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Original article

Different effects of norepinephrine and nerve growth factor on atrial fibrillation vulnerability

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ABSTRACT

Background: The sympathetic nerve plays an important role in atrial fibrillation (AF) vulnerability. Norepinephrine (NE) has a relationship with AF and nerve growth factor (NGF) injection can induce sympathetic innervation. However, the mechanisms of NE and NGF on AF vulnerability remain unclear.
Methods: Four groups of rabbits were studied: the control group, the NGF group, the NE group, and the NGF + valsartan + metoprolol group. After receiving drugs for 15 days, induced AF was observed, and left atrium (LA) tissues were obtained. Immunocytochemical staining of cardiac nerves and ionic remodeling were performed using anti–growth-associated protein 43 (GAP43), anti-tyrosine hydroxylase (TH) antibodies, and patch clamp.
Results: The incidence of AF was significantly higher ($p < 0.01$) in the NGF group and the NE group than in the control group and the NGF + valsartan + metoprolol group. The nerve densities for TH and GAP43-positive at the LA were significantly higher ($p < 0.01$) after NGF, but the nerve densities decreased after NE. $I_{Ca,L}$ was increased while instant outward K+ channel current (Ito) was decreased in the LA of rabbits after treatment with NGF and NE. Metoprolol and valsartan can reverse the $I_{Ca,L}$ and Ito remodeling and the vulnerability to AF. However, these drugs did not inhibit the effect of NGF on sympathetic sprouting.
Conclusions: The effects of NE and NGF on AF vulnerability have a relationship with the ionic remodeling, while the sympathetic hyperinnervation did not have a strong association with the induction of AF.

Introduction

Basic and clinical studies have shown that the autonomic nerve system plays an important and crucial role in all phases of atrial fibrillation (AF), including its onset, maintenance, and termination [1–4]. This is demonstrated by the relation of AF to states of increased adrenergic tone and electrical remodeling [5,6]. Experimental animal studies suggest that significant nerve sprouting and sympathetic hyperinnervation are present in a canine model of sustained AF [7,8]. Furthermore, a study in patients with persistent AF showed heightened atrial sympathetic innervation [9]. These studies suggest that atrial sympathetic hyperinnervation may be the substrate for AF.

Previous studies have demonstrated that high levels of norepinephrine (NE) had a relationship with AF and that nerve growth factor (NGF) injection can induce sympathetic innervation. The literature has shown that increased adrenergic tone can induce the changes of atrial L-type calcium current ($I_{Ca,L}$) and transient outward potassium current (Ito). Increased sympathetic nerve activity can increase angiotensin II production, which increases the L-type Ca^{2+} current through protein kinase C-dependent pathways. However, the effects of NE and NGF on AF vulnerability remain unclear. In the present study, NGF and NE were used to induce the changes of atrial sympathetic innervation. Ionic remodeling,

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Table 1
Changes in body weight and heart rate in the four groups.

	Control group ($n=8$)		NGF group ($n=8$)		NE group ($n=8$)		NGF + valsartan + metoprolol group ($n=8$)	
	Baseline	After 15 days	Baseline	After 15 days	Baseline	After 15 days	Baseline	After 15 days
Body weight (kg)	2.4 ± 0.2	2.3 ± 0.3	2.3 ± 0.3	2.4 ± 0.3	2.4 ± 0.3	2.6 ± 0.4	2.5 ± 0.3	2.4 ± 0.3
Heart rate (beats/min)	222 ± 11	223 ± 11	223 ± 13	224 ± 12	220 ± 12	245 ± 13[#]	221 ± 12	211 ± 12

[#] $p < 0.05$ versus the control group, NGF group, and the NGF + valsartan + metoprolol group.
NE, norepinephrine; NGF, nerve growth factor.

sympathetic remodeling, and induced AF were studied to investigate the different mechanisms of NE and NGF on AF vulnerability.

