently, it remains unknown whether higher adiponectin is only a marker or an active participant in the pathogenesis of AF. Previous studies showed that the binding of adiponectin to its receptor, an increase in adiponectin resistance, and the compensatory secretion of adiponectin may be involved in AF. Further research is needed to evaluate the potential mechanisms underlying the association between higher adiponectin and AF.

Atrial remodeling, inflammation, and autonomic dysfunction have been recognized as key pathogenetic factors for AF. It has been suggested in previous studies that

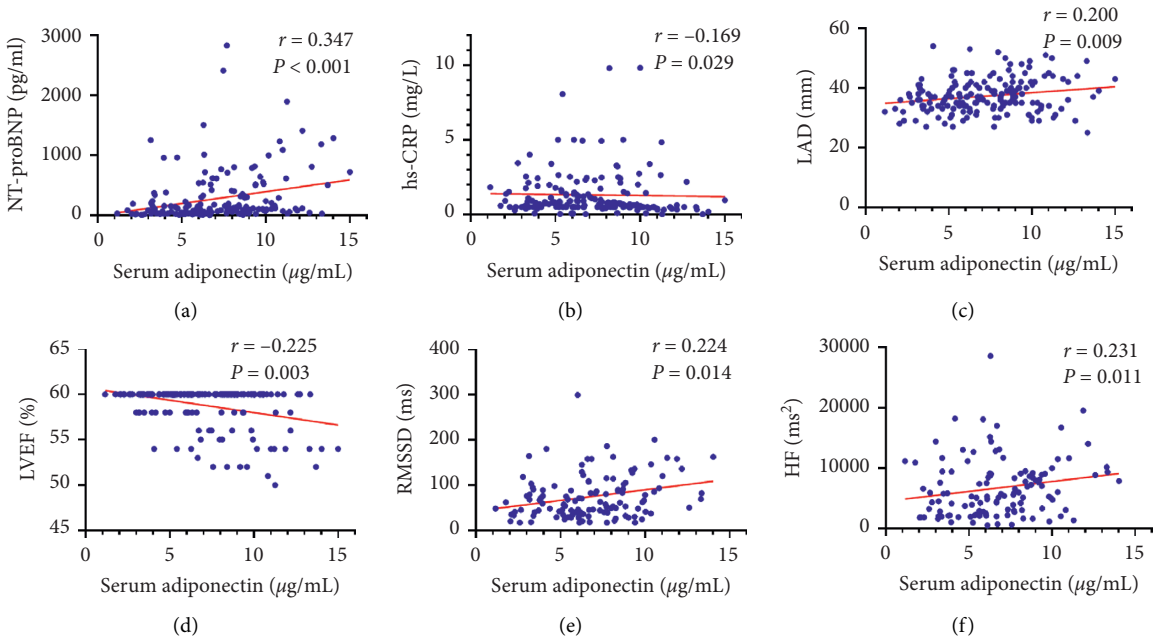


Figure 2: Correlation analyses between serum adiponectin and clinical parameters in the included participants: (a) correlation of adiponectin with NT-proBNP; (b) correlation of adiponectin with hs-CRP; (c) correlation of adiponectin with left atrium diameter (LAD); (d) correlation of adiponectin with LVEF; (e) correlation of adiponectin with root mean square successive difference (RMSSD); (f) correlation of adiponectin with high-frequency power (HF).

Table 2: Correlation between plasma adiponectin concentration and other parameters.

Variable	r	P value
Female	0.256	**0.001**
Age	0.279	**<0.001**
Body mass index	−0.234	**0.015**
NT-proBNP	0.347	**<0.001**
Hs-CRP	−0.169	**0.029**
Left atrium diameter	0.200	**0.009**
LVEF	−0.225	**0.003**
rMSSD	0.224	**0.014**
LF	0.071	0.439
HF	0.231	**0.011**
LF/HF ratio	−0.100	0.275

P values < 0.05 are indicated in bold. NT-proBNP, N-terminal probrain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricle ejection fraction; rMSSD, root mean square successive difference; LF, low-frequency component; HF, high-frequency component.

adiponectin may be associated with these mechanisms. Ybarra et al. [20] found that adiponectin was negatively correlated with left atrial size, which could inhibit atrial interstitial fibrosis and reverse atrial remodeling [18]. However, our study showed a positive correlation between adiponectin and LAD. We speculate that adiponectin may present with a compensatory increase in patients with AF as a protective hormone. Adiponectin is also considered a powerful "anti-inflammatory factor," which acts by binding to adiponectin receptors on the membrane of target cells [21]. Studies have shown that adiponectin can inhibit the expression of scavenger receptors, vascular adhesion molecules, and proinflammatory cytokines (TNF-α, IL-6, IL-1β) in various tissues [22] and inhibit cardiac inflammation and progression by upregulating anti-inflammatory cytokines [23]. Our study also showed a significant negative correlation between adiponectin and hs-CRP, suggesting that adiponectin may have a protective effect in AF patients via its anti-inflammatory effect. In addition, previous studies have also suggested a relationship between adiponectin and autonomic function. In patients with type 2 diabetes, higher adiponectin was reported to be associated with more favorable cardiac autonomic function [24]. Moreover, adiponectin was reported as a positive horizontal and longitudinal predictor of parasympathetic nerve activity in women [25]. Our study showed that adiponectin was positively correlated with RMSSD and HF, which suggests that higher serum adiponectin may be associated with an increased cardiac parasympathetic activity. The implications of this association on the pathogenesis of AF deserve further evaluation.

Previous studies have suggested age and gender differences in the relationship between adiponectin and AF [10, 11]. In our study, although the ROC curve analysis showed that an adiponectin level ≥6.098 ng/mL had a predictive value for the occurrence of AF in the overall participants, the association between adiponectin and AF was mainly observed in women and those aged <65 years. Previous studies showed that circulating BNP can affect plasma adiponectin levels [26, 27] and may explain the controversial results for the relationship between circulating adiponectin levels and the prediction of CVD [28]. It could be inferred that there is a compensatory increase of adiponectin in elderly patients with AF to reduce cardiac remodeling and inflammation. Several possible mechanisms

Table 3: Univariate and multivariate logistic regression analysis for the independent predictors of AF.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
NT-proBNP	1.011 (1.006–1.015)	**<0.001**	1.009 (1.004–1.014)	**<0.001**
Total cholesterol	0.634 (0.436–0.921)	**0.017**	0.418 (0.118–1.478)	0.176
Triglyceride	0.792 (0.624–1.005)	**0.049**	1.010 (0.658–1.549)	0.964
LDL-cholesterol	0.657 (0.431–1.001)	**0.041**	1.358 (0.398–4.636)	0.625
Left atrium diameter	1.294 (1.185–1.412)	**<0.001**	1.149 (1.030–1.281)	**0.013**
LVEF	0.575(0.442–0.748)	**<0.001**	0.856 (0.643–1.138)	0.284
Adiponectin	1.239 (1.101–1.393)	**<0.001**	1.224 (1.018–1.471)	**0.032**

P values <0.05 are indicated in bold. OR, odds ratio; CI, confidence interval; AF, atrial fibrillation; NT-proBNP, N-terminal probrain natriuretic peptide; LDL, low-density lipoprotein; LVEF, left ventricle ejection fraction.

