

Research progress on central autonomic nervous mechanism of acupuncture at Neiguan point in the treatment of atrial fibrillation

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia disease and is associated with several cardiovascular and cerebrovascular diseases. Consequently, the mortality rate of AF has increased in recent years. At present, the treatment of AF is mainly based on medication and radiofrequency ablation, but there are limitations such as adverse reactions and high recurrence rates. Recently, autonomic nervous regulation has become a new treatment for AF. Our previous study showed that acupuncture at Neiguan (PC6) point can treat AF by regulating autonomic balance. The autonomic nervous system can be structurally divided into the central autonomic nervous (CAN) and the peripheral autonomic nervous (PAN). Several studies have shown a correlation between acupuncture and the treatment of AF and CAN. In the clinic, the positive effect of acupuncture on AF has been realized gradually, and growing experimental studies have further discovered the potential mechanism of acupuncture on AF by regulating the CAN. Therefore, this review mainly focuses on summarizing the CAN mechanism related to acupuncture in the treatment of AF to provide new ideas and directions for the treatment of AF.

Keywords: Atrial fibrillation, Acupuncture treatment, Central autonomic nervous system, Neiguan (PC6), Review

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Introduction

Atrial fibrillation (AF) is a common and important arrhythmias with significant health and socioeconomic implications^[1]. Currently, AF affects 33 million people worldwide, and its high morbidity and mortality are related to several potentially serious complications, such as cardiomyopathy, heart rate failure, and stroke^[2]. Modern medical treatments for AF mainly include anti-arrhythmic drugs to promote the maintenance of normal

sinus rhythm and catheter ablation; however, both have obvious limitations^[3–5].

Autonomic nerve modulation is gaining attention in AF research owing to its potential to reduce the side effects of traditional drugs and radiofrequency catheter ablation. Acupuncture is an important component of traditional Chinese medicine (TCM) used clinically to treat many diseases related to autonomic nervous system dysfunction, such as cardiovascular disease, epilepsy, anxiety, and depression^[6–7]. According to the TCM theory, the core function of acupuncture is to restore the balance between yin and yang. The sympathetic and parasympathetic nervous systems are specific manifestations of yin and yang in TCM^[8]. Acupuncture plays an active role in the treatment of AF and has low adverse reactions.

Coumel et al.^[9] originally described the role of the autonomic nervous system in the initiation of AF in the 1970s. Using magnetic resonance imaging (MRI) and simultaneously monitoring autonomic activity in patients with AF, the results showed that there are potential brain circuits that regulate abnormal sympathetic activity in patients to correct the dysregulation of the central autonomic and cardiovascular control^[10]. Animal studies showed that acupuncture can regulate heart rate even after inhibiting autonomic nervous function, suggesting that the regulation of heart rate by acupuncture depends on the CAN^[11]. Zhang et al.^[12] found that acupuncture at Neiguan (PC6) point and non-point activation of brain areas have a relative difference, acupuncture at Neiguan (PC6) point can specifically activate the brain center. Electroencephalogram (EEG) studies indicate that stimulating the Neiguan (PC6) point can increase the connection between regions of the cerebral cortex^[13]. In this review, we summarize the recent clinical applications and autonomic nerve mechanisms related to

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acupuncture in the treatment of AF, using relevant literature from 2000 to 2023 in PubMed, Web of Science, and CNKI databases as targets, with the aim of demonstrating the feasibility of acupuncture in the treatment of AF through CAN regulation from the viewpoint of TCM.

Clinical study of acupuncture in the treatment of AF

Many clinical studies have shown that acupuncture has a protective effect on AF^[14–17]. In 2011, *J Cardiovasc Electrophysiol* published a randomized controlled trial (RCT) report^[18], which showed a statistically significant difference in the recurrence rate of AF during a 12-month follow-up period (recurrence rate was 27% in the amiodarone group, 35% in the acupuncture group, 69% in the sham acupuncture group, and 54% in the control group). Acupuncture can also prevent arrhythmia recurrence after cardioversion in patients with persistent AF. In 2019, the same journal published another RCT^[19] which showed that the early recurrence rate in the acupuncture group was lower than that in the amiodarone group after 3 months.

