International Journal of Neurology and Neurotherapy

Zhai et al., Int J Neurol Neurother 2016, 3:051
DOI: 10.23937/2378-3001/3/3/1051
Volume 3 | Issue 3

ISSN: 2378-3001

Short Review: Open Access

Neurology and Cardiac Arrhythmias

Zhengqin Zhai, Min Tang* and Shu Zhang

Department of Arrhythmia, State Key Laboratory of Cardiovascular Disease, National Clinical Research Center of Cardiovascular Diseases, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

***Corresponding author:** *Min Tang, Department of Arrhythmia, State Key Laboratory of Cardiovascular Disease, National Clinical Research Center of Cardiovascular Diseases, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, NO.167, Beilishi Road, Xicheng District, Beijing, China, Tel: +86-138-1066-5178, Fax: 6833-4688, E-mail: Doctortangmin@hotmail.com*

Abstract

The imbalance of cardiac autonomic nervous system (CANS) is one of the major causes of cardiac arrhythmias and several novel therapies of arrhythmias through modulating the activity of CANS have emerged. This review is aimed to address the relationship between the CANS and cardiac arrhythmias, and the present situation of novel therapies.

Keywords

Cardiac autonomic nervous system, Cardiac arrhythmias, Atrial fibrillation, Ventricular tachyarrhythmias, Denervation, Nerve stimulation, Neuromodulation

Abbreviations

AF: Atrial Fibrillation; BRS: Baroreceptor Stimulation; CANS: Cardiac Autonomic Nervous System; CPVT: Catecholaminergic Polymorphic Ventricular Tachycardia; CSD: Cardiac Sympathetic Denervation; ECNS: Extrinsic Cardiac Nervous System; GP: Ganglionated Plexi; ICNS: Intrinsic Cardiac Nervous System; IVT: Idiopathic Ventricular Tachycardia; LL-TS: Low-Level Tragus Stimulation; LL-VNS: Low-Level Vagal Nerve Stimulation; LQTS: Long QT Syndrome; PAF: Paroxysmal AF; PV: Pulmonary Vein; PVI: Pulmonary Vein Isolation; RDN: Renal Denervation; SCS: Spinal Cord Stimulation; VT: Ventricular Tachyarrhythmias; VNS: Vagal Nerve Stimulation; VF: Ventricular Fibrillation

Introduction

A host of studies on the cardiac innervation have found a complex link known as cardiac autonomic nervous system (CANS), connecting extracardiac nerves, intracardiac ganglia, and myocardial cells. Now it is well known that CANS plays a critical role in regulating the functions of the heart and its imbalance is regarded as one of the major causes of cardiac arrhythmias [1]. With the development of medical technology and the advancement of ideas, several novel therapies of arrhythmias through modulating the activity of CANS have emerged. This review is aimed to address the relationship between CANS and cardiac arrhythmias, and the present situation of novel treatment approaches.

Cardiac autonomic nervous system

Heart is innervated by CANS, which mediates signals from physiologic "sensors" in the heart and great vessels, and can be divided into two components, extrinsic and intrinsic cardiac nervous system (Figure 1) [1,2].

Extrinsic cardiac nervous system

Extrinsic cardiac nervous system (ECNS) is composed of sympathetic cardiac nerves and parasympathetic cardiac branches. The former arises from the stellate ganglia and the caudal halves of the cervical sympathetic trunks, and is subdivided into 4 parts: superior, middle and inferior cervical ganglia and vertebral ganglia, communicating with the spinal nerves C1-4, C3-6, C5-T4, and C4-7 respectively [3-5]. The cardiac nerves from these ganglia innervate the heart by following different courses [6,7]. Parasympathetic cardiac branches are derived from vagus nerves. Its efferent component to the heart includes preganglionic fibers and makes synaptic connections with ganglion cells in the cardiac ganglia [3-5,8].

Intrinsic cardiac nervous system

Intrinsic cardiac nervous system (ICNS) is a complex neural network formed by the nerves and ganglia located around the large vessels and on the heart itself all within the pericardium. Autonomic inputs to the heart converge at several locations and these convergence points form ganglionated plexi (GP) that contain interconnecting ganglia and nerves. The positions of GP are asymmetrical and extensive [3,9]. GPs contain afferent neurons from myocardium and from the extrinsic system [10] and function as the "integration centers" that modulate the interaction between ECNS and ICNS [11].