Table 4: Univariate and multivariate logistic regression analysis for the independent predictors of AF stratified by gender.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Female				
NT-proBNP	1.007 (1.002–1.012)	**0.008**	1.008 (1.000–1.015)	**0.043**
hs-CRP	0.532 (0.274–1.034)	**0.036**	0.764 (0.451–1.293)	0.316
eGFR	0.963 (0.930–0.998)	**0.039**	1.001 (0.944–1.061)	0.977
Left atrium diameter	1.238 (1.082–1.416)	**0.002**	1.169 (0.933–1.463)	0.174
LVEF	0.497 (0.273–0.903)	**0.022**	0.457 (0.116–1.876)	0.283
Adiponectin	1.458 (1.120–1.896)	**0.005**	1.893 (1.160–3.089)	**0.011**
Male				
NT-proBNP	1.014 (1.008–1.021)	**<0.001**	1.012 (1.005–1.019)	**0.001**
Uric acid	0.996 (0.993–1.000)	**0.046**	0.991 (0.984–0.998)	**0.014**
Left atrium diameter	1.345 (1.194–1.515)	**<0.001**	1.228 (1.058–1.425)	**0.007**
LVEF	0.599 (0.450–0.798)	**<0.001**	0.760 (0.528–1.096)	0.142
Adiponectin	1.195 (1.039–1.374)	**0.012**	0.869 (0.664–1.137)	0.306

P values <0.05 are indicated bold. OR, odds ratio; CI, confidence interval; AF, atrial fibrillation; NT-proBNP, N-terminal probrain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; LVEF, left ventricle ejection fraction.

Table 5: Univariate and multivariate logistic regression analysis for the independent predictors of AF stratified by age.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age < 65 years				
NT-proBNP	1.021 (1.008–1.034)	**0.002**	1.018 (1.004–1.033)	**0.015**
Total cholesterol	0.517 (0.265–1.008)	**0.045**	0.346 (0.085–1.408)	0.138
Left atrium diameter	1.308 (1.141–1.498)	**<0.001**	1.277 (1.025–1.589)	**0.029**
LVEF	0.465 (0.257–0.841)	**0.011**	0.402 (0.136–1.189)	0.100
Adiponectin	1.259 (1.054–1.504)	**0.011**	1.453 (1.023–2.064)	**0.037**
Age ≥ 65 years				
NT-proBNP	1.009 (1.004–1.014)	**0.001**	1.008 (1.002–1.014)	**0.005**
Left atrium diameter	1.328 (1.171–1.507)	**<0.001**	1.231 (1.057–1.433)	**0.007**
LVEF	0.613 (0.460–0.817)	**0.001**	0.903 (0.654–1.248)	0.537
Adiponectin	1.253 (1.060–1.481)	**0.008**	1.195 (0.925–1.542)	0.173

P values <0.05 are indicated in bold. OR, odds ratio; CI, confidence interval; AF, atrial fibrillation; NT-proBNP, N-terminal probrain natriuretic peptide; LVEF, left ventricle ejection fraction.

may explain the gender and age differences in the role of adiponectin in AF. Firstly, it has been suggested that the androgen testosterone can inhibit adiponectin secretion by adipocytes [29]. Adiponectin may have different metabolic effects in men. Secondly, with the increase of age, adiponectin receptors may be downregulated or resistance may develop [30], which can cause positive feedback. Although adiponectin levels are higher in elderly individuals, the elevated levels may not have corresponding beneficial effects because the incidence of AF gradually increases with age. The potential age- and sex-specific association between adiponectin and AF should be validated in large-scale studies.

Some limitations of the current study should be noted. Firstly, the sample size of the current study was limited, and the findings should be further verified in large-scale studies.

Table 6: Univariate and multivariate logistic regression analysis for the independent predictors of AF stratified by type of AF.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Paroxysmal AF				
NT-proBNP	1.010 (1.005–1.034)	<0.001	1.009 (1.003–1.015)	**0.002**
Total cholesterol	0.490 (0.301–0.797)	0.004	0.279 (0.087–1.021)	0.054
LDL-cholesterol	0.513 (0.302–0.872)	0.014	1.422 (0.419–4.828)	0.572
Left atrium diameter	1.284 (1.150–1.438)	<0.001	1.164 (1.019–1.328)	**0.025**
LVEF	0.666 (0.512–0.867)	0.002	0.940 (0.738–1.196)	0.614
Adiponectin	1.173 (1.019–1.351)	0.027	1.229 (1.005–1.503)	**0.045**
Persistent AF				
NT-proBNP	1.018 (1.006–1.030)	0.003	1.018 (1.001–1.035)	**0.038**
Left atrium diameter	1.371 (1.161–1.620)	<0.001	1.305 (0.983–1.733)	**0.066**
LVEF	0.649 (0.474–0.887)	0.007	1.311 (0.722–2.380)	0.374
Adiponectin	1.349 (1.092–1.667)	0.005	1.383 (0.822–2.328)	0.222

P values <0.05 are indicated in bold. OR, odds ratio; CI, confidence interval; AF, atrial fibrillation; NT-proBNP, N-terminal probrain natriuretic peptide; LDL, low-density lipoprotein; LVEF, left ventricle ejection fraction.

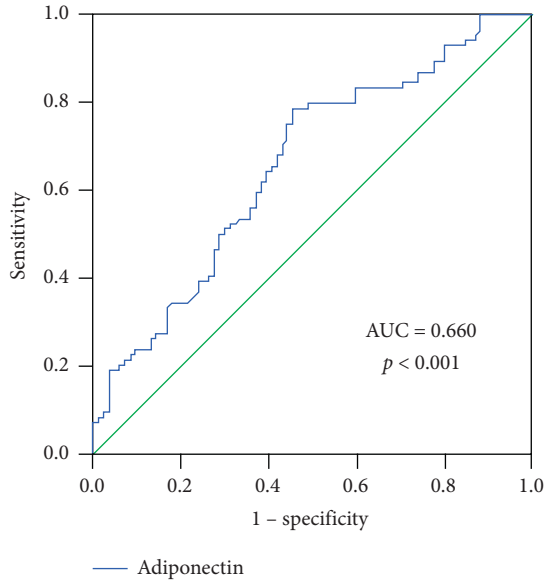


Figure 3: ROC analysis for the predictive efficacy of serum adiponectin for AF. As shown in the ROC analysis, with an optimal cut-off value of 6.098 μg/mL, the sensitivity and specificity of serum adiponectin for predicting AF were 78.6% and 54.8%, with an AUC of 0.660 (95% CI: 577–0.742).