Methods

Preparation of animal model

This study was approved by the animal studies subcommittee of our institutional review board and was in compliance with the guidelines of the National Institutes of Health for the care and use of laboratory animals. Thirty-two adult New Zealand white rabbits (1.5–2.0 kg) were randomly divided into four groups of eight rabbits: the control group, the NGF group, the NE group, and the NGF + valsartan + metoprolol group. In the NGF and NE groups, rabbits were treated with NGF 1 mg/kg (once daily) and NE 1 mg/kg (twice daily) by intraperitoneal injection. In the NGF + valsartan + metoprolol group, rabbits were subjected to NGF (1 mg/kg) by intraperitoneal injection and oral valsartan (10 mg/kg) plus metoprolol (5 mg/kg) once daily. In the control group, rabbits were administered sodium chloride (1 ml) only. The rabbits received drugs for 15 days.

Induction of AF

After 15 days, the rabbits were abdominally anesthetized with sodium pentobarbital (30–40 mg/kg, i.v.), and additional doses were administered when required throughout the experiment. The animals were intubated and ventilated with room air supplemented with low flow oxygen from a mechanical ventilator. Electrocardiogram (ECG) (II, avF) was continuously monitored. Surgery was performed under sterile conditions. A thoracotomy was performed through the third intercostal space, and the heart was exposed after excising the pericardium. The pacing electrodes were attached in the right atrial appendage. Subsequently, pacing was stopped, and the burst pacing (800 beats/min) was repeated to induce AF five times. The duration of S1S1 stimulation lasted for 5 s. AF was defined as irregular atrial rates faster than 500 bpm, lasting >5 s. The number of induced AF episodes and the duration of AF were measured in each rabbit.

Immunohistochemical studies

After induction of AF measurements, the hearts were extracted. Then, tissues were obtained from the left atrium (LA) for immunohistochemical studies. We used anti-growth-associated protein 43 (GAP43) and anti-tyrosine hydroxylase (TH) antibodies for immunocytochemical staining. The tissues were stained in the same session. We determined nerve densities by a computer-assisted image analysis system (Image-Pro Plus 3.0, Media Cybernetics, Rockville, MD, USA). Each slide was examined under a microscope to select 3 fields with the highest density of nerves. The computer then automatically calculated the area occupied by the nerves in the field. The nerve density was the area occupied by the nerves divided by the total area examined ($\mu m^2/mm^2$). The mean density of nerves in these 3 selected fields was used to represent the nerve density of that slide.

Cell isolation and patch clamp technique

Hearts were removed from rabbits, and single rabbit LA myocytes were obtained by the previous dispersion method [10]. The isolated cells were perfused with the Tyrode solution containing (mM): NaCl (136), KCl (5.4), $CaCl_2$ (1), $MgCl_2$ (1), glucose (10), and HEPES (5), with a resulting pH of 7.4; bath solution (mM): NaCl (136), KCl (5.4), $CaCl_2$ (1), $MgCl_2$ (1), glucose (10), HEPES (10), with a resulting pH of 7.4; pipette solution for $I_{Ca,L}$ (mM): CsCl (120), $CaCl_2$ (1), MgCl2 (5), EGTA (11), HEPES (10), Na_2ATP (5), glucose (11); and, pipette solution for Ito (mM): KCl (45), Mg ATP (5), EGTA (10), HEPES (10), glucose (11), K-aspartate (85), and N-pyruvate (5). Ionic currents were recorded using whole cell configuration of the voltage clamp technique using an EPC-9 amplifier (HEKA Instruments, Lambrecht, Germany). Data were sampled with an A/D converter (Digidata 1200, Axon Instruments, CA, USA) and stored for subsequent analysis.

Statistical analysis

Values are shown as the mean ± SD. Statistical comparisons were made using ANOVA. Paired and unpaired comparisons were conducted using Student's *t*-test. Unpaired *t*-tests were used to compare the means of nerve densities. Statistical significance was assumed if *p*-values were less than 0.05.