Stroke is a serious complication of AF. In a retrospective study on the association between acupuncture and stroke risk in patients with AF, the results showed that acupuncture was associated with a reduced risk of stroke in these patients^[20]. In terms of cardiac structure, research has shown that after 3 months of acupuncture treatment, patients in the acupuncture treatment group showed better atrial structural remodeling than those in the sham acupuncture group^[21]. In a 2017 systematic review^[22], 739 patients were included in 13 RCTs comparing acupuncture with conventional drugs, sham acupuncture, or bed rest for the treatment of arrhythmia. A meta-analysis showed that the clinical efficacy of acupuncture for the treatment of paroxysmal supraventricular tachycardia was not lower than that of oral antiarrhythmic drugs. Subgroup analysis showed a significant benefit of acupuncture in the treatment of premature ventricular contraction and sinus tachycardia regardless of the use of oral antiarrhythmic drugs. The main characteristics of electrocardiogram (ECG) in patients with AF are P-wave disappearance and RR interval irregularity, that is, heart rate acceleration and absolute irregularity of heart rhythm. In recent years, clinical studies showed that acupuncture at Neiguan (PC6) point has a good therapeutic effect on cardiovascular diseases^[23]. Some clinical studies showed that acupuncture at Neiguan (PC6) point has the effect of regulating heart rate, which is also the main goal of clinical treatment in AF. Luo et al.^[24] used the method of HRV analysis to observe the physiological regulating effect of acupuncture at Neiguan (PC6)-Jianshi (PC5) point on the cardiac autonomic nerve in healthy people, it was found that acupuncture at Neiguan (PC6) point can regulate the autonomic nerve of the heart in healthy people to a certain extent, that is, it can cause the vagus nerve to excite and the heart rate to slow down.

Clinically, the selection of acupoints for AF treatment reflects dialectical treatment in TCM. Acupoint selection focuses on the interaction between the circulation of meridians and the use of specific acupoints. The main acupoints for AF are Neiguan (PC6), Qihai (RN6), Zhongwan (RN12) and Danzhong (RN17) points, and

the highest selection frequency acupoint is Neiguan (PC6) point^[18–19,25–34] (Table 1). Neiguan (PC6) point, as the collateral point of the pericardium meridian, is frequently used to regulate qi and blood in the heart, and the core prescriptions of acupoint compatibility are Danzhong (RN17), Xinshu (BL15) and Neiguan (PC6) points^[19].

Acupuncture at Neiguan (PC6) point has been widely used in the treatment of AF. However, current clinical research is limited to the transient effect of acupuncture, which can be monitored for 24 h to observe the long-term and sequelae effects of acupuncture at Neiguan (PC6) point in regulating heart rate. Current research on acupuncture methods focuses on hand acupuncture and electroacupuncture, and whether there is a difference between the regulation of heart rate by hand acupuncture and electroacupuncture at Neiguan (PC6) point. There are few studies on the influence of different frequencies and waveforms of electroacupuncture at Neiguan (PC6) point on heart rate. Based on the above, the use of acupuncture at Neiguan (PC6) point to treat AF requires a large sample size and multi-center clinical study to further validate and promote AF.

Mechanism of acupuncture at Neiguan point in the treatment of AF

Neuromodulation: AF treatment using Neiguan point stimulation

Acupuncture at Neiguan (PC6) point excites type II and III afferent fibers of the median nerve^[35], which can reduce the induction of AF^[36]. Neiguan (PC6) point lies between the palmaris longus tendon and the flexor carpi radialis tendon, through which the median nerve trunk passes. Some studies^[37–39] suggested that median nerve stimulation can reduce sympathetic nerve tension and increase vagal nerve tension. Acupuncture is an exogenous physical therapy that has a wide range of functions. In recent years, it has been proved that acupuncture can regulate the connectivity of the brain function network^[40]. Recently, the application of brain functional imaging technology to study the neural mechanisms of acupuncture has aroused wide interest and attention, and research results have shown that acupuncture can benignly adjust the abnormal brain functional network of some diseases^[41].