Moreover, the current analysis was cross-sectional. Large-scale prospective cohort studies are needed to determine the independent association between adiponectin and AF risk according to the age and gender of the participants. In addition, it remains unclear whether elevated adiponectin is a cause or a consequence of AF. Furthermore, in this study, only hs-CRP was measured as an indicator of systematic inflammation and other inflammatory factors such as IL-6, IL-1 β, and TNF-α were not investigated. The associations between adiponectin and these inflammatory factors in AF remain to be evaluated. Finally, other important factors that affect plasma adiponectin levels, such as body fat content and waist circumference, were not measured in our study. Variations in these factors may confound the association between adiponectin and AF in our study population.

5. Conclusion

The present study suggested that adiponectin is correlated with cardiac remodeling, inflammation, and cardiac autonomic function in AF patients. Moreover, the potential independent association between adiponectin and AF may be age- and sex-specific. These results should be confirmed in large-scale prospective studies, and the mechanisms underlying the association between adiponectin and AF should be further investigated in future studies.

Data Availability

The data that support the findings of this study are available from the Renmin Hospital of Wuhan University. But

restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. The data are however available from the authors upon reasonable request and with the permission of the Renmin Hospital of Wuhan University.

Ethical Approval

The study was approved by the ethics committee of Renmin Hospital of Wuhan University. All subjects provided informed consent. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation.

Disclosure

TZ, ZW, and SW are co-first authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

HJ conceived and designed the study. TZ, ZW, and SW collected and analyzed the data. WH, HC, JX, and MW quality control of the study and revision. TZ wrote the paper. The manuscript was approved by all the above authors. TZ, ZW, and SW contributed to the work equally and should be regarded as co-first authors..

Acknowledgments

This work was supported by the National Key R&D Program of China (no. 2017YFC1307800) and the National Natural Science Foundation of China (nos. 81530011 and 81900456).

References

[1] A. D. Beaser and A. S. Cifu, "Management of patients with atrial fibrillation," *JAMA*, vol. 321, no. 11, pp. 1100-1101, 2019.

[2] A. Morillo Carlos, A. Banerjee, and P. Perel, "Atrial fibrillation: the current epidemic," *Journal of Geriatric Cardiology*, vol. 14, pp. 195–203, 2017.

[3] C. J. Lavie, A. Pandey, D. H. Lau, M. A. Alpert, and P. Sanders, "Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis," *Journal of the American College of Cardiology*, vol. 70, no. 16, pp. 2022–2035, 2017.

[4] S. L. Prior, D. R. Gable, J. A. Cooper et al., "Association between the adiponectin promoter rs266729 gene variant and oxidative stress in patients with diabetes mellitus," *European Heart Journal*, vol. 30, no. 10, pp. 1263–1269, 2009.

[5] N. Ouchi, J. L. Parker, J. J. Lugus, and K. Walsh, "Adipokines in inflammation and metabolic disease," *Nature Reviews Immunology*, vol. 11, no. 2, pp. 85–97, 2011.

[6] S. Li, H. J. Shin, E. L. Ding, and R. M. van Dam, "Adiponectin levels and risk of type 2 diabetes," *JAMA*, vol. 302, no. 2, pp. 179–188, 2009.

[7] A. Y. Shiu Lun and S. C. Mary, "Adiponectin and coronary artery disease risk: a bi-directional Mendelian randomization study," *International Journal of Cardiology*, vol. 268, pp. 222–226, 2018.

[8] T. Sente, A. Gevaert, A. Van Berendoncks, C. J. Vrints, and V. Y. Hoymans, "The evolving role of adiponectin as an additive biomarker in HFrEF," *Heart Failure Reviews*, vol. 21, no. 6, pp. 753–769, 2016.

[9] G. Witberg, C. R. Ayers, A. T. Turer et al., "Relation of adiponectin to all-cause mortality, cardiovascular mortality, and major adverse cardiovascular events (from the dallas heart study)," *The American Journal of Cardiology*, vol. 117, no. 4, pp. 574–579, 2016.

[10] T.-H. Kim, J. S. Lee, J.-S. Uhm, B. Joung, M.-H. Lee, and H.-N. Pak, "High circulating adiponectin level is associated with poor clinical outcome after catheter ablation for paroxysmal atrial fibrillation," *EP Europace*, vol. 20, no. 8, pp. 1287–1293, 2018.

[11] D. Hernández-Romero, E. Jover, F. Marín et al., "The prognostic role of the adiponectin levels in atrial fibrillation," *European Journal of Clinical Investigation*, vol. 43, no. 2, pp. 168–173, 2013.

[12] S. Nattel and M. Harada, "Atrial remodeling and atrial fibrillation: recent advances and translational perspectives," *Journal of the American College of Cardiology*, vol. 63, no. 22, pp. 2335–2345, 2014.

[13] Y.-F. Hu, Y.-J. Chen, Y.-J. Lin, and S.-A. Chen, "Inflammation and the pathogenesis of atrial fibrillation," *Nature Reviews Cardiology*, vol. 12, no. 4, pp. 230–243, 2015.

[14] P. S. Chen, L. S. Chen, M. C. Fishbein, S. F. Lin, and S. Nattel, "Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy," *Circulation Research*, vol. 114, p. 15009, 2014.

[15] Heart Rate Variability: Standards of Measurement, Physiological Interpretation and Clinical Use, "Task force of the European society of cardiology and the North American society of pacing and electrophysiology," *Circulation*, vol. 93, pp. 1043–1065, 1996.

[16] J. R. Kizer, D. Benkeser, A. M. Arnold et al., "Associations of total and high-molecular-weight Adiponectin with all-cause and cardiovascular mortality in older persons," *Circulation*, vol. 126, no. 25, pp. 2951–2961, 2012.

[17] F. Macheret, T. M. Bartz, L. Djousse et al., "Higher circulating adiponectin levels are associated with increased risk of atrial fibrillation in older adults," *Heart (British Cardiac Society)*, vol. 101, no. 17, pp. 1368–1374, 2015.

[18] M. Shimano, R. Shibata, Y. Tsuji, H. Kamiya, T. Uchikawa, and S. Harata, "Circulating adiponectin levels in patients with atrial fibrillation," *Circulation Journal*, vol. 72, no. –4, p. 1120, 2008.

[19] B. J. Choi, J. H. Heo, I.-S. Choi et al., "Hypoadiponectinemia in patients with paroxysmal atrial fibrillation," *Korean Circulation Journal*, vol. 42, no. 10, pp. 668–673, 2012.