Results

Changes in body weights and heart rates

As shown in Table 1, after 15 days, there was no difference in the weights between any of the groups. In the NE group, the heart rates were significantly higher than that in the control, NGF, and NGF + valsartan + metoprolol groups (245 ± 13 beats/min vs. 223 ± 11 beats/min, 224 ± 12 beats/min, 211 ± 12 beats/min, respectively; $p < 0.05$). Although not statistically significant, there was a slight decrease in heart rates after 15 days in the NGF + valsartan + metoprolol group (221 ± 12 vs. 211 ± 12 beats/min; $p > 0.05$).

AF vulnerability

In the present study, AF was defined as a period of more than 5 s of fibrillation waves on the surface ECG. The results of AF inductions are shown in Table 2. AF was not induced in the control group. However, AF was induced in 6 NE rabbits and 5 NGF rabbits. The mean duration of induced AF was not significantly different between the NGF group and the NE group. Only one rabbit had AF induced in the NGF + valsartan + metoprolol group. The incidence of AF was significantly higher ($p < 0.01$) in the NGF

Table 2
Characteristics of AF induction.

	Control group ($n=8$)	NGF group ($n=8$)	NE group ($n=8$)	NGF + valsartan + metoprolol group ($n=8$)
Rabbits of induced AF	0	5*	6*	1
Mean duration of AF (s)	0	11.1 ± 11.8*	15.1 ± 13.4*	0
Longest duration of AF (s)	0	23	29	0

* $p < 0.05$ versus the control group and the NGF + valsartan + metoprolol group.
AF, atrial fibrillation; NE, norepinephrine; NGF, nerve growth factor.

group and the NE group (62.5% and 75%) than in the control group and the NGF + valsartan + metoprolol group (0% and 12.5%), respectively.

Sympathetic nerve density

Immunohistochemical staining showed that the nerve densities for TH and GAP43-positive at the LA were significantly higher ($p < 0.01$) in the NGF group and the NGF + valsartan + metoprolol group than in the control and NE groups. Furthermore, the density of positive nerves was significantly higher ($p < 0.01$) in the control group than in the NE group. Figs. 1 and 2 show typical examples of sympathetic nerve distribution in the four groups as determined using the marker.

Changes of $I_{Ca,L}$ and Ito

$I_{Ca,L}$ was studied 5 min after cell membrane rupture in all cells to avoid contaminating effects of $I_{Ca,L}$ rundown. Fig. 3 shows a typical example of calcium current recorded from a cell of LA in the control, NGF, NE, and NGF + valsartan + metoprolol groups. The NGF and the NE groups had a significant increase in $I_{Ca,L}$ current densities; however, there was no significant difference between the control group and the NGF + valsartan + metoprolol group. For example, when a test potential of 0 mV current densities were -9.27 ± 0.64 pA/pF in the NGF group and -10.13 ± 0.68 pA/pF in the NE group against -6.24 ± 0.53 pA/pF in the control group and -6.82 ± 0.52 pA/pF in the NGF + valsartan + metoprolol group ($p < 0.05$).

Ito currents were recorded under conditions designed to eliminate I_{Na} and I_{Ca}. Fig. 3 shows recordings of steady-state currents from a cell of LA in the control group, the NGF group, the NE group, and the NGF + valsartan + metoprolol group. The current voltage (I–V) relations for Ito in the 4 groups are illustrated in Fig. 4B. Ito current densities were significantly reduced in the NGF group and the NE group at all test potentials positive to 0 mV, i.e. at +70 mV 8.57 ± 0.72 pA/pF in the control group to 5.12 ± 0.69 pA/pF in the NGF group and to 5.04 ± 0.64 pA/pF in the NE group. However, there was no significant difference between the control group and the NGF + valsartan + metoprolol group.

Discussion

The results of the present study show that experimental chronic high plasma NE and NGF levels create atrial substrate for AF and increase the incidence of inducible AF and its duration. The effects of NE and NGF on AF vulnerability have a relationship with the ionic remodeling, while the sympathetic hyperinnervation did not have a strong association with the induction of AF.

