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Cardiac autonomic nerve distribution and arrhythmia[☆]

Quan Liu, Dongmei Chen, Yonggang Wang, Xin Zhao, Yang Zheng

Department of Cardiovascular Disease, the First Hospital of Jilin University, Changchun 130021, Jilin Province, China

Abstract

OBJECTIVE: To analyze the distribution characteristics of cardiac autonomic nerves and to explore the correlation between cardiac autonomic nerve distribution and arrhythmia.

DATA RETRIEVAL: A computer-based retrieval was performed for papers examining the distribution of cardiac autonomic nerves, using “heart, autonomic nerve, sympathetic nerve, vagus nerve, nerve distribution, rhythm and atrial fibrillation” as the key words.

SELECTION CRITERIA: A total of 165 studies examining the distribution of cardiac autonomic nerve were screened, and 46 of them were eventually included.

MAIN OUTCOME MEASURES: The distribution and characteristics of cardiac autonomic nerves were observed, and immunohistochemical staining was applied to determine the levels of tyrosine hydroxylase and acetylcholine transferase (main markers of cardiac autonomic nerve distribution). In addition, the correlation between cardiac autonomic nerve distribution and cardiac arrhythmia was investigated.

RESULTS: Cardiac autonomic nerves were reported to exhibit a disordered distribution in different sites, mainly at the surface of the cardiac atrium and pulmonary vein, forming a ganglia plexus. The distribution of the pulmonary vein autonomic nerve was prominent at the proximal end rather than the distal end, at the upper left rather than the lower right, at the epicardial membrane rather than the endocardial membrane, at the left atrium rather than the right atrium, and at the posterior wall rather than the anterior wall. The main markers used for cardiac autonomic nerves were tyrosine hydroxylase and acetylcholine transferase. Protein gene product 9.5 was used to label the immunoreactive nerve distribution, and the distribution density of autonomic nerves was determined using a computer-aided morphometric analysis system.

CONCLUSION: The uneven distribution of the cardiac autonomic nerves is the leading cause of the occurrence of arrhythmia, and the cardiac autonomic nerves play an important role in the occurrence, maintenance, and symptoms of arrhythmia.

Key Words

cardiac autonomic nerve; sympathetic nerve; parasympathetic nerve; vagus nerve; arrhythmia; norepinephrine; catecholamine; adrenergic receptor; acetylcholine; muscarinic M receptor; tyrosine hydroxylase; acetylcholine transferase

Research Highlights

(1) The distribution of cardiac sympathetic and parasympathetic nerves was examined. Sympathetic nerves function on cardiac adrenergic receptors through the release of norepinephrine and catecholamine. The adrenergic receptors include α and β isoforms, and the regulatory functions of sympathetic nerves are mainly regulated by a β -adrenergic effect.

(2) The main markers of cardiac autonomic nerves are tyrosine hydroxylase and acetylcholine transferase. Immunohistochemical staining revealed that cardiac autonomic nerves are unevenly distributed in different sites, and are mainly located at the surface of the atrium and pulmonary vein, forming a ganglia plexus.

Quan Liu[☆], Ph.D.,
Professor, Department of
Cardiovascular Disease, the
First Hospital of Jilin
University, Changchun
130021, Jilin Province, China

Corresponding author: Yang
Zheng, Chief physician,
Doctoral supervisor,
Department of
Cardiovascular Disease, the
First Hospital of Jilin
University, Changchun
130021, Jilin Province, China
Zhengyang1288@126.com

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(3) Cardiac autonomic nerves play an important role in the occurrence, maintenance and symptoms of arrhythmia.

INTRODUCTION

The autonomic nervous system is also termed the vegetative nervous system. Cardiac autonomic nerves are mainly distributed in cardiac vessels, glands and other sites. The central nerves are localized within the brain and spinal cord, while peripheral nerves include visceral efferent fibers and visceral sensory afferent fibers, forming the visceral motor nerve and visceral sensory nerve, respectively.

DISTRIBUTION AND CHARACTERISTIC OF CARDIAC AUTONOMIC NERVES

Cardiac autonomic nerves include sympathetic and parasympathetic systems. Sympathetic nerves can excite the heart, while parasympathetic nerves inhibit the heart. Atrial autonomic nerves are composed of parasympathetic and ventricular autonomic nerves, and are mainly sympathetic.