[20] Y. Juan, R. Eugenia, and P. Francesc, "Relationship between adiponectin and left atrium size in uncomplicated obese patients: adiponectin, a link between fat and heart," *Obesity Surgery*, vol. 19, pp. 1324–1332, 2009.

[21] Y. J. Peng, T. L. Shen, Y. S. Chen, H. J. Mersmann, B. H. Liu, and S. T Ding, "Adiponectin and adiponectin receptor 1 overexpression enhance inflammatory bowel disease," *Journal of Biomedical Science*, vol. 25, no. 1, p. 24, 2018.

[22] Y. Wang, X. Wang, W. B. Lau et al., "Adiponectin inhibits tumor necrosis factor-α-induced vascular inflammatory response via caveolin-mediated ceramidase recruitment and activation," *Circulation Research*, vol. 114, no. 5, pp. 792–805, 2014.

[23] P. Bobbert, C. Scheibenbogen, A. Jenke et al., "Adiponectin expression in patients with inflammatory cardiomyopathy

indicates favourable outcome and inflammation control," *European Heart Journal*, vol. 32, no. 9, pp. 1134–1147, 2011.

[24] C. S. Hansen, V. Dorte, and J. Marit Eika, "Adiponectin, biomarkers of inflammation and changes in cardiac autonomic function: whitehall II study," *Cardiovascular Diabetology*, vol. 16, no. 153, 2017.

[25] R. Van De Wielle and N. Michels, "Longitudinal associations of leptin and adiponectin with heart rate variability in children," *Frontiers in Physiology*, vol. 8, p. 498, 2017.

[26] K. Nakanishi, M. Nishida, R. Yamamoto, M. Koseki, T. Moriyama, and K. Yamauchi-Takihara, "Association between N-terminal pro-brain natriuretic peptide and adiponectin in healthy Japanese men," *Clinica Chimica Acta*, vol. 460, pp. 138–141, 2016.

[27] M. A. Allison, M. H. Criqui, A. S. Maisel et al., "Adiponectin is independently associated with NT-proBNP: the multi-ethnic study of atherosclerosis," *Nutrition, Metabolism and Cardiovascular Diseases*, vol. 25, no. 8, pp. 780–786, 2015.

[28] O. Tsukamoto, M. Fujita, M. Kato et al., "Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 53, no. 22, pp. 2070–2077, 2009.

[29] L. Frederiksen, K. Højlund, D. M. Hougaard et al., "Testosterone therapy decreases subcutaneous fat and adiponectin in aging men," *European Journal of Endocrinology*, vol. 166, no. 3, pp. 469–476, 2012.

[30] Y. Wang, X. L. Ma, and W. B. Lau, "Cardiovascular adiponectin resistance: the critical role of adiponectin receptor modification," *Trends in Endocrinology & Metabolism*, vol. 28, no. 7, pp. 519–530, 2017.

Hindawi
Cardiology Research and Practice
Volume 2021, Article ID 8869264, 6 pages
https://doi.org/10.1155/2021/8869264

Research Article

Effects and Mechanisms of Cutting Upper Thoracic Sympathetic Trunk on Ventricular Rate in Ambulatory Canines with Persistent Atrial Fibrillation

Jie Cai, Min Tang, Hao Liu, Shiao Ding, Rongxin Lu, Wei Wang, Nan Ma, Ju Mei, and Zhaolei Jiang

Department of Cardiothoracic Surgery, Xinhua Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, 200092, China

Correspondence should be addressed to Ju Mei; ju_mei63@126.com and Zhaolei Jiang; wojiangzhaolei@163.com

Received 17 September 2020; Revised 27 December 2020; Accepted 18 January 2021; Published 2 February 2021

Academic Editor: Manoel Otavio C Rocha

Objective. The purpose is to observe the effects and neural mechanism of cutting upper thoracic sympathetic trunk (TST) on the ventricular rate (VR) during persistent atrial fibrillation (AF). *Methods*. Twelve beagle dogs were halving to the control group and experimental group, 6 dogs for each group. Both groups were performed with left atrial rapid pacing (600 beats/min) to induce sustained AF. The experimental group underwent cutting upper TST after a sustained AF model was established, while the control group received thoracotomy without cutting TST. Bilateral stellate ganglion (SG) and left atrial myocardium were harvested for tyrosine-hydroxylase (TH) immunohistochemical staining. *Results*. After cutting upper TST for 30 minutes, the average VR was 121.5 ± 8.7 bpm (95% CI, 114.8 to 128.0) in the experimental group, which was significantly slower than that of the control group (144.5 ± 4.2 bpm (95% CI, 141.5 to 148.0)) ($P < 0.001$). After cutting upper TST for 1 month, the average VR of the experimental group (106.5 ± 4.9 bpm (95% CI, 102.0 to 110.0)) was also significantly slower versus that of the control group (139.2 ± 5.6 bpm (95% CI, 135.0 to 143.8)) ($P < 0.001$). Compared with the control group, both left stellate ganglion (LSG) and right stellate ganglion (RSG) of the experimental group caused neural remodeling characterized by decreased ganglionic cell density and reduced TH staining. TH-positive component was significantly decreased in the left atrium of the experimental group compared with the control group. *Conclusions*. Cutting upper TST could reduce fast VR during persistent AF. Cutting upper TST induced bilateral SG neural remodeling and reduced sympathetic nerve density in the left atrium, which could contribute to the underlying mechanism of VR control during AF.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, which has high morbidity and mortality [1]. Both rhythm and rate controls are acceptable strategies in managing patients with AF [2]. Autonomic nerve activity has been associated with an increase in atrial arrhythmogenesis by acting as a trigger that can induce atrial tachyarrhymias such as atrial tachycardia (AT) and AF [3–5]. Increasing sympathetic nerve activity plays an important role in the occurrence and maintenance of AF [6–8]. Thoracic sympathetic trunk (TST) is the most important resource of cardiac sympathetic nerve, which has become a novel target for AF management [6–9].

Stellate ganglion (SG) is the most important component of upper TST [7, 9]. At present, few studies have achieved blocking TST by ablating or resecting SG to inhibit the induction of paroxysmal atrial tachycardia (PAT) or paroxysmal atrial fibrillation (PAF) [8, 10]. However, resecting the upper part of SG may cause Horner's syndrome; the effects of cutting TST by only resecting the lower part of the left stellate ganglion (LSG) on persistent AF and cardiac neural remodeling still remain uncertain. The purpose of this study is to observe the effects of cutting upper TST by only

resecting the lower part of LSG on the ventricular rate (VR) during persistent AF in ambulatory canines. Also, this study observes the effects of cutting upper TST on the cardiac neural remodeling of the bilateral SG and left atrium in the canine model of persistent AF, which may be a possible mechanism of the antiarrhythmic effect of cutting upper TST.