Previous studies have shown that heterogeneous nerve sprouting and sympathetic hyperinnervation were documented in a canine model of sustained AF [8,11]. In another study, Olgin et al. [1] reported that sympathetic atrial denervation by phenol creates heterogeneous autonomic innervation, facilitating sustained AF. Furthermore, Jayachandran et al. [7] used positron emission tomography imaging to document that dogs with AF had inhomogeneous changes of atrial sympathetic innervation. The authors proposed that sympathetic hyperinnervation may strengthen the generation and maintenance of AF. However, in the present study, rabbits were treated with NGF and NE by intraperitoneal injection to induce sympathetic sprouting. The results showed that AF was induced easily while the sympathetic innervation decreased in the NE group. Furthermore, sympathetic innervation increased in the NGF + valsartan + metoprolol group

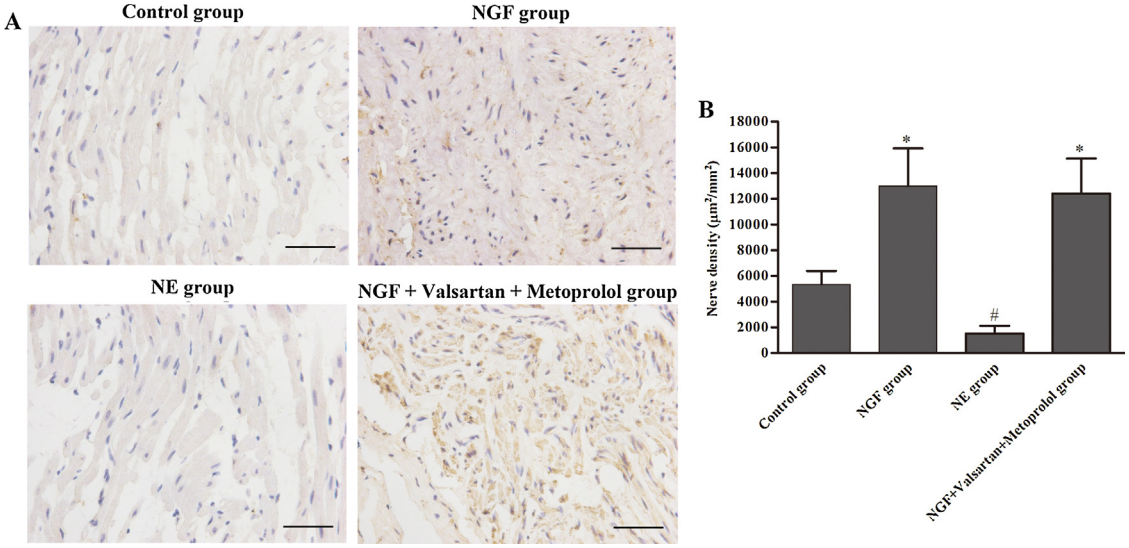

Fig. 1. (A) Growth-associated protein 43 staining of cardiac nerves (brown twigs) in the left atrium. (B) Results of immunocytochemical studies at different groups. Scale bar: 50 μm. *$p < 0.01$ versus control group and NE group; #$p < 0.01$ versus control group. NE, norepinephrine; NGF, nerve growth factor.