Distribution of cardiac sympathetic nerves

The sympathetic nerve originates from the hypothalamus and projects out of spinal cord T₁₋₅ segments, where it exchanges into neurons in the cervicothoracic ganglion and the stellate ganglion, producing sympathetic postganglionic fibers, and then travels below the epicardium^[1] to control cardiac function^[2]. Release of norepinephrine and catecholamines activates adrenergic receptors in the myocardial cell membrane to accelerate rhythm and atrioventricular junction conduction, and strengthen the contraction of atrial and ventricular muscles.

Adrenergic receptors are divided into α and β subtypes, including α_1 , α_2 , β_1 , β_2 and β_3 ^[3]. The functions of sympathetic nerves are mainly regulated by a β adrenergic effect, with the β_1 receptor dominant in heart and β_1 receptor content especially high in ventricular muscle; more than 75% of β_1 receptors are visible in myocardial fibers. The distribution of β receptors within human cardiac tissue is markedly higher than that for α receptors. Cardiac tissue, similar to other organs, is innervated by sympathetic nerves, and possesses presynaptic and postsynaptic adrenergic receptors. Presynaptic α receptors are

mainly the α_2 subtype, which can inhibit nerve endings and release noradrenaline after excitation; this receptor reduces stimulation on postsynaptic α and β receptors through a feedback mechanism. Postsynaptic α receptors are mainly the α_1 subtype. The density of α receptors within the left and right ventricles is very similar.

Distribution of cardiac parasympathetic nerve

Cardiac parasympathetic preganglionic fibers originate from the medulla, and project out of dorsal vagal nucleus or ambiguous nucleus to enter the thoracic cavity along the bilateral neck. The ganglion is located at the junction of the pulmonary vein, inferior vena cava and lower left atrium, as well as the atrioventricular groove. The ganglial plexus in these tissues is mainly distributed in the adipose tissue below the epicardial membrane, with a small part in the myocardium, and few in the endocardium. These adipose tissues form island-like fat pad structures on the epicardial membrane, where parasympathetic postganglionic fibers changed into neurons in the intracardiac ganglion to innervate the sinoatrial node, atrioventricular bundle and its branches and atrial muscle^[4].

Parasympathetic nerves regulate cardiac function through the release of acetylcholine, which is an important neurotransmitter for central and peripheral nerves, as well as for sympathetic and parasympathetic nerve preganglionic neurons. In the central nervous system, cholinergic neurons are critical for autonomic nerve regulation. These neurons are located in the ventral medulla oblongata, dorsal nucleus of vagus nerve, salivatory nucleus and nucleus of the solitary tract. Parasympathetic nerves release acetylcholine, which subsequently acts on muscarinic cholinergic M receptors on the myocardial cell membrane, leading to a slowing of cardiac rhythm and atrioventricular conduction velocity, as well as attenuation of myocardial contractility. The M receptor is divided into M1, M2, M3, M4 and M5 subtypes, which are all G-protein coupled receptors and are expressed in the heart.

The autonomic nervous system is unevenly distributed within the heart. The vagus nerve is mainly distributed in the sinus node, atrioventricular node, atrial septum and atrial tissue, but is rarely seen in the ventricular muscle. By contrast, sympathetic fibers can be found in the sinus

node, atrioventricular node, atrial tissue, and ventricular surface. The right vagus nerve mainly dominates the right atrium, especially the sinoatrial node, while the left vagus nerve mainly dominates the atrioventricular node. The right sympathetic nerve innervates the right side of the heart and the ventricular anterior wall, while the left sympathetic nerve is responsible for the left side of the heart and the ventricular posterior wall. The distribution and density of cardiac autonomic nerves are the main differences distinguishing humans from other experimental animal models^[5-7].

Functions of cardiac autonomic nerves

Regulation of periodic variation

The cardiac autonomic nerves mainly act on the sinus node, stimulating and inhibiting the nerve to delay or accelerate the heartbeat cycle.

Regulation of intensity change

The cardiac autonomic nerves directly act on the myocardium. Inhibiting the nerves can attenuate myocardial contraction intensity, while exciting the nerves can enhance myocardial contraction strength.

Regulation of conduction change

The cardiac autonomic nerves mainly acts on the stimulus-transmitting system, and plays a negative role on the contraction conduction velocity and inhibition of nerves, and a positive role in nerve excitation.