The effect of acupuncture is achieved by regulating the neural-endocrine-immune network, which has multi-links and multi-target^[42]. Its effects mainly depend on the generation, conduction, integration, and output of acupuncture information among the acupoints, brain, and effective organs^[43]. Central integration of the nervous system is the basis of the effects of acupuncture^[44–46]. The acupoint is the initial site of acupuncture. Local acupuncture stimulation activates various receptors and peripheral nerve endings to form an afferent impulse that rapidly exerts its effect through the nerve reflexes. There are two types of body surface autonomic reflexes: the body surface sympathetic reflex and the body surface parasympathetic reflex, which are determined by the autonomic innervation of the organ and the spinal cord segment at the site of stimulation and are affected by the intensity and type of stimulation. The regulation

Table 1
Summary of the literatures on atrial fibrillation treatment using acupuncture

Author	Acupuncture methods	Acupuncture prescription	Population of study	Needle retention time	Acupuncture manipulation
Lomuscio et al. ^[18]	Filiform needle acupuncture	Neiguan and Shenmen	Patients with persistent atrial fibrillation after electrical cardioversion	15–20 min	Unspecified
Yin et al. ^[19]	Filiform needle acupuncture	Neiguan	Patients with persistent atrial fibrillation after pulmonary vein isolation	20 min	Twirling supplementation and draining method
Cui et al. ^[25]	Filiform needle acupuncture	Neiguan and Shenmen	Patients with persistent atrial fibrillation after pulmonary vein isolation	Unspecified	Twirling supplementation and draining method
Zhao et al. ^[26]	Filiform needle acupuncture + moxa-moxibustion	Neiguan, Zusanli, and Guanyuan	Patients with sinus bradycardia after modified maze surgery for persistent atrial fibrillation	20 min	Lifting and thrusting, twisting and flattening
Zhao et al. ^[26]	Filiform needle acupuncture + moxa-moxibustion	Neiguan, Zusanli, and Guanyuan	Patients with sinus bradycardia after modified maze surgery for persistent atrial fibrillation	30 min	Lifting and thrusting, twisting and flattening
Xv and Zhang ^[28]	Filiform needle acupuncture	Neiguan, Danzhong, Qihai, Zhongwan, and Zusanli	Patients with paroxysmal atrial fibrillation	60 min	Lifting and thrusting
Xia et al. ^[29]	Filiform needle acupuncture	Neiguan, Ximen, Sanyinjiao, and Xuehai	Patients with paroxysmal rapid atrial fibrillation	No needle retained	Flat reinforcing and flat reducing, lifting, and inserting reducing methods
Han ^[30]	Filiform needle acupuncture	Neiguan, Ximen, Sanyinjiao, and Xuehai	Patients with paroxysmal atrial fibrillation	30 min	Flat reinforcing and reducing, lifting and thrusting reinforcing and reducing
Yan et al. ^[31]	Filiform needle acupuncture	Neiguan, Shenmen, Danzhong, Jueyinshu, Xinshu, and Geshu	Patients with paroxysmal atrial fibrillation	30 min	Lifting and thrusting
Xv ^[32]	Filiform needle acupuncture	Neiguan, Ximen, Sanyinjiao, and Xuehai	Patients with paroxysmal atrial fibrillation	30 min	Flat reinforcing and reducing, lifting and thrusting reinforcing and reducing
Jonkman and Jonkman-Buidin ^[33]	Filiform needle acupuncture	Ququan, Taixi, Shenshu, Yinxi, Neiguan, Taichong, Hegu, Sanyinjiao, Geshu, Fenglong, Lieque, and Fengchi	Patients with drug-resistant atrial fibrillation	30 min	Lifting and thrusting
Dilber et al. ^[34]	Filiform needle acupuncture	Zusanli, Shenmen, and Neiguan	Patients with paroxysmal atrial fibrillation	25 min	Lifting and thrusting

of visceral function by acupuncture is coordinated by the spinal cord and supraspinal center. The acupuncture-induced splanchnic reflex is an important nerve reflex that regulates the functions of the cardiovascular and gastrointestinal organs^[47]. The heart and small intestine meridians regulate the heart rate, and this function may be achieved through changes in the corresponding nuclear group neuropeptides. The nerve structure and its transmitter are the structural and material basis of the channel-*zang-fu* connection, and peptidergic nerves and neuropeptides are part of this structure^[48–49].

The mechanism of cardiac autonomic nerve innervation by acupuncture at Neiguan point

Neiguan (PC6) point is located in the middle nerve distribution area, which belongs to the cervical 7-thoracic 2 nerve segment, and the heart, is located in the thoracic 1-thoracic 5 nerve segment. Neiguan (PC6) point is connected to the heart through both long reflexes that passes through the central nervous system and short reflexes independent of the central nervous system^[50].