2. Methods

The animal protocol was approved by the Institutional Animal Care and Use Committee in Xinhua Hospital, Shanghai Jiaotong University School of Medicine, and conformed to the Guide for Care and Use of Laboratory Animals (XHEC-F-2018-057). Twelve mature healthy male beagle dogs (Animal Laboratory Center, Xinhua Hospital, Shanghai Jiaotong University School of Medicine) weighing 15–25 kg were randomly halving to the control group and experimental group, 6 dogs for each group. The control group was merely performed with rapid left atrial pacing (600 beats/min) to induce persistent AF. The experimental group was disposed with rapid left atrial pacing (600 beats/min) and received cutting upper TST after persistent AF was documented.

2.1. Establishment of the Sustained AF Model. All canines of both groups were disposed with rapid left atrial pacing to construct a persistent AF model. Each canine was injected with Zoletil (10–15 mg/kg, intramuscular) to induce anesthesia and maintained with 2%~4% isoflurane after endotracheal intubation and mechanical ventilation and then underwent thoracotomy through the fourth intercostal space on the left chest. Two epicardial pacing electrodes were stitched onto the left atrial appendage separately at a distance of 2 centimeters, which was connected to an Implantable Wireless Device of Electrocardiography (ECG) Acquisition and Stimulator (Ensen-ESST-79-5, Enshi Medical Technology (Shanghai) Co., Ltd.). Another two electrodes were stitched to the subcutaneous tissue of the left chest to record ECG signal. After pacing parameters were set appropriately (pacing model, continuously stimulating; voltage, 1500 mV; frequency, 10 Hz; pulse width, 1 ms), the implantable device was subcutaneously positioned on the left chest. Each canine received 3-day antibiotics after surgery with 0.5 g/d cefuroxime. After one week of postoperative recovery, rapid (600 bpm) left atrial pacing was then given continuously for one week. After one week, the stimulating model of the device was turned off to determine the presence of sustained AF (lasting >48 hours) [11, 12]. If the canine was not sustained AF, the atrial pacing continued for another week and the ECG was monitored weekly until sustained AF was documented.

2.2. Cutting Upper Thoracic Sympathetic Trunk and Recording VR. After the establishment of sustained AF, canines were continuously monitored for another 2 weeks. The canines of the experimental group then underwent the procedure of cutting upper TST by only resecting the lower part of LSG through the left third intercostal space, while the canines of the control group only received the thoracotomy without cutting upper TST. After the left third intercostal thoracotomy, honeycomb and adipose tissue were separated around the base of the 7th cervical vertebra and the first rib, and LSG was exposed on the top of the left thoracic cavity (Figure 1(a)); then the lower part of LSG was resected (Figure 1(b)).

ECG was recorded, respectively, at different time points (for the experiment group, before anesthesia, 30 minutes after anesthesia and before cutting TST, 30 minutes after cutting TST; for the control group, before anesthesia, 30 minutes after anesthesia and before thoracotomy, 30 minutes after thoracotomy). Each canine received 3-day antibiotics with 0.5 g/d cefuroxime after the second surgery. ECG was recorded again after one month of recovery. ECG was used for VR analysis. Then, the dog was euthanized.

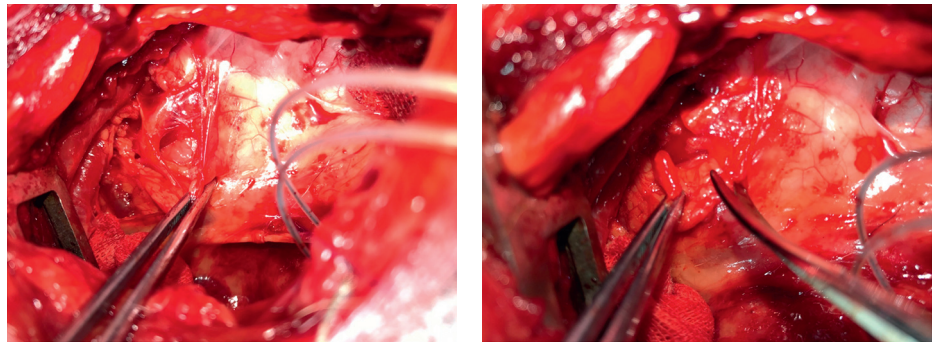
2.3. Immunohistochemistry Studies. Bilateral SG tissue and left atrial myocardial tissue of all dogs were obtained and fixed in 4% formalin for 45 mins, followed by storage in 70% alcohol for tyrosine-hydroxylase (TH) immunohistochemical staining using an anti-TH antibody (22941, Immunostar, USA). The tissues were paraffin-embedded and cut into 5 μm thick sections routinely. All slides were examined manually under a DP72 microscope (Olympus, Tokyo, Japan). A blinded observer pictured randomly select 200X fields with the highest ganglion cell density. The mean number of ganglion cells and the mean percentage of TH-negative ganglion cells were calculated. The densities of TH-positive nerves within the left atrial myocardial tissue were determined with Image J software.

2.4. Data Analysis. The data were reported as mean ± standard deviation (SD) and 95% confidence interval (CI). All data were tested for normality using the D'Agostino and Pearson normality test. Paired t-test was performed to compare the differences at different experimental time points in the same group. Independent t-test was performed to compare the differences between the experimental group and control group. For the data with nonnormality, Wilcoxon rank-sum test was used to compare the data between groups. A P value of ≤ 0.05 was considered statistically significant.

3. Results

3.1. Sustained AF Model Establishment. After left atrial rapid pacing for 3~6 weeks, a stable sustained AF model was successfully developed in all canines. There was no significant difference in AF inducing duration between the experimental group (4.2 ± 0.8 weeks (95% CI, 3.6 to 4.8)) and the control group (4.5 ± 1.0 weeks (95% CI, 3.7 to 5.3)) ($P = 0.541$, $t = -0.632$).

3.2. Effects of Cutting Upper TST on VR during AF. Table 1 shows the effects of cutting upper TST on VR during AF at different time points in both the experimental group and the



(a) (b)

Figure 1: Cutting upper TST. (a) LSG (yellow arrow) was exposed on the top of the left thoracic cavity. (b) The lower part of LSG was resected (yellow arrow).

Table 1: The effects of cutting upper TST on VR during AF.