CNS has yin-yang nature in its physiological function. The activation of its sympathetic component is related to the increased heart rate and ventricular contraction, and the enhanced atrioventricular conductivity. However, its parasympathetic component functions in contrary to its sympathetic component [12].

Physiological Function of CNS

It is well known that the characteristic of physiological function of CNS is its ying-yang nature. Its sympathetic influences on cardiac

Citation: Zhai Z, Tang M, Zhang S (2016) Neurology and Cardiac Arrhythmias. Int J Neurol Neurother 3:051. doi.org/10.23937/2378-3001/3/3/1051

Received: May 09, 2016: **Accepted:** June 15, 2016: **Published:** June 25, 2016

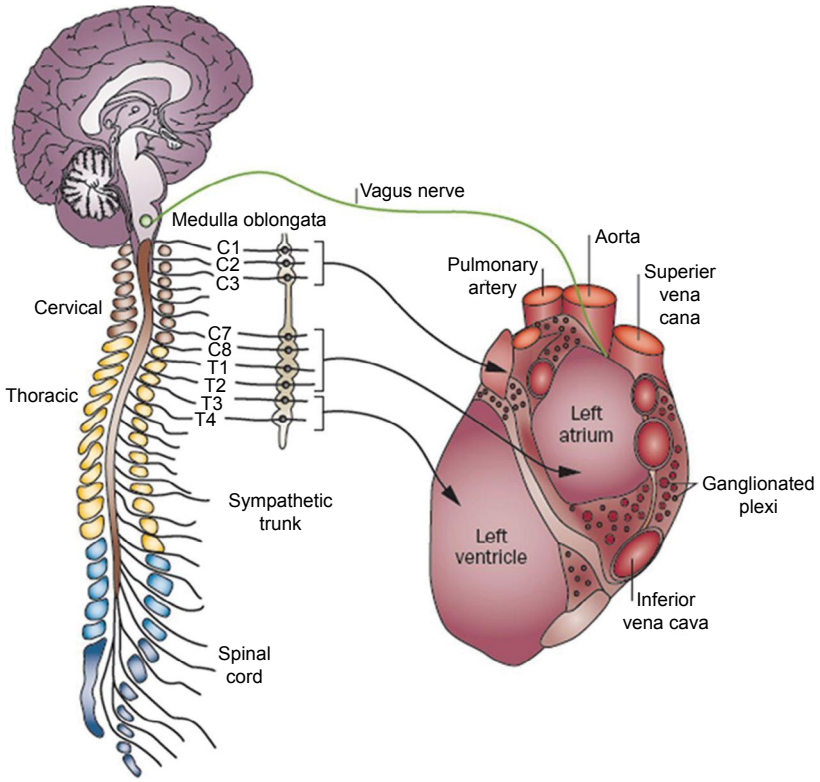

Figure 1: Scheme of autonomic innervation of the heart. The cardiac sympathetic ganglia consist of cervical ganglia, stellate (cervicothoracic) ganglia, and thoracic ganglia. Parasympathetic innervation comes from the vagus nerves. Reprinted from Shen et al. [2] with permission of the publisher. Copyright © American Heart Association, Inc.

electrophysiology are similar on both atrial and ventricular myocytes. Electrophysiologically, sympathetic stimulation could shorten action potential duration and reduce transmural dispersion of repolarization [13,14]. Besides, sympathetic activation can also increase heart rate and ventricular contraction, and enhance atrioventricular conductivity [12,15]. In contrast, parasympathetic stimulation decreases heart rate and ventricular contraction, and slows atrioventricular conductivity [12]. In addition, parasympathetic stimulation prolongs action potential duration and effective refractory period in ventricles, while in atrium, reduces the effective refractory period, increases spatial electrophysiological heterogeneity, and promotes early after depolarization toward the end of phases 3 in the action potential [13, 16-19], which is different with sympathetic activation.

Interaction between CANS and tachyarrhythmias

Atrial fibrillation: Although the mechanism responsible for atrial fibrillation (AF) has not been completely understood, it is well known that CANS plays an important role in its initiation and maintenance [20].