Yan et al. stimulated the median nerve, ulnar nerve, and muscle in Neiguan (PC6) point area on both sides

of rats, and observed their influence on the ECG of rats with acute myocardial ischemia. The results showed that stimulation of the median nerve could improve the ECG of myocardial ischemia; however, stimulation of the ulnar nerve had a weak effect and muscle stimulation had no effect. The median nerve may be the main pathway of signal transmission at Neiguan (PC6) point^[51].

Needling at Neiguan (PC6) point produces a nerve impulse in the afferent type II and III median nerve fibers, that is integrated into the spinal cord, and finally transmitted by the sympathetic adrenergic nerve to regulate cardiovascular function^[35]. Lomuscio et al.^[18] showed that acupuncture at Neiguan (PC6) point, Shenmen (HT7), and Xinshu (BL15) points may prevent arrhythmia recurrence after electrical cardioversion in patients with persistent AF. Acupuncture treatment for AF makes it possible to use somatosensory stimulation to achieve nerve regulation.

Dorsal nucleus of vagus nerve (DMV) and nucleus ambiguus (NA) are well-known areas of cardiac inhibition. Horseradish peroxidase method demonstrated that the preganglionic neurons innervating the heart in the dorsal vagal nucleus were distributed from the superior to the inferior door, with dense supra embolic neurons. Preganglionic vagal fiber in rat heart originates from

DMV and NA, reach and innervate the cardiac conduction system, myocardium, and coronary vessel wall. The nucleus tractus solitarius (NTS) is located on the dorsal side of the medulla oblongata, which is the first-order center of the vagus nerve sensory afferent and participates in the regulation of cardiovascular, respiratory, and gastrointestinal functions as well as, the first-order sensory relay station of the cardiovascular baroreceptor reflex and gastrointestinal sensation. In rats, the most prominent medullary nuclei are the subnucleus and the DMV. There are also a few projections to NA and nucleus raphe magnus^[52–53]. Because of the complexity of brain function, many brain regions participate in various higher neural networks, which belong to both the central autonomic and limbic system networks. Therefore, the mechanism of acupuncture in the treatment of AF is closely related to the integration of central autonomic nervous system.

The mechanism of central autonomic nerve innervation by acupuncture treatment

In addition to the clinical observations, several experimental studies have shown that acupuncture inhibits AF. Magnetic resonance imaging and monitoring of autonomic nervous activity indicate that arrhythmia in patients with AF, is not caused by a single central structure, but by a network system in the brain called the CAN. In a healthy state, the CAN maintains homeostatic by controlling cardiovascular responses. The CAN is mainly related to the anterior cingulate cortex, insular cortex, amygdala, periaqueductal gray (PAG), ventrolateral medulla, and nucleus tractus solitarius in the lower part of the brainstem^[10].

The study showed that acupuncture at the Neiguan (PC6) point can also regulate the heart rhythm in patients with AF. Lin^[54] proposed that the regulation of heart rhythm by acupuncture is a type of surface-visceral reflex activity mediated by the autonomic nervous system *via* acupoint stimulation. Gao et al.^[55] found that the integrity of the surface-visceral reflex pathway and functional integrity of the cardiac vagus and sympathetic nerves were necessary for acupuncture to regulate heart rhythm. Furthermore, some animal studies revealed that acupuncture can regulate heart rate despite autonomic nervous function blockade by drugs, indicating that acupuncture regulation of heart rate depended on the autonomic nervous system and the integrity of the central nervous system^[11]. Zhang et al.^[12] found that acupuncture at Neiguan (PC6) point and non-acupoint-activated brain areas showed relative differences, indicating that acupuncture at Neiguan (PC6) point can specifically activate certain brain regions. Some EEG studies indicated that stimulation of the Neiguan (PC6) point can increase the connection between cerebral cortex regions^[13], whereas other studies have shown that the mechanism of acupuncture in treating AF is by regulating nerve signal transmission and neurotransmitters release, which affect endocrine balance in cells and chemical messengers in body fluids^[56].

Acupuncture at Neiguan (PC6) point potentially activates a sensory pathway that projects to several areas of the central nervous system and ultimately regulates the autonomic nervous system through long circulation

pathways in the hypothalamus, mesencephalon, and medulla oblongata^[36]. Changes in heart rate at specific acupoints are the result of shifts in the sympathetic nervous system and vagal dominance, which are mediated by an external network of cortical and subcortical regions^[57]. Acupuncture acts by downregulating autonomic nerve activity through the skin tactile receptors to the brainstem, hypothalamus, and other central structures^[58].