Parameter	Experimental group (bpm)	Control group (bpm)	t value	P value
Before (AF baseline)	157.3 ± 7.9	154.2 ± 5.8	0.787	0.450
After anesthesia and before cutting upper TST	143.7 ± 5.2*	146.0 ± 3.0*	−0.954	0.362
After cutting upper TST for 30 minutes	121.5 ± 8.7*	144.5 ± 4.2	−5.829	<0.001
After cutting upper TST for 1 month	106.5 ± 4.9*	139.2 ± 5.6*	−10.763	<0.001

*$P < 0.05$ versus AF baseline.

control group. After the establishment of sustained AF, average VR during AF was 157.3 ± 7.9 bpm (95% CI, 151.0 to 163.7) in the experimental group and 154.2 ± 5.8 bpm (95% CI, 149.8 to 158.8) in the control group ($P = 0.450$, $t = 0.787$) before anesthesia in ambulatory dogs (AF baseline). After anesthesia and before cutting upper TST, there was no significant difference on average VR between the experiment group (143.7 ± 5.2 bpm (95% CI, 139.8 to 148.0)) and control group (146.0 ± 3.0 bpm (95% CI, 143.6 to 148.4)) ($P = 0.362$, $t = -0.954$). After cutting upper TST for 30 minutes, the average VR was 121.5 ± 8.7 bpm (95% CI, 114.8 to 128.0) in the experimental group, which was significantly slower than that of the control group (144.5 ± 4.2 bpm (95% CI, 141.5 to 148.0)) ($P < 0.001$, $t = -5.829$). After cutting upper TST for 1 month, the average VR of the experimental group (106.5 ± 4.9 bpm (95% CI, 102.0 to 110.0)) was significantly slower versus that of the control group (139.2 ± 5.6 bpm (95% CI, 135.0 to 143.8)) ($P < 0.001$, $t = -10.763$).

3.3. Effects of Cutting Upper TST on Neural Remodeling of LSG. LSG tissues were successfully harvested for analyses in all canines. Figure 2 shows an example of neural remodeling in LSG of the control group and experimental group. Compared with that of the control group, neural remodeling characterized by decrease ganglionic cell density and reduced TH staining were visible under low power field in all LSG studied after cutting upper TST for 1 month in the experimental group. Compared with that of the control group (76.3 ± 0.8, 95% CI: 74.8–77.9), the mean ganglionic cell number was significantly decreased in the LSG of the experimental group (58.7 ± 2.3, 95% CI: 54.1–63.2) ($P < 0.001$, $t = 7.160$). The mean percentage of TH-negative ganglionic cells in LSG of the experimental group (28.2% ± 3.2%, 95% CI: 21.9%–34.5%) was significantly higher than that in LSG of the control group (6.3% ± 0.6%, 95% CI: 5.1%–7.5%) ($P < 0.001$, $t = 6.711$).

Right SG (RSG) of all canines was successfully obtained for analyses. Figure 3 shows an example of neural remodeling in RSG of the control group and experimental group. TH staining showed TH-negative ganglion cells (red arrows) and TH-positive ganglion cells (brown color). Compared with the control group (73.5 ± 2.3, 95% CI: 69.0–78.0), the mean ganglionic cell quantity of RSG was significantly decreased in the experimental group (63.2 ± 1.6, 95% CI: 60.1–66.2) ($P = 0.004$, $t = 3.713$). Besides, the mean percentage of TH-negative ganglionic cells in RSG of the experimental group (12.8% ± 0.9%, 95% CI: 11.1%–14.6%) was significantly higher than that of the control group (5.4% ± 0.8%, 95% CI: 3.8%–7.1%) ($P < 0.001$, $t = 6.074$).

3.4. Effects of Cutting Upper TST on Neural Remodeling of the Left Atrium. Left atrial myocardial tissues of all canines were successfully obtained for analyses. Figure 4 shows a typical example of neural remodeling in the left atrium between the two groups. Compared with that of the control group (4.1‰ ± 0.4‰, 95% CI: 3.3‰–4.9‰), the mean TH-positive area ratio in the left atrial myocardium was significantly decreased in the experimental group (2.2‰ ± 0.2‰, 95% CI: 1.8‰–2.6‰) ($P = 0.002$, $t = 4.041$).

4. Discussion

This study demonstrated the following: (1) cutting upper TST is efficient in controlling fast VR during AF in ambulatory dogs with pacing induced sustained AF and (2)