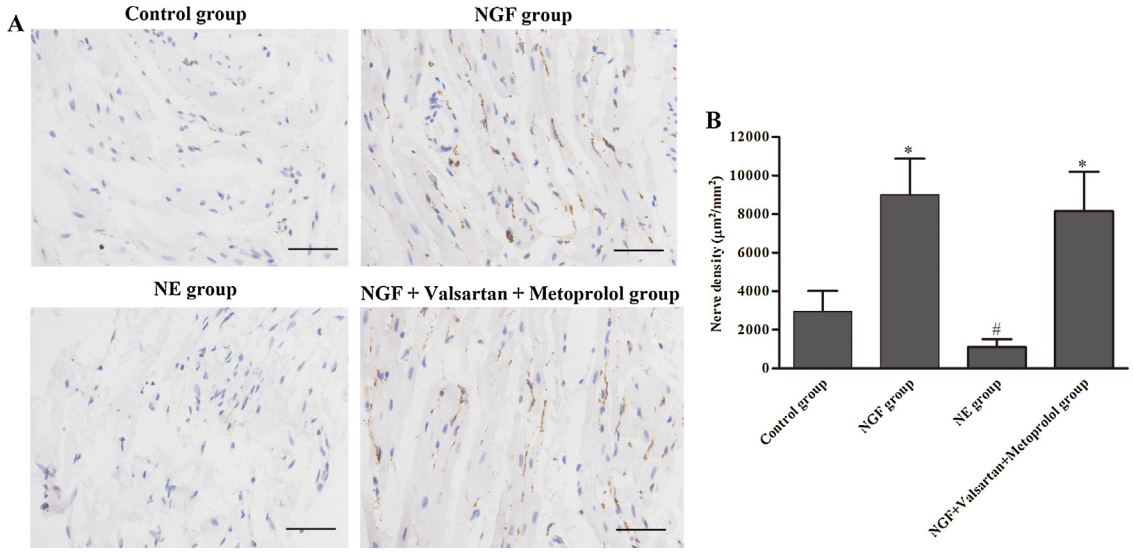

Fig. 2. (A) Tyrosine hydroxylase staining of cardiac nerves (brown twigs) in the left atrium. (B) Results of immunocytochemical studies at different groups. Scale bar: 50 μm. $^{*}p < 0.01$ versus control group and NE group; $\#p < 0.01$ versus control group. NE, norepinephrine; NGF, nerve growth factor.