ECNS and AF: The interaction between ECNS and AF has been approved by several studies. Patients with idiopathic paroxysmal atrial fibrillation (PAF), most appear to be vagally dependent, while in most patients with structural heart diseases, PAF episodes appear more sympathetically mediated [21]. Besides, the incidence of AF in patients with increased sympathetic activity increased as well [22] and in some cases, variations of the autonomic tone were observed before the occurrence of PAF [23,24]. Several studies have shown that beta-adrenergic agonists and the combination of sympathetic activation and acetylcholine infusion could facilitate the induction of AF [25-28] and beta-receptor blockade and atropine were effective in preventing recurrence of AF or decreasing AF inducibility [29-31]. Beside, it was also observed that in rapid atrial pacing induced AF models, simultaneous sympathovagal discharges were common triggers for AF and cryoablation of extrinsic sympathovagal nerves eliminated PAF, which further supported the interrelationship between ECNS and the initiation and maintenance of AF [32].

ICNS and AF: Previous studies provided substantial evidences of the interrelationship between ICNS and AF. The abnormal focal firing in PV is regarded as the major trigger of AF and the four of the left atrial GP each innervates one of the four PVs [9,33,34]. Related to this, a study demonstrated that stimuli applied to PVs would not induce AF unless there was simultaneous simulation of the adjacent GP [35]. Similarly, Po and colleagues showed that focal firing originating from the PV and AF could be induced by injection of acetylcholine into the adjacent GP [36]. It has also been shown that focal AF could be induced or eliminated by stimulating or interrupting the ICNS [37]. Besides, in animal models of AF, a significant increase of sympathetic and/or parasympathetic neurons was present in atrial intrinsic cardiac ganglia [22,38,39]. All these data approve that ICNS is a critical element in the genesis and maintenance of AF.

CANS and non-inherited ventricular tachyarrhythmias: Participation of CANS in the genesis of non-inherited ventricular tachyarrhythmias (VT) has been observed in several studies, most with elevated sympathetic activity that could reduce the ventricular fibrillation (VF) threshold and provoke VT [40-46]. The increased vagal activity seems to be protective in most cases, especially in the presence of elevated sympathetic tone [47-49]. Sympathetic hyperactivity may partly due to sympathetic nerve sprouting in heart. An association between a history of ventricular arrhythmias and an increase of sympathetic nerves in the heart of patients was discovered by Cao et al. [50], and was further approved by a experiment, which found the increased sympathetic nerve sprouting was along with a high-yield model of spontaneous VT [50,51]. Besides, an alteration in neurotransmitters also contributes to sympathetic hyperactivity. The impairment of catecholamine reuptake contributes to myocardial catecholamine overexposure and thus VT after experimental myocardial infarction [52]. As to the protective effect of increased vagal activity against VT, its evidences are mainly obtained by vagal nerve stimulation [53]. We will discuss it later.

CANS and inherited ventricular tachyarrhythmias: For the patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) or long QT syndrome (LQTS), the occurrences of VT are often precipitated by increased sympathetic activity and could be prevented by beta-blockage. CPVT is associated with sympathetic

hyperactivity [54-56], and beta-blockage has great efficacy in preventing CPVT related cardiac events [57,58]. As for patients with LQTS, early after depolarization-induced triggered activity is thought to be the primary arrhythmogenic trigger of VT and sympathetic hyperactivity could create the substrate for this trigger and prolong the QT interval in LQTS type 1 and 2 [14,59-63]. However, LQTS type 3 has VT triggered by increased vagal tone [64]. Administration of beta-blockage and left cervicothoracic sympathetic denervation are effective in preventing VT in patients with LQTS type 1 and 2, but have no evident effect in type 3 [65].

Besides LQTS type 3, Brugada syndrome and idiopathic ventricular tachycardia (IVT) have also been reported to be associated with vagal hyperactivity. Most VT episodes in patients are observed during periods of high vagal tone [66-70]. A sudden increase of vagal activity before the onsets of VF was reported in patients with Brugada syndrome, and the ST-segment elevation could be augmented by parasympathomimetic agents, while be reduced by sympathomimetic agents [71,72]. For patients with IVT, J-wave elevation is associated with VF onsets and sudden cardiac death [73-75], and bradycardia could result in the augmentation of J-wave amplitude [76,77], while isoproterenol infusion may eliminate J-wave and suppress VF [78]. All these data demonstrate a critical role of vagal hyperactivity in the occurrence of VT in patients with Brugada syndrome or IVT.