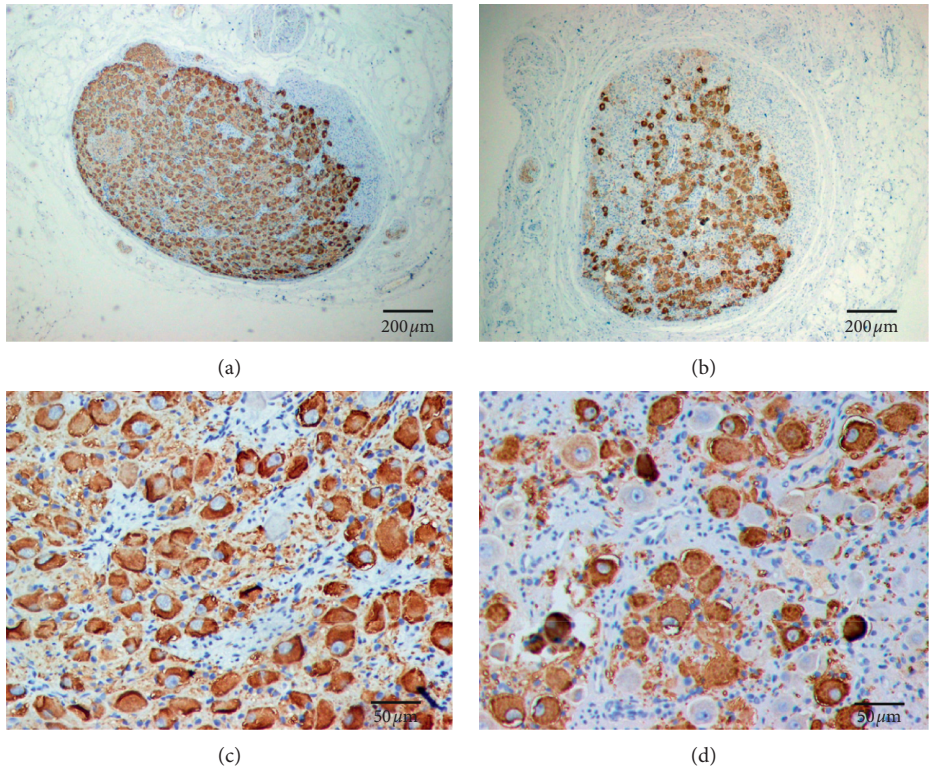


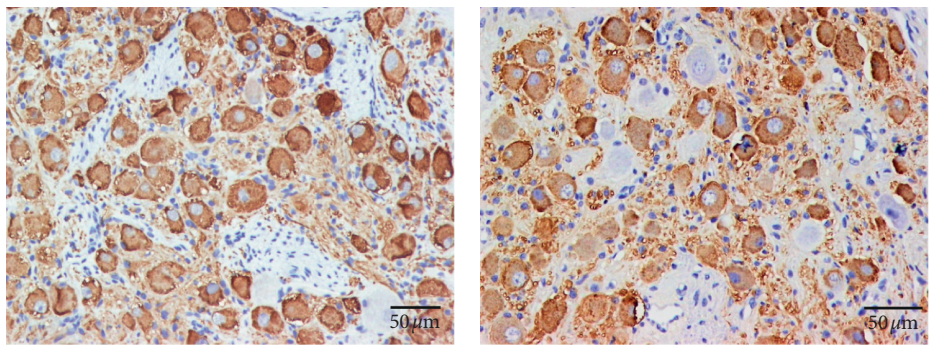
Figure 2: TH staining of LSG in both control group and experimental group. (a) The LSG of the control group seen at low magnification. (b) The LSG of the experimental group seen at low magnification. Compared with that of the control group, TH staining of LSG was weaker in the experimental group. (c) The LSG of the control group seen at high magnification. TH staining showed TH-negative ganglion cells (red arrows) and TH-positive ganglion cells (brown color) in LSG. (d) The LSG of the experimental group seen at high magnification. Compared with that of the control group, TH staining showed that the number of ganglionic cells was significantly decreased, but the quantity of TH-negative ganglion cells was significantly increased in the LSG of the experimental group. Effects of cutting upper TST on the neural remodeling of right SG (RSG).

cutting upper TST could cause cardiac neural remodeling and reduce the sympathetic density in bilateral SG in canines with sustained AF, which is beneficial to inhibit cardiac sympathetic activity and control fast VR during persistent AF.

4.1. The Relationship between Cutting Upper TST and VR during AF. Persistent AF can induce cardiac remodeling including electrical remodeling, which may have fast VR and decrease cardiac function. Both rhythm and rate controls are acceptable strategies in managing patients with persistent AF [2, 13]. The autonomic nervous system plays an important role in the occurrence and maintenance of AF [3–5]. In the last few decades, alternative strategies of VR control including vagal nerve stimulation (VNS) were developed [11, 12, 14, 15]. Upper TST is the most important resource of the cardiac sympathetic nerve, which has become a novel target for AF management [6–9].

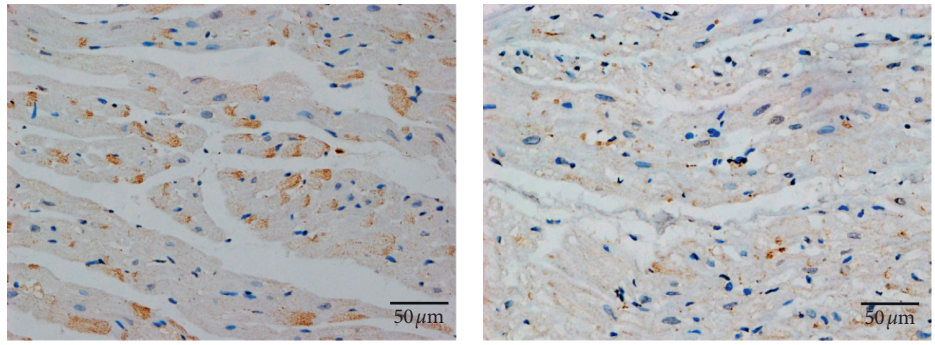
SG is the most important component of upper TST, which is a sympathetic ganglion formed by the fusion of the inferior cervical ganglion and the first thoracic ganglion [7, 9]. Previous studies have shown that SG nerve activity (SGNA) was related to VR acceleration and spontaneous cardiac arrhythmias, and decreasing SGNA may be useful in inhibiting cardiac arrhythmias and reducing fast VR [16–18]. Shen et al. demonstrated that chronic left low-level VNS could effectively suppress left SGNA and reduce the incidence of PAT in ambulatory dogs [14]. In addition, Chinda et al. also found that intermittent VNS could lead to reduced SGNA and VR control during persistent AF in ambulatory dogs [12]. However, the effects of cutting upper TST by only resecting the lower part of LSG on persistent AF and cardiac neural remodeling are uncertain. In this study, we observed the effects of cutting upper TST by only resecting the lower part of LSG on VR. Compared with that of the control group, the average VR was significantly slower at both 30 minutes and one month after cutting upper TST in the experimental group. Our results demonstrated that cutting upper TST was efficacious in controlling fast VR and tachyarrhythmias during persistent AF in ambulatory dogs.

4.2. Cutting Upper TST Causes Bilateral SG Neural Remodeling in Canines with Sustained AF. Sympathetic tone is important in cardiac arrhythmogenesis. Several studies have shown that SGNA was related to VR acceleration and cardiac arrhythmias, and decreasing SGNA may be helpful in inhibiting cardiac arrhythmias [16–18]. Previous studies have shown



(a) (b)

Figure 3: TH staining of RSG in both control group (a) and experimental group (b). (a) The RSG of the control group seen at high magnification. TH staining showed TH-negative ganglion cells (red arrows) and TH-positive ganglion cells (brown color) in RSG. (b) The RSG of the experimental group seen at high magnification. Compared with that of the control group, TH staining showed that the number of ganglionic cells was significantly decreased, but the quantity of TH-negative ganglion cells was significantly increased in the RSG of the experimental group.



(a) (b)

Figure 4: TH staining of the left atrium in both control group (a) and experimental group (b). (a) The left atrium of the control group seen at high magnification. (b) The left atrium of the experimental group seen at high magnification. TH staining showed that the TH-positive component (red arrows) was significantly decreased in the left atrium of the experimental group compared with that of the control group.

that the VNS could suppress SGNA, inhibit the occurrence of PAF, or decrease VR during AF by inducing SG neural remodeling. These studies showed that VNS caused neural remodeling of the SG with a decreased density of TH-positive ganglion cells and more TH-negative ganglion cells [12, 14].

In this study, the mean ganglionic cell number was significantly decreased in both LSG and RSG of the experimental group compared with that of the control group. The mean percentage of TH-negative ganglionic cells in LSG and RSG of the experimental group was significantly higher than that in LSG and RSG of the control group. The results demonstrated that cutting upper TST induced bilateral SG neural remodeling, which was one of the possible mechanisms of VR control of cutting upper TST. However, the neural remodeling of LSG appeared to be more significant than that of RSG.

4.3. Cutting Upper TST Causes Cardiac Neural Remodeling in Canines with Sustained AF. The cardiac nervous system includes the intrinsic cardiac nervous system (ICNS) which is composed of nerve structures that are inside the heart and the extrinsic cardiac nervous system (ECNS) which is composed of nerve structures that are outside of the heart. Both the ECNS and ICNS are known to be related to an increase in atrial arrhythmogenesis or fast VR [6, 19, 20]. Choi et al. have shown that there was a significant temporal relationship between extrinsic cardiac nerve activity (ECNA; including stellate ganglion nerve activity and vagal nerve activity) and intrinsic nerve activity (ICNA; including epicardial ganglionated plexi nerve activity and ligament of Marshall nerve activity), indicating that there is a communication between ECNS and ICNS [19]. Stimulating the ECNS via VNS has been shown to be effective in suppressing the occurrence of AF and reducing VR during persistent AF [12, 14, 15].