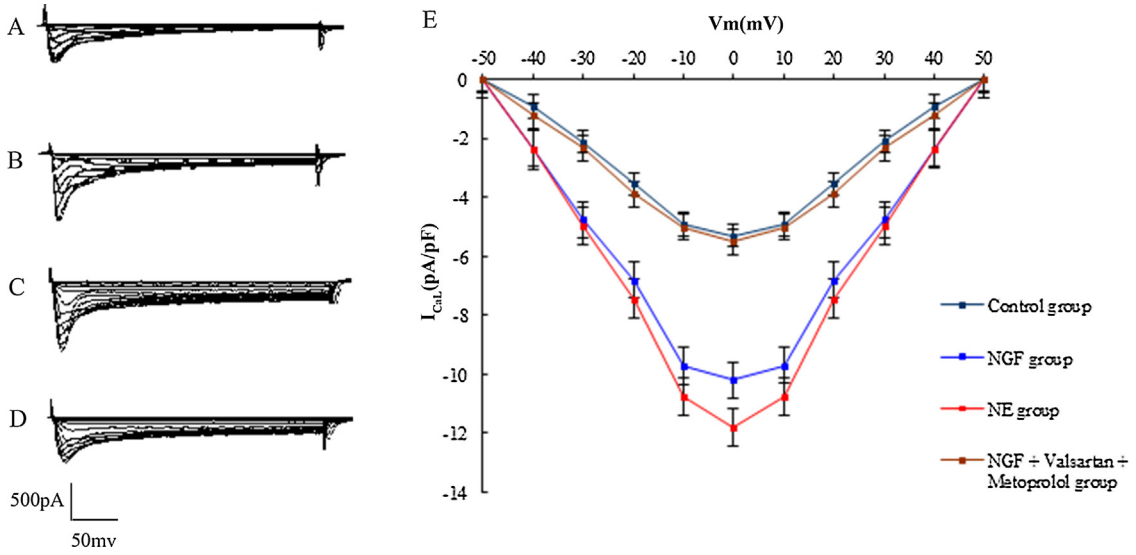

Fig. 3. (A–D) Recordings of $I_{Ca,L}$ obtained with the voltage protocol shown in the inset at 0.1 Hz in representative cells obtained from the four groups. $I_{Ca,L}$ was elicited from a holding potential of −50 mV, with 200 ms pulses, increasing from −50 mV to +50 mV in 10 mV steps. The inactivation was at −60 mV with 1000 ms, increasing from −56 mV to +10 mV in 10 mV steps. To avoid the 'run-down' effects, $I_{Ca,L}$ was measured between 5 and 15 min after rupturing the membrane patch in each cardiomyocyte from the control and pacing groups. When the testing potential was depolarized at +10 mV, $I_{Ca,L}$ reached its peak. (E) Ica, L current density–voltage relationships of the currents. The

although AF was not induced. These findings suggest that sympathetic hyperinnervation may not have a critical role in the generation and maintenance of AF.

The ionic properties of the atria play an important role in determining the occurrence and properties of AF [12–14]. Shortening of the atrial refractory period and the atrial action potential may be caused by a net decrease of inward ionic currents (Na^+ or Ca^{2+}), a net increase of outward currents (K^+), or a combination of both. Moreover, clinical [15,16] and experimental studies [17] consistently indicate important pathways: the downregulating effect of AF on the $I_{Ca,L}$ and the Ito and the role of the $I_{Ca,L}$ downregulation in arrhythmogenic action potential abnormalities associated with AF.

On the other hand, the crucial role of cytosolic calcium increase, in particular calcium overload, in the changes induced by AF has been recognized widely [18,19]. Thus, several lines of evidence point to a central role for intracellular calcium overload in induced AF remodeling. This might be responsible for decreased contractility as well as for the remodeling processes that convey the vulnerability to AF [20]. In the present study, $I_{Ca,L}$ was increased, and AF was induced easily at a chronic high plasma NE level. The increased $I_{Ca,L}$ may increase cytosolic calcium then induce calcium overload and the vulnerability to AF. The downregulating $I_{Ca,L}$ in persistent AF or rapid atrial pacing in the previous study could be atrial myocytes adapting to counteract the cytosolic calcium overloading.

Ultimately, the effect of beta-blockers on atrium remodeling and AF suppression has not been well studied. Metoprolol was useful in preventing AF recurrence in patients with persistent AF who were successfully cardioverted to sinus rhythm [21]. Previous reports have suggested that there is a reduction in the development or recurrence of AF in patients treated with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARB) [22,23]. Studies suggest that the renin–

