Int J Clin Exp Med 2020;13(3):1636-1642
www.ijcem.com /ISSN:1940-5901/IJCEM0102472

*Original Article*

# The effects of statins on autonomic nervous function in rats with atrial fibrillation and the related mechanisms

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Received November 27, 2018; Accepted January 3, 2020; Epub March 15, 2020; Published March 30, 2020

**Abstract:** Objective: To assess the effect of statins on autonomic nervous function in rats with atrial fibrillation (AF). Methods: 45 SD rats were randomly and equally assigned into control, AF model, and statin treatment groups. The atrial effective refractory period (AERP) was measured using the S1S2 pre-procedure stimulation method, and the AF induction rate was also measured. Heart rhythm variation analysis software was used to reveal the autonomic nervous function. Western blot was adopted to analyze the expressions of tyrosine hydroxylase (TH) and choline acetyl transferase (CHAT) in atrial tissues. ELISA was employed to quantify the expression of the inflammatory cytokines, including transformation growth factor-β1 (TGF-β1), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP). Results: The expression of nuclear factor-kappa B (NF-κB). The AF rats had a shortened AERP and a higher AF induction rate. The autonomic nervous function indexes including SDNN, SDANN, RMSSD, and the SDNNindx were decreased in the AF group, had a higher low frequency (LF)/high frequency (HF) ratio and an enhanced TH but a decreased CHAT expression, and TGF-β1, TNF-α, CRP, and NF-κB were upregulated ($P<0.05$ compared to the control group). The statin group had an elongated AERP, decreased AF induction, higher SDNN, SDANN, RMSSD and SDNNindx, a decreased LF/HF, lower TH expression but higher CHAT, and TGF-β1, TNF-α, CRP, and NF-κB were downregulated ($P<0.05$ compared to the AF group). Conclusion: Statin drugs can suppress inflammation to improve the AF condition via suppressing the expression and function of cardiac autonomic nerves.

**Keywords:** Atrial fibrillation, autonomic nerves, rosuvastatin calcium, inflammatory factor, NF-κB

## Introduction

Atrial fibrillation (AF) is the most commonly occurring heart arrythmia, so it is attracting research interest among clinicians [1]. With a progressively increasing AF incidence as the population ages, AF presents persistent and more severe symptoms [2]. A survey on the incidence of AF in China showed that AF makes up a large proportion of the incidence of cardiac arrythmia across all age groups, but the majority of cases occur in people older than 60 years [3, 4]. AF is progressive, and its influence is mainly seen in an abnormal atrial electrophysiology. The surface electrocardiogram indicates the depolarized peak of the atrium, the presence of the P wave, and the progression of the sinus rhythm into the fibrillation wave [5]. A lot of factors can induce AF, including coronary heart disease, hypertension, heart failure, and congenital heart disease, along with other clinical conditions such as systemic inflammation, pulmonary artery embolism, and hyperthyroidism [6, 7]. AF can aggravate myocardial ischemia, and can cause a stasis of the atrial blood to form a left atrial thrombosis, leading to cardiac dysfunction, or even a cerebral/pulmonary embolism to cause a stroke or even death [8, 9]. The autonomic nervous system can regulate the cardiovascular system via complicated mechanisms [10]. Previous studies found that the imbalance of the autonomic nervous system, including the sympathetic and parasympathetic nerves, is closely correlated with the pathogenesis of cardiac arrhythmia [11, 12].

The current major drugs for AF include those used for normalizing the heart rhythm toward a normal sinus pattern, and other commonly-used treatment approaches include electrical

conversion, radiofrequency ablation therapy and surgery, and among these, radiofrequency ablations are the most widely used in clinics [13, 14]. Recent studies found that statins can be used to correct AF by reducing its occurrence and frequency [15]. However, the related mechanism of statins in treating AF has not been fully illustrated. This study aimed to use a rosuvastatin calcium drug to investigate autonomic nervous function and expression in AF rats, along with the related mechanisms.