Hypothalamus

The hypothalamus is an important part of the autonomic nervous system and brain for acupuncture treatment of arrhythmias. The hypothalamus plays a key role in regulating blood pressure through the outflow of sympathetic signals to the muscle vascular bed. Electroacupuncture can improve the cardiovascular system and regulate blood pressure by regulating the balance between the sympathetic and parasympathetic nerves^[25]. In normal animals, electrical stimulation of the hypothalamus near the midline can cause hyperactivity of the sympathetic nervous system, and arrhythmias such as ventricular premature contractions (HVE). HVE is induced by hypothalamic stimulation and almost disappeared after bilateral stellate ganglion removal, and the function of the buffering nerve also directly affected the occurrence of HVE^[59–60].

The paraventricular nucleus (PVN) of hypothalamus is an integrated area of the central nervous system that plays an important role in the regulation of sympathetic nervous system efferent functions, and participates in the regulation of stress and endocrine and cardiovascular activities^[61–62]. The PVN is an important component of acupuncture in improving cardiac function. It can be divided into two ways: one is that acupuncture can regulate the activity of the autonomic nerve and exert a protective effect on the myocardium by inhibiting the abnormal excitation of neurons in the PVN, regulating the release of central neurotransmitters and reducing inflammatory factors in the central nervous system. Second, it may be related to the multi-channel regulation of neuro-immune networks, such as reducing the secretion of hypothalamic-pituitary-adrenal axis substances under stress. A specific neural activation map showed that acupuncture activated the positive expression of c-Fos in the PVN, indicating that acupuncture intervention activated PVN neurons and that the PVN participated in the acupuncture effect^[63]. The PVN is the central integration area of sympathetic efferent activity and is the most important central location^[64].

The PVN has many pathways that regulate cardiovascular disease, including the projection of enkephalinergic neurons to the rostral ventrolateral medulla (RVLM) to regulate cardiovascular reflex activity^[65]. A study demonstrated that the hypotensive effect of electroacupuncture varied before and after blocking opioid receptors in the PVN, and that the hypotensive effect of electroacupuncture was reversed after the blockade. It has been suggested that the PVN and its projection to the RVLM play an important role in the hypotensive effect of electroacupuncture through the opioid receptor mechanism^[66]. In a study on the regulation of the neuroendocrine axis,

acupuncture was shown to block the increase in norepinephrine and neuropeptide Y in the hypothalamic-pituitary-adrenal axis and sympathetic ganglia, and regulate the blood pressure of the ganglia^[67].

The arcuate hypothalamic nucleus (Arc) are involved in regulating cardiac vessels. Recent studies have shown that the cardio vascular response induced by acupuncture was mediated by direct and indirect projections from the Arc to RVLM. Electroacupuncture can activate Arc and vIPAG neurons through direct glutamatergic fiber projection and over-activation of synapses. Additionally, pre-cannabinoid receptor-induced inhibition of gamma-aminobutyric acid (GABA) release can depress vIPAG neurons, and the excitability of vIPAG neurons leads to the excitability of raphe nucleus pulposus, which inhibits RVLM neurons^[68–69]. Zhou and Longhurst^[70] studied the role of Arc in acupuncture-induced hypotension and decreased sympathetic excitability, and the results showed that electroacupuncture stimulation of Jianshi (PC5) and Neiguan (PC6) points in anesthetized cats activated long loop pathways including Arc neurons, vIPAG, raphe nucleus, and RVLM.

The PVN and Arc are involved in the regulation of sympathetic excitatory cardiovascular responses through projections to the RVLM^[71–72]. Recent studies have shown that GABA type A, neuropeptide Y1, and opioid receptors in the PVN mediated the sympathetic inhibitory response elicited by the Arc^[69]. It was concluded that PVN neurons participate in the regulation of the acupuncture effect and acupuncture improved the myocardial effect through a single PVN nucleus and the cooperative action of multiple brain nuclei. The neural mechanisms through which acupuncture improves cardiac function are complex. The PVN may form a neural pathway with other central nervous systems such as the NTS and ventral medulla oblongata (VLM)^[73–74], and jointly coordinate and participate in the regulation of cardiovascular diseases by acupuncture, which is currently unclear.