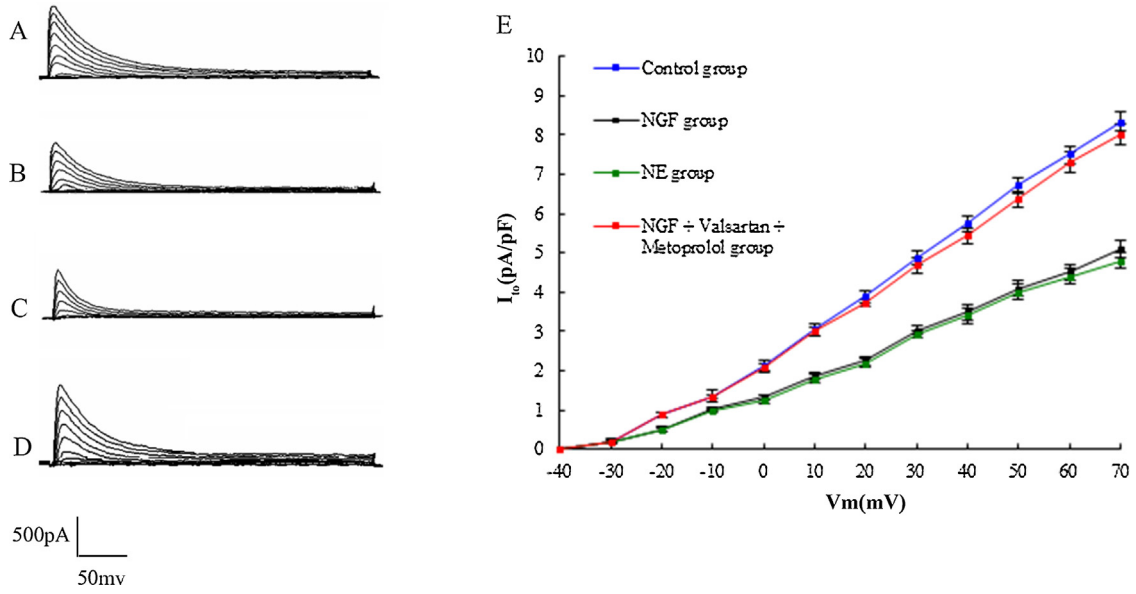

Fig. 4. (A–D) Recordings of Ito obtained with the voltage protocol shown in the inset at 0.2 Hz in representative cells obtained from the four groups. The cardiac cells were held at a holding potential of −80 mV, depolarized to −40 mV for 25 ms to inactivate sodium currents, and then depolarized in 10 mV increments over 500 ms to a test potential of +70 mV. Ito was measured as the difference between the peak amplitude and the current remaining at the end of the pulse. This outward current activated rapidly, inactivated transiently, and then reached steady levels. Ito was activated at −30 mV, the current density increased with the increase of test potential, and the peak was reached at +70 mV. (E) Ito current density–voltage relationships of the currents. The density of Ito was decreased significantly from (8.35 ± 0.65) pA/pF in the control group to (5.10 ± 0.42) pA/pF in the NGF group and (4.92 ± 0.39) pA/pF in the NE group ($n = 6$, $p < 0.05$). NE, norepinephrine; NGF, nerve growth factor.

angiotensin–aldosterone system could affect ion channels, action potential period and impulse propagation, and facilitate re-entry. Angiotensin II increases $I_{Ca,L}$ through protein kinase C-dependent pathways [24]. Patients with persistent AF who were treated with ARB combined with amiodarone had lower recurrence of AF, when compared with those treated with amiodarone alone [25]. ACE inhibition has also been shown to have important beneficial effects on electrical remodeling [26,27]. In our study, we found that metoprolol and valsartan can reverse the $I_{Ca,L}$ and Ito remodeling and vulnerability to AF. However, these drugs cannot inhibit the effect of NGF on sympathetic sprouting. Therefore, our results showed that the sympathetic hyperinnervation does not have a strong association with the induction of AF.

Limitations

This study has several limitations. First, we did not perform functional electrophysiological measurements and blood pressure. Therefore, atrial effective refractory period (AERP), action potential duration and dispersion of AERP, and blood pressure are not available for comparison with the magnitude of nerve sprouting. Second, in this study, we measured the sympathetic nerve density in the LA and did not measure the sympathetic nerve density in the right atrium and pulmonary veins. Whether NGF or NE by intraperitoneal injection creates heterogeneous sympathetic sprouting in the atrium is unknown. Third, we did not investigate substrate changes in the atria, such as changes of echocardiography and concentration of interstitial fibrosis. To our knowledge, high plasma NE level can induce myocardial hypertrophy and fibrosis. Hence, the current study cannot provide further insight into whether myocardial fibrosis has an impact on AF vulnerability in the NGF or NE groups should be further investigated. Finally, we did not observe the effects of NE and ARB/beta blocker combination on the AF vulnerability. Despite these limitations, the findings of this study suggest that experimental chronic high plasma NE and NGF levels create atrial substrate for AF and increase the incidence of inducible AF and its duration.

Conclusions

The effects of NE and NGF on AF vulnerability have a relationship with ionic remodeling, while the sympathetic hyperinnervation did not have a strong association with the induction of AF in an experimental rabbit model.

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Conflict of interest

The authors declare that there is no conflict of interest.

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