## Materials and methods

### *Experimental animals*

A total of 60 healthy SD rats (males and females, 2 months old, SPF grade, body weight 250±20 g) were purchased from the laboratory animal center of Qingdao University (Qingdao, Shandong, China) and were kept in an SPF grade facility. The housing conditions were kept at 21±1°C and 50-70% relative humidity, with 12 h light/dark cycle. The animal experiments followed the protocol design and were performed by experienced technicians to minimize pain. The ethical committee of the Affiliated Hospital of Jining Medical University (Jining, Shandong, China) approved this study.

### *Major reagent and equipment*

Acetylcholine was purchased from Sigma (US) and rosuvastatin calcium was purchased from AstraZeneca (UK). The Western blot reagent was purchased from Beyotime (China). The ECL reagent was purchased from Amersham Biosciences (US). Rabbit anti-mouse tyrosine kinase (TH) monoclonal antibody, rabbit anti-mouse choline acetyl transferase (CHAT) monoclonal antibody, rabbit anti-mouse NF-κB monoclonal antibody, and goat anti-rabbit horseradish peroxidase (HRP) labelled IgG secondary antibody were purchased from Cell Signaling (US). ELISA kits for transformation growth factor-β1 (TGF-β1), tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) were purchased from BD (US). Other common reagents were purchased from Sangon (US). A model V6004 animal electrocardiogram monitor was purchased from SurgiVet (US). A four-electrode cannula was purchased from Medtronic (US). A model LEAD7000 multi-electrode electrophysiology controller was purchased from Jinjiang Bio (China). A LabSystems Version 1.3.1 microplate reader was purchased from Bio-Rad (US). An ultrasonic rupture apparatus was purchased from Tianxiang Instrument (China).

### *Animal model preparation and grouping*

A total of 45 healthy SD rats were fed under normal conditions for 2 weeks, and then they were randomly divided into 3 groups (N = 15 each), including a control group, an AF group, which received acetylcholine-$CaCl_2$ mixture for preparing the AF model, and a statin group, which received 5 mg/kg/d rosuvastatin calcium for 2 weeks by gavage at 2 weeks after the AF model preparation.

### *Rat AF model generation*

Based on previous studies [16], the AF group rats received a 0.1 mL/100 g Ach-$CaCl_2$ (10 mg/ml $CaCl_2$ and 60 μg/ml acetylcholine) mixture for 1 week through a tail vein injection. After surgery, 24 ml/kg saline was replenished using an intraperitoneal injection. The control group rats underwent an identical procedure as those in the model group, but they received an equal dose of PBS instead.

### *Measurement of the electrophysiological indexes and the autonomic nervous function analysis*

10 days after treatment, all the rats were anesthetized using 1% pentobarbital sodium and were fixed on an operating table. With their chest cavities open, the atrial effective refractory periods (AERP) of the left atriums and the AF induction rates were measured. Tracheal intubation was performed, and the chest cavity was opened to expose the right atrium. A programmed electrical stimulus was performed using a four-electrode cannula, and S1S2 programmed stimuli was used to measure the AF induction rates. The endpoint of the stimuli was defined when S1-S2 has been shortened from 30 ms longer than AERP progressively to 5 ms. S1S1 programmed stimuli was utilized to measure the electrophysiological indexes using S1-S1 duration at 300 ms and 5 ms intervals. AERP was measured until no AF occurred. Heart rhythmic variation (HRV) analysis software and a dynamic electrocardiogram were used to analyze the autonomic nervous function. SDANN was defined as the standard deviation of the R-R interval average; SDNN was calculated as

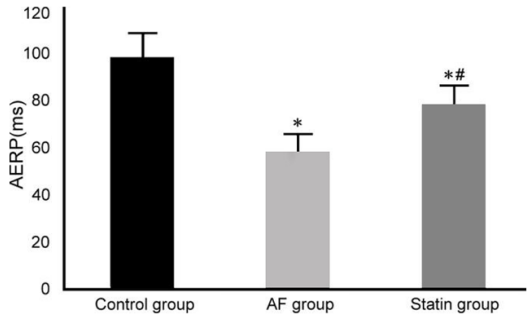


**Figure 1.** AERP analysis of all groups. *, $P<0.05$ compared to the control group; #, $P<0.05$ compared to the AF group.

the standard deviation of the R-R interval average with 5 min intervals within 24 h; RMSSD is the averaged square of the deviation with the adjacent R-R interval difference; the SDNNindx interval was based on the average of the R-R interval standard deviation with 5 min intervals within 24 h. The low frequency (LF)/high frequency (HF) ratio was calculated based on the HRV spectral measurement.