In addition, cardiac autonomic nerves possess antagonistic actions against the myocardial threshold value, contraction velocity, refractory period duration, chronaxie and metabolism. When the cardiac autonomic nerves are disturbed, arrhythmia often occurs, which is the abnormal origin, frequency, rhythm, conduction velocity and conduction sequence of cardiac excitation.

Arrhythmia type

Improvement of autorhythmicity

The alteration of sinoatrial node pacemaker function and the appearance of ectopic pacemaker activity can both cause arrhythmias, which are divided into a normal autorhythmicity mechanism change and an abnormal autorhythmicity mechanism formation^[8].

Trigger of activity

Impulse formation results from the after-depolarization (depolarization of the second threshold after the first action potential)^[8].

Reentry

Following one impulse transmission, the myocardial tissue can turn back along another circular pathway and excite again, which is an important mechanism leading to fast arrhythmia. The circular pathway is divided into an anatomical circular pathway and a functional circular pathway. The anatomical circular pathway is dependent on the presence of an anatomical loop, in which reciprocal conduction is blocked or the effective refractory period is not consistent in each site, and the turning-back impulse drops beyond the refractory period of the previously excited myocardium^[8].

MARKERS ASSOCIATED WITH THE DISTRIBUTION OF CARDIAC AUTONOMIC NERVE

The main markers used for identification of cardiac autonomic nerves are tyrosine hydroxylase and acetylcholine transferase. Tyrosine hydroxylase is a rate-limiting enzyme for catalyzing the synthesis of catecholamine neurotransmitter, and is highly expressed in the sympathetic ganglia and sympathetic noradrenergic neurons; the expression level may represent the distribution of sympathetic nerves in the heart^[9]. Acetylcholine transferase is the synthesis enzyme of acetylcholine and a specific marker of cholinergic neurons. Acetylcholine transferase expression can accurately display cholinergic nerve distribution and activity, and be used to determine the distribution and redistribution of the vagus nerve.

Measurement of nerve density

The nerve distribution density was determined with a computer aided morphometric analysis system, where the colored autonomic nerve was recognized by computer, the pixel area was calculated and the nerve density represented as the area of measured nerve/the total area ($\mu\text{m}^2/\text{mm}^2$). Each section was observed under 40 × magnification, and three visual fields with the maximal nerve density were selected to calculate the average nerve density of each section^[10].

Protein gene product 9.5

Protein gene product 9.5 is a specific ubiquitin hydroxyl hydrolase in nerve fibers, and can serve as an axonal marker^[11-13]. Protein gene product 9.5-positive nerve fibers can be labeled using immunofluorescence or immunohistochemistry. At present, protein gene product 9.5 is widely used in clinical studies of peripheral nerve injury, and can also label the cardiac autonomic

nerve^[14].

Growth associated protein

Growth associated protein is a fast transport membrane phosphorylated protein expressed in the growth hillock of sprouting axons, and is widely distributed in the autonomic nervous system where it plays a critical role in neural development, axon regeneration, synaptic reconstruction and neurotransmitter release. The presence of this protein can be used to evaluate the activity of autonomic nerve growth. Nerve growth factor is the most important neurotrophic factor for support of neuronal differentiation, maturation, survival, repair after injury and axonal regeneration, and the expression level of nerve growth factor is related to the density of local sympathetic nerves^[15].

REGULATION OF CARDIAC AUTONOMIC NERVES ON CARDIAC RHYTHM

Basic experiments and clinical studies have confirmed that the mechanism of arrhythmia reentrant is predominantly related to cardiac anatomy, while cardiac autonomic nerves can directly or indirectly induce cardiac arrhythmia by altering its electrophysiological characteristics. Autonomic nerve abnormalities may lead to cardiac dysfunction and increase the incidence of arrhythmia^[16]. The cardiac autonomic nerves play an important role in the occurrence of arrhythmias, and its maintenance and symptoms^[17-19].

The cardiac α receptor is involved in intricate signaling mechanisms and influences ion exchange through transmembrane ion channels. Under normal conditions, the α_1 adrenergic receptor-mediated electrophysiological responses occur as a result of decreased autorhythmicity and a prolonging refractory period, and can theoretically prevent arrhythmia. When myocardial ischemia occurs, the α_1 adrenergic effect is enhanced and fatal arrhythmia can occur *via* numerous mechanisms including accumulation of local catecholamine storage, increased α_1 receptor density, enhanced receptor signaling and an uneven excitatory α_1 adrenergic receptor response. However, there is insufficient evidence to prove that α receptor excitation may induce or prevent arrhythmia in other pathological conditions.