Midbrain

The PAG is a relay station of the central nervous system that transmits and integrates information regarding injuries and sexual stimuli. The PAG is an important part of the midbrain^[75], which is located around the midbrain aqueductal region^[76]. The PAG can release opioid peptide, 5-hydroxytryptamine(5-HT), GABA, D-serine, substance P, and other neurotransmitters to participate in the regulation of pain, fear, anxiety, respiration, phonation, and other physiological functions^[77–79]. In addition, activation of the PAG can cause changes in blood pressure and heart rate^[80], and the direct projection between the PAG and Arc is one of the mechanisms of acupuncture in treating hypertension^[81]. The main inhibitory effect of the PAG on cardiovascular function lies in the excitatory projections of glutamate and cholinergic neurons between the PAG and Arc. The enhanced activation of these projections may be due to the inhibition of sympathetic excitation through electroacupuncture^[81–82]. Electroacupuncture at Neiguan (PC6) and Jianshi (PC5) points attenuates the excitatory response of sympathetic nerves activated by the Arc and vIPAG,

activates glutamate neurons, and prolongs the effect of electroacupuncture^[81].

To further explore the reciprocal neural circuitry between the Arc and vIPAG when electroacupuncture inhibited the reflex elevation of blood pressure, they injected the Arc or vIPAG of rats with retrograde transport of microsphere tracers and found that the cells were labeled with retrograde microspheres in the vIPAG or Arc, which confirmed the direct connection between the two nuclei, suggesting that the long-term inhibition of cardiovascular function by electroacupuncture was related to the neural circuit between the Arc and vIPAG^[82].

Medulla

The medulla oblongata is an important regulation center for cardiovascular sympathetic, excitatory activity and maintains the arterial blood pressure, and function. When blood pressure is elevated, the activity of baroreceptors located in the carotid sinus and aortic arch is increased, resulting in a decrease in blood pressure through a negative feedback regulatory mechanism; baroreceptor activity is attenuated when blood pressure is decreased. The regulatory function decreases, thus stabilizing blood pressure. Studies^[83] have shown that the key pathway responsible for regulating this baroreceptor reflex is located in the brainstem, particularly in the medulla oblongata. Arterial baroreceptor afferent fibers project to the caudal part of the NTS, which in turn emits excitatory projections to the caudal ventrolateral medulla (CVLM), and neurons in the CVLM could inhibit the activity of RVLM.

The RVLM is a key brain region that maintains the central and sympathetic nervous systems, sympathetic vasoconstriction, and blood pressure. Thus, inhibition of the RVLM can result in decreased sympathetic nervous system tension, sympathetic vasodilation, and decreased blood pressure. The RVLM is an important source of pre-motor sympathetic neurons, which can regulate sympathetic nervous system signal outflow to the mediolateral column of the spinal cord and directly affect sympathetic nervous system activity. Some studies have shown that electroacupuncture can inhibit the increase in extracellular glutamate in the RVLM through opioid regulation, thus attenuating the visceral sympathetic excitatory reflex and eventually regulating the cardiovascular function^[84]. Studies^[85–86] have shown that the activation of enkephalin, endorphin, and their related δ -opioid receptors in RVLM plays an important role in the regulation of blood pressure by electroacupuncture. Electroacupuncture stimulation of Jianshi (PC5) and Neiguan (PC6) points in adult Sprague-Dawley male rats could inhibit the action of gastric distension induced by the above-mentioned mechanism, and the action could be reversed by microinjection of naloxone into the RVLM^[85]. In addition, the release of opioids and GABA also mediates the inhibition of RVLM nerve channels^[69,87], resulting in the weakening of sympathetic arousal and counter-response and lowering of reflex blood pressure. Guo et al.^[88] found that electroacupuncture could regulate the activity of the RVLM to decrease blood pressure.