*Western blot for the sympathetic nerve marker TH, the parasympathetic nerve marker CHAT, and the NF-κB protein expressions*

The myocardial tissues were lysed on ice using a lysis buffer for a 15-30 min incubation. The tissues were ruptured using an ultrasound treatment (5 s, 4 times), and then they were centrifuged at 4°C at 10,000 g for 15 min. The supernatant was saved and the protein was quantified for storage at -20°C. Western blotting was performed through separation in a 10% SDS-PAGE solution, which was transferred to a PVDF membrane at 100 mA for 1.5 h. A non-specific binding background was removed using 5% defatted milk powder incubation at room temperature for 2 h. Primary antibodies (1:500 for anti-TH, 1:2000 for anti-CHAT, and 1:2000 for anti-NF-κB) were used for the 4°C incubation overnight. The next day, the membrane was rinsed in PBST and was incubated in a 1:2000 goat anti-rabbit secondary antibody for 30 min at room temperature. The membrane was developed for 1 min, followed by an x-ray exposure to observe the results. Protein imaging processing software and Quantity One software were used to scan the X-ray film to measure the band intensity. All the experiments were repeated four times (n = 4) for the statistical analysis.

*ELISA for measuring the TGF-β1, TNF-α and CRP expressions*

All the groups were treated for 6 h, and the rats were anesthetized using 10% hydrate chloral. Blood samples were collected from the abdominal aorta and were centrifuged at 2000 rpm for 10 min to extract the upper phase for separating the serum, which was saved at -80°C for further use. An ELISA kit was used to measure the expressions of TGF-β1, TNF-α, and CRP in the supernatant. All the experimental procedures followed the test kit's instruction manual. The linear regression function was calculated based on the concentration of the standard samples and the respective absorbance (A) value. The sample concentration was calculated based on the value of the samples on the regression curve.

*Statistical analysis*

SPSS 16.0 software was used for the statistical analysis. The enumeration data were presented as a ratio followed by a chi-square analysis. The measurement data were presented as the means ± standard deviations (SD). The comparisons of the means among multiple groups were adopted using a one-way analysis of variance (ANOVA). Statistical significance was defined as $P<0.05$.

## Results

*Statin elongates rat AERP*

Electrophysiological parameters were used to measure the rats' AERP levels. The results showed a significantly shortened AERP of the atrial tissues in the AF rats ($P<0.05$ compared to the control group). The statin group received rosuvastatin calcium treatment and showed a significant elongation of AERP ($P<0.05$ compared to the AF group, **Figure 1**).

*Statin decreases the AF induction rate of all groups*

We further analyzed the AF induction rates among all the groups of rats. The results showed a significant increase in the AF induction rate (14/20, 70.0%) in the AF group, with statistical significance compared to the control group (1/20, 5.0%, $P<0.05$). The statin group received rosuvastatin calcium treatment and

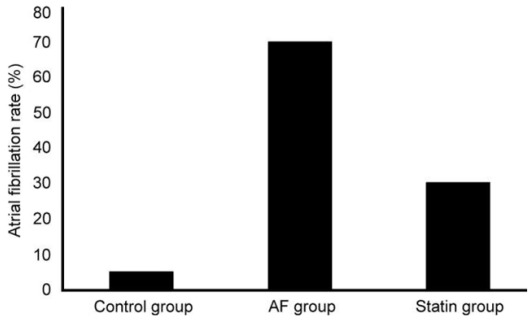


**Figure 2.** AF induction rate analysis. *, *P*<0.05 compared to the control group; #, *P*<0.05 compared to the AF group.

showed a significant decrease in the AF induction rate (6/20, 30.0%, P<0.05 compared to the AF group, **Figure 2**).