The sympathetic nervous system is considered to be important in fatal arrhythmia. Following central or peripheral adrenergic stimulation, exogenous catecholamines and stress can activate the

sympathetic nervous system, increase the vulnerability of the normal and ischemic heart and increase the incidence of arrhythmia. β receptor blockers can prevent this sympathetic nervous system activation, and accordingly prevent the occurrence of arrhythmia. The supraventricular tachycardia that occurs in some reentrant mechanisms is more likely to occur after activation of the sympathetic nervous system, and vagal activation can inhibit the reentrant tachycardia involving the atrioventricular node, and even terminate the attack. For atrial muscle with pathological damage, activation of the sympathetic nervous system can promote the occurrence of atrial fibrillation. In clinical treatment, sympathetic nerve excitation-related arrhythmia is frequently seen in patients with acute myocardial ischemia or myocardial infarction, as well as in long QT interval syndromes and in tension conditions.

β receptor blockers can prevent the occurrence of sudden cardiac death in patients with coronary heart disease and heart failure. The β receptor may directly influence impulse formation and conduction, increase cellular and Purkinje fiber automaticity at the atrioventricular junction, increase the early after-depolarization, prolong the QT interval, increase repolarization dispersion, reduce ventricular fibrillation threshold and increase the degree of T wave electrical alterations. β receptor blockers can also prevent myocardial ischemia-induced ventricular fibrillation.

Mechanisms of β receptor blockers preventing myocardial ischemia-induced ventricular fibrillation

These mechanisms include reducing myocardial oxygen consumption to prevent myocardial ischemia, suppression of central and local release of catecholamines and reversal of the adverse effects of catecholamines on myocardial electrophysiology, thus maintaining the electrical stability of ischemic myocardium and improving ventricular fibrillation threshold^[20], reducing the circadian rhythm peak of catecholamine release, attenuating the damage of catecholamine to atherosclerotic plaque, preventing sudden death especially during sleep and in early morning, inhibiting platelet aggregation function, and improving myocardial diastolic function and local motion abnormality.

Influence of cardiac autonomic nerve on cardiac rhythm

Atrial fibrillation: Sympathetic nerve excitability can shorten the atrial refractory period, while vagus nerve excitation makes the atrial refractory period irregular, leading to paroxysmal atrial fibrillation. Sympathetic

nerve- and vagus nerve-mediated atrial fibrillation has different clinical characteristics. Vagus nerve-mediated paroxysmal atrial fibrillation is mainly found in patients with non-organic heart disease. At night, at rest, and after meals, especially after dinner drinking, the vagal activity is enhanced, and the heart rate slows and shows a sinus bradycardia heartbeat prior to episodes of atrial fibrillation. Parasympathetic nerve-mediated atrial fibrillation is frequently seen in patients with organic heart disease, and occurs during the day, especially in the morning, when the subject is emotional or exercising. Prior to atrial fibrillation onset the heart rate accelerates.

Supraventricular tachycardia: Enhancement of vagal activity can terminate or reduce the incidence of supraventricular tachycardia, especially when the atrioventricular node is part of the reentrant ring. Increased sympathetic nerve activity is beneficial for the occurrence and maintenance of supraventricular tachycardia.

Ventricular tachycardia: Ventricular arrhythmia occurs when enhanced vagal activity causes sinus bradycardia or vagal activity weakening induces sinus tachycardia. The autonomic nerve has various effects on ventricular arrhythmia under different conditions. In general, vagal excitation slows down heart rate and prolongs the diastolic blood supply time and its negative inotropic effect, thus reducing myocardial oxygen consumption, directly influencing cardiac electrophysiological properties and ultimately suppressing ventricular arrhythmia. The inhibitory effect of vagus nerve impulses on ventricular arrhythmias is more apparent in acute myocardial ischemia than in non-acute myocardial ischemia. This may be due to the fact that the function of nerve fibers and receptors is destroyed in the infarction region, thus weakening the role of the vagus nerve^[21-22].