However, some studies have shown that there may be an interaction between the NTS and RVLM during acupuncture treatment. The NTS is a complex network of excitatory and inhibitory neurons that integrate sensory inputs, and transmit signals to other parts of the brain. The RVLM contains pre-sympathetic neurons that control and maintain cardiovascular functions. To assess whether there is a direct pathway between the two nuclei, using c-Fos immunohistochemistry combined with retrograde labeling of colored microspheres to track the pathway. After injection into the RVLM, retrograde microspheres labeled cells in the NTS, revealing a possible direct projection from the NTS to the RVLM. More than 10% of the NTS neurons were activated by low-frequency and low-intensity stimulation within 30 minutes of electroacupuncture, and these neurons formed a connection between the NTS and RVLM. This study found that the neural circuit from the NTS to the RVLM may be involved in the regulation of cardiovascular responses and other physiological functions induced by electroacupuncture. The RVLM is the basic center of cardiovascular sympathetic activity, and its afferent projections pass through the NTS. The RVLM is associated with the PVN in terms of physiological function^[89-91]. The study suggests that the NTS may serve as an integrated center that bidirectionally regulates the heart rate of rats with arrhythmia by acupuncture at Neiguan (PC6) point^[92]. The somatosensory afferents and visceral nociceptive afferents of heart and stomach induced by acupuncture at Neiguan (PC6) and Zusanli (ST36) points converge at the NTS, which is an integrated center of acupuncture that regulates heart and stomach function^[93]. Stimulation of the auricular concha area can activate general visceral sensory afferent fibers projecting from the auricular branch of the vagus nerve to the NTS, and activate the efferent fibers innervating the viscera by contacting with visceral motor nucleus, thus regulating visceral function^[94].

Research has shown that there is a direct projection between the nucleus raphe pallidum (NRP) and RVLM, and acupuncture can activate serotonin neurons in the NRP, which can be projected onto the RVLM sympathetic nervous system, reducing sympathetic arousal, vascular reflexes, and blood pressure^[95]. The mechanism by which electroacupuncture inhibit the increase in blood pressure may be by activating Arc neurons in the hypothalamus, the vPAG in the midbrain, and NRP neurons, which subsequently inhibit the activity of premotor sympathetic neurons in the RVLM^[96]. The research^[95] showed that when the electric needle stimulated the Jianshi (PC5) and Neiguan (PC6) points of anesthetized cats, it activated the 5-HT nerve channel element in the NRP, and 5-HT could be projected into the RVLM to activate 5-HT-1A receptor, thus inhibiting the sympathetic excitatory cardiovascular reflex. The GABA neurons of the RVLM and 5-HT neurons in the NRP mediate the mechanism by which electroacupuncture attenuates sympathetic excitatory cardiovascular reflexes^[47]. Therefore, acupuncture at different acupoints through somatic sensation and afferent nerves transmits different signals to the central nervous system, activating different neurons in the thalamus and brainstem, and finally regulating the autonomic nerve in RVLM.

Conclusions and future perspectives

Clinically, the cores of acupoint compatibility are Danzhong (RN17), Xinshu (BL15), and Neiguan (PC6) with filiform needle for 30 minutes (Table 1). Our previous studies showed that electroacupuncture at Neiguan (PC6) point can treat AF by regulating the balance of autonomic nerves. According to the literature, acupuncture at Neiguan (PC6) point can also be used to treat AF by regulating the CAN. The central brain regions are mainly concentrated in the hypothalamus, midbrain, and medulla oblongata. Electroacupuncture at Neiguan (PC6) point stimulates median and deep peroneal nerves evoking activity in the (PVN) and (Arc) in the hypothalamus. The neurotransmitters in the Arc including acetylcholine and L-glutamate (L-Glu) and tyrosine hydroxylase (TH). The PVN mainly releases L-Glu and TH neurotransmitters to activate the RVLM in the brainstem, and projection of the PVN to the RVLM occurs through opioid receptors. The vPAG neurotransmitters including 5-HT and GABA, which activate this brain region and project to the RVLM. In the medulla, the CVLM and NTS release GABA neurotransmitters that project to the RVLM (Figure 1). Further efferents from the VLM to the intermediolateral column of the spinal cord regulate cardiac sympathetic activity through the cervical sympathetic chain and stellate ganglion. In contrast, peripheral vagal activity is directly regulated through the NA and DMV in the brainstem.

In conclusion, acupuncture at Neiguan (PC6) point regulates the release of neurotransmitters in the central autonomic nerve-related brain areas, thus regulating the activity of peripheral autonomic nerves. This review systematically elucidated the CAN mechanism of acupuncture at Neiguan (PC6) point in the treatment of AF, and provided important information for basic and clinical research on the acupuncture treatment of AF in the future.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Jing Huang conceived and wrote the manuscript. Yongjun Chen, Taiyi Wang, and Jinglan Yan helped with the figure and drafted the manuscript. All authors approved the final version of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