*Statin improves autonomic nervous function*

We further analyzed the changes in the rat autonomic function indexes, including SDNN, SDANN, RMSSD, and the SDNNindx, plus the LF/HF ratio. The results showed that the AF rats had decreased autonomic nervous function indexes including SDNN, SDANN, RMSSD, and the SDNNindx, and elevated LF/HF ratios (P<0.05 compared to the control group). After they were treated with rosuvastatin calcium, the rats in the statin group had elevated autonomic nervous function indexes SDNN, SDANN, RMSSD, and an elevated SDNNindx, plus a lower LF/HF ratio (P<0.05 compared to the AF group, **Table 1**).

*Lower TH and higher CHAT in the rats' heart tissues after statin treatment*

Western blot was used to analyze the expressional change of TH and CHAT in the rats' heart tissues. The results showed enhanced TH expressions representing parasympathetic nerves in the AF rats' heart tissues, plus a decreased CHAT expression related to the parasympathetic nerves (P<0.05 compared to the control group). The statin group received rosuvastatin calcium treatment and had lower TH expressions and higher CHAT expressions (P<0.05 compared to the AF group, **Figure 3**).

*Statin decreases the secretions of the inflammatory factors in all groups*

ELISA was used to measure the expressional changes of the inflammatory factors TGF-β1, TNF-α, and CRP in the rat serum. The results showed that AF rats had enhanced expressions of the inflammatory factors TGF-β1, TNF-α, and CRP (P<0.05 compared to the control group). The statin group utilized rosuvastatin calcium treatment and showed decreased secretions of the inflammatory factors TGF-β1, TNF-α, and CRP (P<0.05 compared to the AF group, **Figure 4**).

## Discussion

The pathogenesis mechanism of AF consists of the reentrant and induction mechanisms of AF. The pathological changes of AF consist of abnormalities in the atrial electrical rhythm and a dysregulation of the atrial electrical activity. Instead, a rapid and irregular atrial fibrillation wave can cause acute cardiac arrhythmia [17, 18]. Inflammation is closely related to AF occurrence and maintenance and to AF complications such as embolism. AF frequently occurs during surgery or trauma. The stressed condition of the body induces the secretion, activation, and release of large amounts of inflammatory factors, suggesting a probable relationship between inflammation and AF pathogenesis [19, 20]. This study demonstrated the enhanced secretions of the inflammatory factors including TGF-β1, TNF-α, and CRP in the AF rat model, further confirming the correlation between AF and inflammation.

Statin drugs are mainly used for managing blood lipids, with additional functions for anti-inflammation and improving endothelial cells [21]. Recent studies showed that statin drugs can alleviate ischemia-reperfusion injuries in myocardial tissues, and can prevent or manage cardiac arrythmia to a certain extent [22]. Rosuvastatin calcium is one selective HMG-CoA reductase inhibitor. As a statin drug, it can facilitate the absorption and catabolism of low density lipoprotein (LDL), inhibit liver biosynthesis of very low density lipoproteins (VLDL), and treat hypercholesterolemia [23]. This study utilized rosuvastatin calcium to treat a rat AF model, and demonstrated shortened AERP and an enhanced AF induction rate in an AF model group. Rosuvastatin calcium treatment effectively facilitates the elongation of rat AERP and decreases the AF induction rate. These results suggest that rosuvastatin calcium has effects on cardiomyocytes as it can reduce the incidence of AF.

**Table 1.** Autonomic nervous function analysis

| Group | SDNN (ms) | SDANN (ms) | RMSSD (ms) | SDNNindx (ms) | LF/HF |
|---|---|---|---|---|---|
| Control | 131±21.4 | 125.6±18.6 | 33.5±9.7 | 52.2±5.6 | 5.2±0.8 |
| AF | 81.5±13.2* | 78.3±12.5* | 19.4±8.7* | 33.1±6.3* | 3.1±0.7* |
| Treatment | 110.6±18.5*,# | 118.2±11.7# | 29.3±7.1# | 41.1±5.1*,# | 4.7±0.7# |

One-way ANOVA. *, $P<0.05$ compared to the control group; #, $P<0.05$ comparing to AF group.