Sympathetic and parasympathetic agonists can also cause arrhythmia, although the mechanism is very complicated and includes reciprocal inhibition and simultaneous activation. The interaction between sympathetic nerves and the vagus nerve involves inhibition of norepinephrine release from adrenergic nerve endings following muscarinic receptor activation, while activation of the preganglionic $\alpha 1$ receptor at parasympathetic nerve endings is blocked. Neuropeptide Y and norepinephrine at the sympathetic nerve endings can reduce the release of acetylcholine and norepinephrine^[23]. At the same time, activation of

the vagus nerve is beneficial for the sinus node, but negatively effects the atrioventricular node, the conduction tract and the ventricular muscle; these effects are markedly different from the distribution density of the vagus nerve^[24-25]. In addition, central nervous system and peripheral nervous system stimulation can induce cardiac arrhythmia.

DATA SOURCES AND METHODOLOGY

Data retrieval

A computer-based retrieval was performed in domestic and foreign databases between January 1992 and December 2011 for papers examining the distribution of cardiac autonomic nerves^[26-27] using the key words of "heart, autonomic nerve, vagus nerve, sympathetic nerve, nerve distribution, rhythm, and atrial fibrillation". A total of 165 studies were selected on November 2012.

Inclusion criteria

Publications examining cardiac autonomic nerve distribution were selected, and articles published in the authoritative journals were preferred in the same field.

Exclusion criteria

Reproduced studies, conference abstracts, comments, essays or letters were excluded, and all remaining studies were carefully screened by reading the title and abstract. A total of 46 papers were selected for final analyses.

Flowchart of screening results (Figure 1)

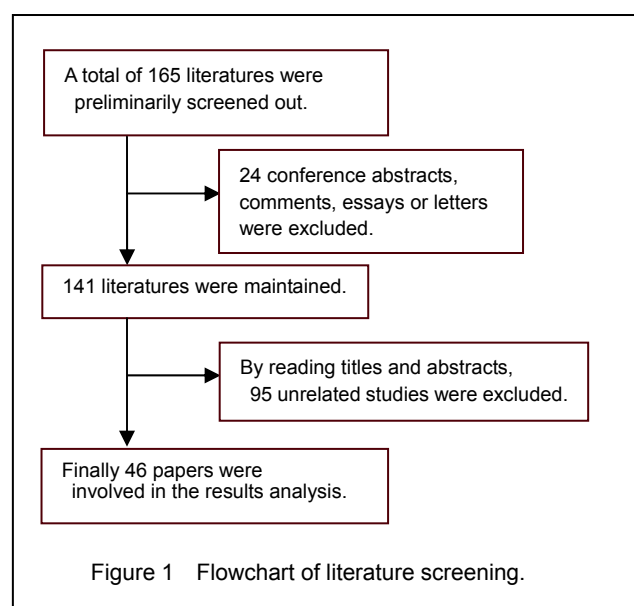


Figure 1 Flowchart of literature screening.

Literature on the distribution of cardiac autonomic nerve (Table 1)

Table 1 Literature on the distribution of cardiac autonomic nerve in the database