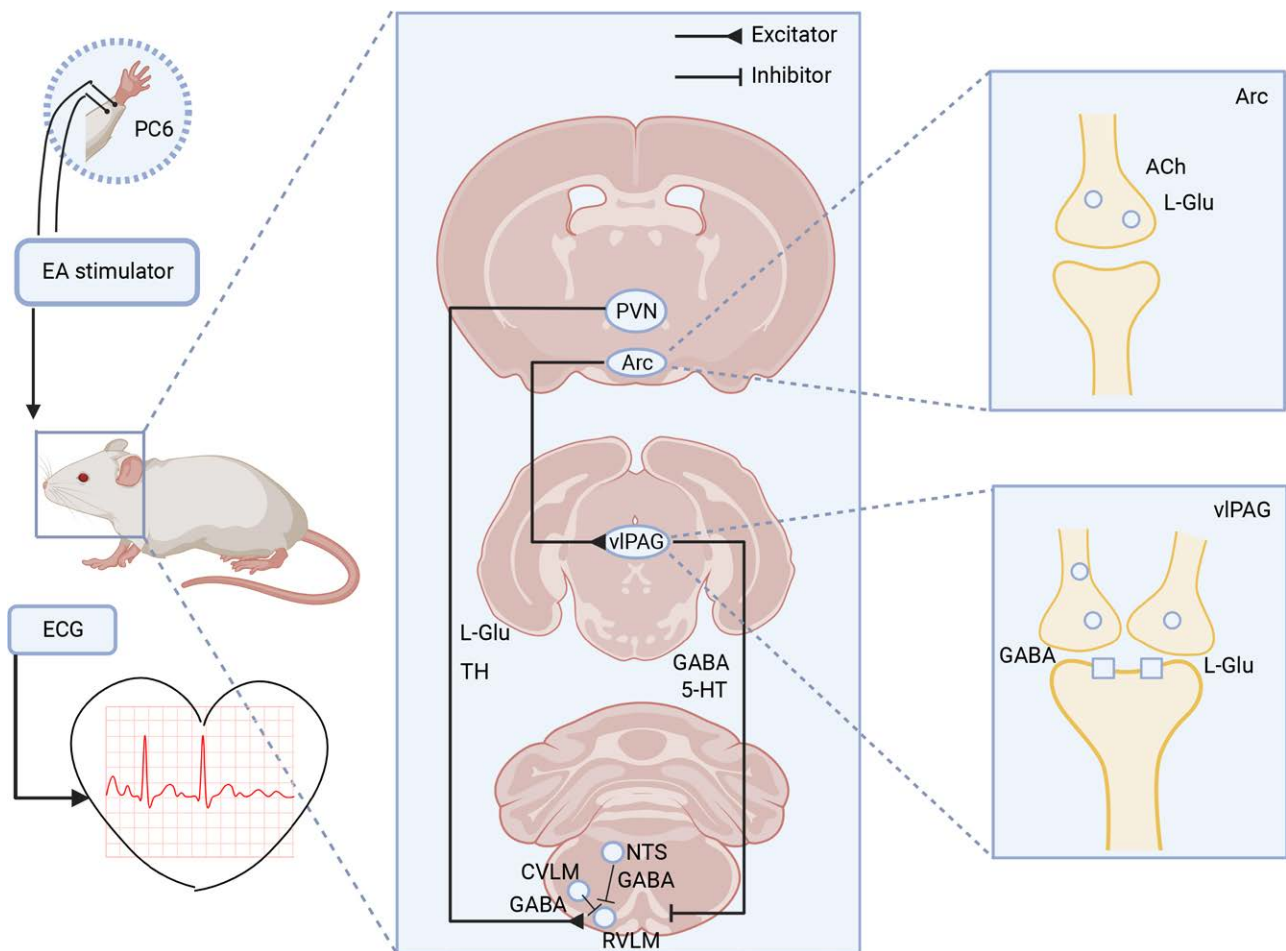


Figure 1. The central autonomic nervous mechanism of electroacupuncture at Neiguan (PC6) point in the treatment of atrial fibrillation in rats. 5-HT: 5-Hydroxytryptamine; ACh: Acetylcholine; ECG: Electrocardiogram; GABA: Gamma-aminobutyric acid; L-Glu: L-glutamate; PVN: Paraventricular nucleus; TH: Tyrosine hydroxylase; EA: Electroacupuncture; Arc: Arcuate hypothalamic nucleus; viPAG: ventrolateral periaqueductal gray; NTS: Nucleus tractus solitarius; RVLM: Rostral ventrolateral medulla; CVLM: Caudal ventrolateral medulla.

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None.

Data availability

All data generated or analyzed during this study are included in this published article.

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