Therapeutic Neuromodulation for Tachyarrhythmias

GP ablation

GP ablation is the major way to modulate intrinsic cardiac nervous system to treat cardiac tachyarrhythmias. For patients with AF, GP ablation alone could significantly decrease the occurrence of PV firing and inducibility of AF [10,79,80]. Its effect has been further supported by a meta-analysis and other clinical trials. In the treatment of AF, addition of GP ablation to PV isolation (PVI) confers better outcomes than PVI alone no matter during a short or long-term follow-up period, and GP ablation alone is inferior to PVI alone [79-82]. Of note, the identification of GP sites is very important. There are two main approaches to the GP sites: selective and anatomic location. The selective approach is performed by high-frequency stimulation, and GP sites were identified as sites showing a vagal response [79,83]. The latter was first reported by Katrisis and colleagues [84], based on the autonomic innervation of the heart, experiences of selective location, and then ablations were delivered to the presumed GP sites [84]. However, there is no available data of GP ablation in the treatment of patients with ventricular arrhythmias.

Vagal nerve stimulation (VNS)

Low-level vagal nerve stimulation (LL-VNS), defined as combination of intensity and frequency without effect on heart rate or atrioventricular conduction, has been found to be protective against cardiac tachyarrhythmias (Figure 2) [1].

For patients with AF, several studies have found that LL-VNS can prevent and reverse atrial remodeling, shorten AF duration and suppress the occurrence or inducibility [85-90]. The mechanism of LL-VNS may be very complex. It is reported that LL-VNS have both anticholinergic and antiadrenergic effects and its inhibition of the GP may be responsible for protective effect on AF [85,86,88,90].

For the treatment of VT, experimental studies showed that VNS could increase VF threshold, and protect against ventricular arrhythmias [53,91-93]. However, there is no available data on its performance in patients with ventricular arrhythmias, and the clinical trials designed to assess the efficacy of VNS among patients with heart failure didn't provide positive results involving ventricular arrhythmias [94-96].

LL-VNS with the electrodes located in vagosympathetic trunk or cervical vagus nerve, is invasive and needs surgery. In 2013, a novel noninvasive approach of VNS by simulating the auricular branch of the vagus nerve at the anterior protuberance of the outer ear was reported by Yu and colleagues [97]. In several studies on animals or humans, LL-TS has been shown to be effective in the prevention or treatment of AF [85,97-105], and may be a promising alternative to VNS.

Spinal cord stimulation (SCS)

SCS of T1-T5 appears to have an antiarrhythmic effect on cardiac tachyarrhythmias [106,107]. For AF, SCS could prolong atrial