In this study, we not only found that cutting upper TST could cause both LSG and RSG neural remodeling, but also found that cutting upper TST could reduce the sympathetic nerve density in the left atrial myocardial tissue. Compared with that of the control group, TH-positive component was significantly decreased in the left

atrium of the experimental group. The results indicate that cutting upper TST could reduce cardiac sympathetic outflow, which may be another possible mechanism of VR control of cutting upper TST.

5. Study Limitations

The present study has two limitations. Firstly, we did not evaluate the SG function by directly recording SGNA. Secondly, we only observed the effect of cutting upper left TST. The effect of cutting upper right TST or bilateral TST should be studied in the future.

6. Conclusions

Cutting upper TST could reduce fast VR during AF in ambulatory dogs with pacing induced sustained AF. Cutting upper TST induced bilateral SG neural remodeling and reduced the sympathetic nerve density in the left atrium, which could contribute to the underlying mechanism of VR control during AF.

Data Availability

The data are stored in the Department of Cardiothoracic Surgery, Xinhua Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai (200092), China.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Jie Cai and Min Tang contributed equally to this work.

Acknowledgments

The authors are grateful for the financial support from the National Natural Science Foundation of China (Grant nos. 81570290, 81600264, and 81974023), the Science and Technology Commission of Shanghai Municipality (Grant nos. 19411963800 and 20Y11910700), and Shanghai Young Physician Training Program, National Key Clinical Specialty.

References

[1] Y. Guo, Y. Tian, H. Wang, Q. Si, Y. Wang, and G. Y. H. Lip, "Prevalence, incidence, and lifetime risk of atrial fibrillation in China," *Chest*, vol. 147, no. 1, pp. 109–119, 2015.

[2] C. T. January, L. S. Wann, H. Calkins et al., "2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation," *Journal of the American College of Cardiology*, vol. 74, no. 1, pp. 104–132, 2019.

[3] Y. Hou, Q. Zhou, and S. S. Po, "Neuromodulation for cardiac arrhythmia," *Heart Rhythm*, vol. 13, no. 2, pp. 584–592, 2016.

[4] M. J. Shen and D. P. Zipes, "Role of the autonomic nervous system in modulating cardiac arrhythmias," *Circulation Research*, vol. 114, no. 6, pp. 1004–1021, 2014.

[5] D. Linz, A. D. Elliott, M. Hohl et al., "Role of autonomic nervous system in atrial fibrillation," *International Journal of Cardiology*, vol. 287, pp. 181–188, 2019.

[6] P.-S. Chen, L. S. Chen, M. C. Fishbein, S.-F. Lin, and S. Nattel, "Role of the autonomic nervous system in atrial fibrillation," *Circulation Research*, vol. 114, no. 9, pp. 1500–1515, 2014.

[7] Z. Jiang, Y. Zhao, A. Doytchinova et al., "Using skin sympathetic nerve activity to estimate stellate ganglion nerve activity in dogs," *Heart Rhythm*, vol. 12, no. 6, pp. 1324–1332, 2015.

[8] A. Y. Tan, S. Zhou, M. Ogawa et al., "Neural mechanisms of paroxysmal atrial fibrillation and paroxysmal atrial tachycardia in ambulatory canines," *Circulation*, vol. 118, no. 9, pp. 916–925, 2008.

[9] J. A. Armour, "Functional anatomy of intrathoracic neurons innervating the atria and ventricles," *Heart Rhythm*, vol. 7, no. 7, pp. 994–996, 2010.

[10] Q. Zhou, J. Hu, Y Guo 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*, vol. 18, no. 1, pp. 38–42, 2013.

[11] Z. Jiang, Y. Zhao, W.-C. Tsai et al., "Effects of vagal nerve stimulation on ganglionated plexi nerve activity and ventricular rate in ambulatory dogs with persistent atrial fibrillation," *JACC: Clinical Electrophysiology*, vol. 4, no. 8, pp. 1106–1114, 2018.

[12] K. Chinda, W.-C. Tsai, Y.-H. Chan et al., "Intermittent left cervical vagal nerve stimulation damages the stellate ganglia and reduces the ventricular rate during sustained atrial fibrillation in ambulatory dogs," *Heart Rhythm*, vol. 13, no. 3, pp. 771–780, 2016.

[13] S. Nattel and M. Harada, "Atrial remodeling and atrial fibrillation," *Journal of the American College of Cardiology*, vol. 63, no. 22, p. 2335, 2014.

[14] M. J. Shen, T. Shinohara, H.-W. Park et al., "Continuous low-level vagus nerve stimulation reduces stellate ganglion nerve activity and paroxysmal atrial tachyarrhythmias in ambulatory canines," *Circulation*, vol. 123, no. 20, pp. 2204–2212, 2011.

[15] S. Stavrakis, M. B. Humphrey, B. J. Scherlag et al., "Low-level transcutaneous electrical vagus nerve stimulation suppresses atrial fibrillation," *Journal of the American College of Cardiology*, vol. 65, no. 9, pp. 867–875, 2015.

[16] B.-C. Jung, A. S. Dave, A. Y. Tan et al., "Circadian variations of stellate ganglion nerve activity in ambulatory dogs," *Heart Rhythm*, vol. 3, no. 1, pp. 78–85, 2006.

[17] M. Ogawa, S. Zhou, A. Y. Tan et al., "Left stellate ganglion and vagal nerve activity and cardiac arrhythmias in ambulatory dogs with pacing-induced congestive heart failure," *Journal of the American College of Cardiology*, vol. 50, no. 4, pp. 335–343, 2007.

[18] S. Zhou, B.-C. Jung, A. Y. Tan et al., "Spontaneous stellate ganglion nerve activity and ventricular arrhythmia in a canine model of sudden death," *Heart Rhythm*, vol. 5, no. 1, pp. 131–139, 2008.

[19] E.-K. Choi, M. J. Shen, S. Han et al., "Intrinsic cardiac nerve activity and paroxysmal atrial tachyarrhythmia in ambulatory dogs," *Circulation*, vol. 121, no. 24, pp. 2615–2623, 2010.

[20] Y. Zhang, B. J. Scherlag, Z. Lu et al., "Comparison of atrial fibrillation inducibility by electrical stimulation of either the extrinsic or the intrinsic autonomic nervous systems," *Journal of Interventional Cardiac Electrophysiology*, vol. 24, no. 1, pp. 5–10, 2009.