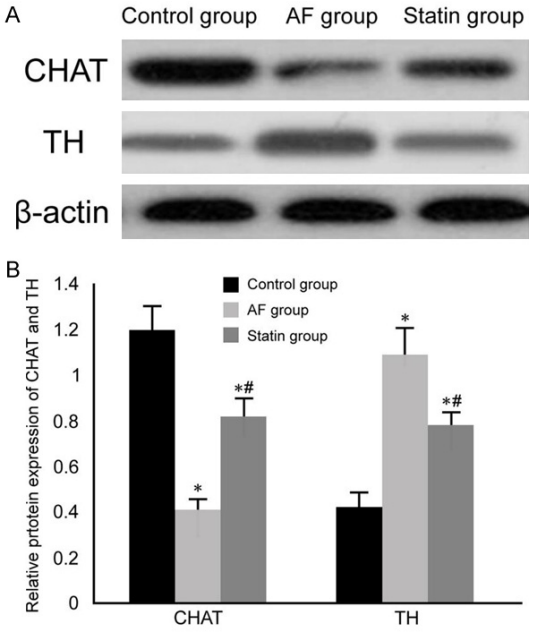


**Figure 3.** TH and CHAT expressions in the rat heart tissues. A. TH and CHAT expressions in the rat heart tissues by Western blot. B. TH and CHAT expression analysis of the rat heart tissues. *, $P<0.05$ compared to the control group; #, $P<0.05$ comparing to the AF group.

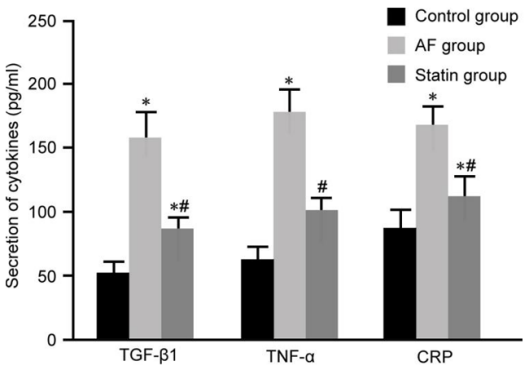


**Figure 4.** Expressional change of the serum inflammatory factors of all the groups of rats. *, $P<0.05$ compared to the control group; #, $P<0.05$ compared to the AF group.

A further analysis showed that rosuvastatin calcium can suppress the secretion of inflammatory factors in AF rats. This can be attributed to the wide and complicated regulation of autonomic nerves on the central sympathetic/parasympathetic nerves and the peripheral sympathetic/parasympathetic nerves on myocardial muscle, forming a cardiac network regulatory system by autonomic nervous system [23]. The stimuli by inflammation can send sensory information to the central region, and the parasympathetic nerves and vagal efferent nerves can distribute and intervene in the inflammatory response to further mediate cardiac arrhythmia [24, 25]. This study demonstrated decreased autonomic nervous system function indexes including SDNN, SDANN, RMSSD, and SDNNindx, plus the elevated LF/HF ratio, while the sympathetic nerve marker TH was up-regulated, and the down-regulation of the parasympathetic nervous related CHAT. Statin drug treatment can alter the expressions of the autonomic nervous function indexes in AF rats, including a decreased TH expression and an increased CHAT expression. These results showed that statin drugs can suppress inflammation and affect myocardial function via modulating endogenous autonomic nervous expression and heart function. This study provides evidence for the possible use of statin drugs to prevent and to manage AF in clinics, and further studies can be performed to understand the related mechanisms, for the initial phase of clinical trials.

## Conclusion

Statin drugs can improve AF progression by inhibiting the autonomic nervous expression and heart function and by suppressing the inflammatory response.

## Disclosure of conflict of interest

None.

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