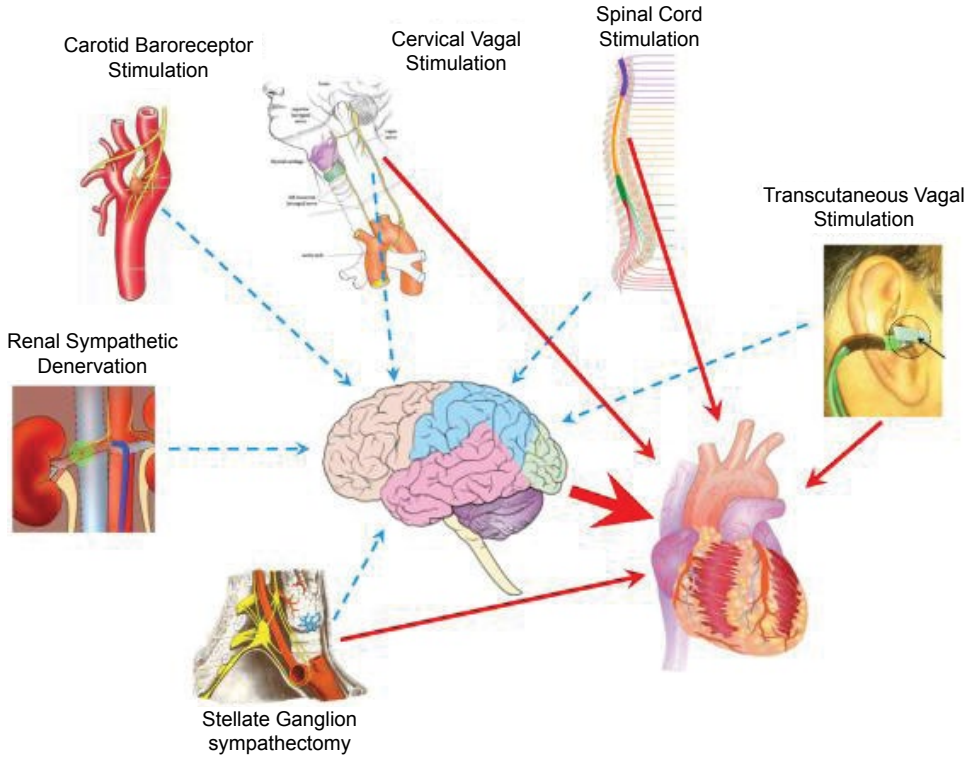

Figure 2: Schematic representation of various approach of neuromodulation. Solid lines indicate direct effects on cardiac autonomic nervous system, while dashed lines indicate effects on cardiac autonomic nervous system, possibly through neuroal reflexes involving the brain or spinal cord. The thick red arrow denotes that many of the beneficial effects of neuromodulation depend on the brain to process the neural inputs. Reprinted from Hou et al. [1] with permission of the publisher, Copyright © Elsevier.

effective refractory periods and reduce AF burden and inducibility in animal models, suggesting that SCS may represent a treatment option [108,109]. Furthermore, a study indicates that long-term SCS shows sustained protection against AF and that the efficacy of arrhythmia stabilization increases with duration of treatment [110].

For the treatment of VT, it is reported that SCS could reduce the episodes of VT in animal model of post-infarction heart failure, acute myocardial infarction or ischemia-reperfusion [47,106,107,111]. However, there are limited clinical data on SCS. Grimaldi et al. demonstrated its effect on the occurrence of VT episodes in 2 patients [112]. More clinical studies on the protection of SCS against cardiac arrhythmias are needed to further confirm these findings mentioned above.

Cardiac sympathetic denervation (CSD)

CSD is mainly used to prevent the cardiac events in patients with inherited VT [113,114]. Several clinical studies have shown that CSD is associated with a significant reduction in the incidence of VT symptoms and the episodes of VT, especially in patients with LQTS or CPVT [57,115-119]. Besides, CSD has also shown benefits in treatment of patients with structural heart diseases. In a clinical study involving patients with VT storm and structural heart diseases, CSD could also reduce the burden of implantable cardioverter-defibrillator shocks [120]. However, although CSD has been approved to be highly effective in prevention of cardiac events of patients with VT, especially LQTS and CPVT, it is rarely used in clinical practice. The complex surgery of CSD or its high rate of complications, such as Horner syndrome may be the main reasons. Collura and colleagues reported a safe and effective video-assisted thoracoscopic surgery of CSD, with several important advantages, including a more accurate sympathetic chain resection and a lower risk of Horner syndrome [113,116]. Nagels et al. has also reported a percutaneous approach to CSD, and it may be an alternative to surgical intervention [116].

Renal denervation (RDN)

Originally used to manage the blood pressure in patients with hypertension, while in a large multicenter clinical trial, RDN doesn't show benefit on systolic blood pressure in patients with refractory hypertension compared to control [121]. However, RDN may have protective effect on cardiac arrhythmias. In animal experiments, RDN could suppress the atrial remodeling after rapid atrial pacing and reduce the occurrence of VT during left ventricular ischemia and reperfusion [122,123]. Besides, there is also evidence indicating that RND reduces atrial sympathetic nerve sprouting, structural alterations in goats with persistent AF [124]. In patients with AF and refractory hypertension, RND has been reported to provide incremental AF suppressing after PVI or improve the outcomes of PVI [125,126]. These results indicate that an addition of RDN to PVI may be beneficial in patients with AF and/or refractory hypertension.

Baroreceptor stimulation (BRS)

Although BRS is regarded as a new promising approach to control blood pressure and manage heart failure [127,128], there are interests in its impact on cardiac arrhythmias. Liao and colleagues have shown that low-level BRS could reduce the occurrence of ventricular arrhythmias during acute ischemia in dogs [129] and it has also been reported that low-level BRS prolonged the effective refractory period and attenuated rapid atrial pacing induced atrial remodeling in rabbits and could inhibit atrial fibrillation [130,131]. These data appear to indicate that low-level BRS may have protective effect on arrhythmias, while the related studies are rare and there are no clinical studies.

Conclusion

Comprehensive studies on the characteristics and mechanism of cardiac autonomic nervous system in initiating and maintaining arrhythmias have brought out several novel therapeutic approaches to arrhythmias. However, the related clinical trials are limited, and the mechanisms of these therapies are also not completely elucidated. More larger-scale clinical studies and animal experiments are necessary in the future.

Acknowledgement

The work was supported by the National Natural Science Foundation of China (Grant 81441018 to Min Tang and 61527811 to Cong Wang).

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