First author	Source	Publication time	Research results
Armour ^[28]	<i>Anat Res</i>	1997	Cardiac autonomic nerve gathered on the surface of atrium and large vein, forming ganglion plexuses, then elicited axons to dominate the atrium and large vein, thereby constituting the atrial and venous autonomic neural network. There are four ganglion plexuses at the junction of pulmonary vein and left atrium, the right anterior ganglion plexus, right inferior ganglion plexus, left superior ganglion plexus, and left inferior ganglion plexus.
Chiou ^[29]	<i>Circulation</i>	1997	Ganglion plexus dominating the atrium and pulmonary vein gathered in the fat pad between superior vena cava and aorta, effective ablation of this fat pad can selectively enable an atrial denervation and has no influence on ventricular innervation.
Chow ^[30]	<i>Anat Rec</i>	2001	Immunohistochemical analysis was used to observe the human cardiac autonomic nerve-dominant conduction system in the aging process from infancy to senescence, results found that cardiac sympathetic nervous system is dominant in the infancy, sympathetic and parasympathetic nerve contribute to innervate the heart in the adulthood, in addition, the physiological changes in the developmental process were observed.
Kawano ^[31]	<i>Heart Vessels</i>	2003	The nerve distribution density was observed by point count method under the microscope, and the autonomic nerve distribution was evaluated. The number of atrial positive nerve was more than that of ventricular positive nerve, the number of acetylcholine esterase positive nerve below endocardial membrane was more than that below epicardial membrane, varying density distribution of sympathetic and parasympathetic nerve is beneficial for the cardiac functions in physiological and pathological conditions.
Chevalier ^[32]	<i>Heart Rhythm</i>	2005	A cardiac histology and quantitative study of pulmonary vein nerve distribution in 43 cases of adult autopsy revealed that, the distribution characteristics of four pulmonary veins are more at proximal end than at distal end, more at left superior than at right inferior, more at epicardial membrane than at endocardial membrane, more at left atrium than at right atrium, more at posterior wall than at anterior wall.
Tan ^[33]	<i>J Am Coll Cardiol</i>	2006	A total of 192 sections from atrium and pulmonary vein junction of 8 autopsy cases showed that, in longitudinal distribution, adrenergic and cholinergic nerve density reached the peak at the junction of the left atrium and pulmonary veins, which was higher than that at pulmonary vein distal end and at left atrial proximal end; in the transverse distribution, these two kinds of nerves had a higher density at the upper segment of left superior pulmonary vein, the anterior superior segment of right superior pulmonary vein, and the lower segment of two inferior pulmonary veins than that at other segments, also higher at epicardial membrane than that at endocardial membrane, the distribution characteristics conform that foci of excitation in pulmonary vein is far more than the other part.
Ma ^[34]	<i>International Journal Cardiovascular Disease</i>	2007	By using neuron specific protein 9.5, we found that the specific protein 9.5 particles at the left atrium mainly distributed in the orifices of pulmonary veins.
Ulphani ^[35]	<i>Heart Rhythm</i>	2010	The morphology of cardiac parasympathetic nervous system was observed with neural staining, the atrial and ventricular epicardial and endocardial surface has rich nerve innervation, the parasympathetic nerve density on the surface of the heart is different in the epicardial and endocardial membrane.

CONCLUSION

The regulatory effects of sympathetic and parasympathetic nerves on cardiac function are complex, and show different influences and electrophysiological properties at different cardiac sites. The parasympathetic nerves function in the atrium and conduction system, while sympathetic nerves function in the ventricle. Both systems can shorten the atrial refractory period, but have reverse effects on the electrophysiological properties of the atrioventricular node and the ventricles. Sinus rhythm frequency is maintained by vagus nerve activity. Thus, stimulation of sympathetic nerves may shorten the refractory

periods in the right atrium, right ventricle and left ventricle, as well as maintain, extend or shorten the atrioventricular nodal conduction time. When the atrioventricular nodal conduction time is maintained constantly, the atrial and ventricular refractory period is still shortened. The heart rate is the same between daytime waking state and nocturnal sleep state and the QT interval at night is prolonged, suggesting that the sinus heart rate and atrioventricular conduction time cannot completely reflect the degree of cardiac autonomic nerve activity in other parts of the heart. The cardiac autonomic nervous system plays an important role in the occurrence, maintenance and symptoms of arrhythmia. The majority of arrhythmia reentry mechanisms are related to cardiac anatomy, although

the majority of fast arrhythmia episodes are usually paroxysmal, indicating that one or more factors plays a key or auxiliary function in the occurrence of arrhythmia. The autonomic nervous system can affect cardiac electrophysiological properties and accordingly induce cardiac arrhythmia. A large number of clinical trials using β receptor blockers have confirmed that intervention can prevent sudden cardiac death. Central and peripheral nerve stimulation also triggers arrhythmia, as can drugs that excite sympathetic and parasympathetic nerves and various kinds of pressure load tests.

As vagal preganglionic fibers are localized in the atrial fat pad, there are fewer nerve fibers across the fat pad that directly enters the atrial muscle. Therefore, radiofrequency ablation of the fat pad can remove atrial vagus nerve control and^[36] provide partial treatment of atrial fibrillation^[37]. Thoracoscopic detection for epicardial ablation can reduce vagus nerve-mediated atrial fibrillation, and clinical studies have shown that it is feasible to remove the atrial vagal nerve by direct ablation of the fat pad, which is a safe and effective procedure for some patients with atrial fibrillation^[38].

Author contributions: Yang Zheng supervised the study concept. Quan Liu had full access to the database retrieval of NCBI, Wanfang and CNKI, analyzed the extracted data, and performed statistical analysis. Dongmei Chen, Yonggang Wang and Xin Zhao were responsible for the data retrieval, modification and proofreading. All authors approved the final version of the manuscripts.

Conflicts of interest: None declared.

Author statements: The manuscript is original, has not been submitted to or is not under consideration by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application disputations.

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