Advances in Vagus Nerve Stimulation for Inflammatory and Apoptotic Mechanisms in Chronic Heart Failure: A Postprint

Authors: Hu Yuchi, Dai Songyuan, Zhao Ling, Zhao Lulu, Zhao Ling

Date: 2023-12-11T00:00:00+00:00

Abstract

The vagus nerve, as a crucial component of the cardiac autonomic nervous system, plays a significant role in the therapeutic management of chronic heart failure. In recent years, numerous studies have demonstrated that vagus nerve stimulation confers cardioprotection and retards the progression of chronic heart failure by attenuating the expression of inflammatory cytokines and associated proteins, apoptosis-related proteins, and by ameliorating myocardial function and ventricular remodeling. However, reports on the role of the vagus nerve in the inflammatory and apoptotic mechanisms of chronic heart failure remain relatively limited. Therefore, this review summarizes the anatomy of the cardiac vagus nerve, potential therapeutic mechanisms, practical parameters for vagus nerve stimulation, and recent applications along with the latest clinical advances of vagus nerve stimulation in the inflammatory and apoptotic pathways of chronic heart failure, thereby providing a reference for future investigations.

Full Text

Advances in the Application of Vagus Nerve Stimulation in Inflammation and Apoptosis Mechanisms of Chronic Heart Failure

HU Yuchi, DAI Songyuan, ZHAO Ling*, ZHAO Lulu**

Department of Cardiology, the First Affiliated Hospital of Kunming Medical University, Kunming 650500, China

Corresponding author: ZHAO Ling, Professor; E-mail: zhaoling580@126.com

Abstract

As a crucial component of the cardiac autonomic nervous system, the cardiac vagus nerve plays a significant role in the management of chronic heart failure. In recent years, several studies have found that vagus nerve stimulation protects cardiac function and delays the progression of chronic heart failure by reducing the expression of inflammatory factors and related proteins, apoptosis-related proteins, and improving myocardial function and ventricular remodeling. However, there are limited reports related to the mechanism of inflammation and apoptosis of the vagus nerve in chronic heart failure. Hence, this article reviews the anatomy of the cardiac vagus nerve, potential treatment mechanisms, practical parameters of vagus nerve stimulation, and the recent applications and clinical progress of vagus nerve stimulation in inflammation and apoptosis mechanisms in chronic heart failure, in order to provide a reference for future related research.

Key words: Heart failure; Vagus nerve stimulation; Chronic heart failure; Inflammation; Apoptosis; Review

---

Chronic heart failure (CHF) is a clinical syndrome characterized by symptoms and/or signs caused by structural and/or functional abnormalities of the heart [1]. In recent years, the incidence and mortality of CHF have shown an upward trend [2]. Although pharmacological and device-based therapies are relatively mature, their efficacy in improving prognosis and clinical outcomes remains suboptimal. Vagus nerve stimulation (VNS) represents a novel therapeutic approach for CHF that has been widely applied in animal and clinical studies, demonstrating certain efficacy as well as safety [3-8]. While VNS shows beneficial effects in CHF treatment, its therapeutic mechanisms have not been definitively established for many years. Therefore, this review examines the anatomy of the cardiac vagus nerve, potential therapeutic mechanisms, practical VNS parameters, and recent applications and clinical advances of VNS in CHF inflammation and apoptosis mechanisms, providing a reference for subsequent VNS applications in CHF.

1. Anatomy and Function

1.1 Anatomy

The vagus nerve originates from the dorsal vagal nucleus and nucleus ambiguus in the medulla oblongata [9], with the cardiac vagus nerve emerging from these nuclei. The cardiac vagus nerve descends through the neck into the thoracic cavity, passing through the inferior vena cava and pulmonary veins, as well as the junction of the lower left atrium, which serves as the ganglion of the cardiac vagus nerve. Additionally, ganglia of the cardiac vagus nerve are present in the fat pads of the atrioventricular groove. Postganglionic fibers emanate from these ganglia, traverse the atrioventricular groove, and are widely distributed in the

subendocardium, regulating cardiac ganglion activity and thereby controlling heart rate and baroreflex modulation [10].

1.2 Function

In healthy individuals, the cardiac vagus nerve and cardiac sympathetic nerve maintain a stable dynamic equilibrium through mutual dependence and antagonism, ensuring normal cardiac function. However, under pathological conditions, excessive activation of cardiac sympathetic nerves and excessive inhibition of cardiac vagus nerves disrupt this dynamic balance, exacerbating myocardial fibrosis and even leading to irreversible ventricular remodeling, ultimately resulting in cardiac decompensation and heart failure. Vagus nerve functions include regulating carbon monoxide to influence cardiac function and myocardial contractility [11]; VNS can increase acetylcholine (ACh) release, reduce oxidative stress [3], restore cardiac autonomic balance, inhibit inflammatory responses, and decrease myocardial cell damage [4]. Therefore, CHF treatment can be achieved by inhibiting sympathetic nerve activation and exciting the vagus nerve.

2. Possible Mechanisms of VNS in CHF Treatment

With deepening research, several mechanisms of VNS in CHF treatment have been proposed, supported by animal and clinical studies. The following are widely recognized mechanisms in current research.

2.1 Improving Autonomic Imbalance

A crucial mechanism of VNS is improving autonomic imbalance. Related studies have confirmed that VNS can regulate autonomic imbalance, thereby alleviating CHF symptoms and improving prognosis [5-8]. Additionally, VNS can relieve vagal nerve inhibition, prevent excessive sympathetic activation, and delay cardiac remodeling, reducing the risk of life-threatening tachyarrhythmias. Research indicates that norepinephrine levels significantly decrease with VNS application in CHF treatment, demonstrating that the cardiac vagus nerve can antagonize cardiac sympathetic nerves and improve cardiac autonomic imbalance [12].

2.2 Inhibiting Inflammatory Response

Inflammation plays an important role in CHF development. Studies have confirmed that VNS can inhibit inflammatory responses and has the potential to suppress macrophage activation and tumor necrosis factor (TNF) synthesis [13]. STAVRAKIS et al. [14] found that low-level transcutaneous VNS (LL-VNS) can inhibit inflammatory responses in humans, and CHF patients treated with VNS showed significantly reduced inflammatory factors in myocardium, including TNF-α and interleukin (IL)-8.

2.3 Regulation of Nitric Oxide (NO)

VNS influences cardiac function by regulating NO release. NO, produced by endothelial nitric oxide synthase, promotes myocardial relaxation, regulates myocardial contractility, facilitates coronary perfusion, and plays important roles in regulating cell growth, programmed cell death, vasodilation, and antithrombosis [15]. ALLEN et al. [16] found that low-voltage, high-frequency VNS can significantly alter NO release in the left ventricle, thereby regulating myocardial contractility, reducing myocardial oxygen consumption, and exerting cardioprotective effects.

2.4 Heart Rate Control

The vagus nerve also plays an important role in heart rate control. The prevailing theory suggests that VNS reduces heart rate, thereby inhibiting sympathetic excitation and pro-inflammatory cytokine formation while promoting NO formation and gap junction protein expression in myocardium [17]. Furthermore, VNS affects cardiac function by reducing heart rate, prolonging ventricular diastolic filling time, and decreasing myocardial oxygen consumption.

3. VNS Parameters and Mechanistic Research

3.1 VNS Parameter Settings

VNS is an invasive neuromodulation method consisting of a pulse generator, spiral electrodes wrapped around the vagus nerve, and a connecting lead. For optimal efficacy, the device is typically placed on the left cervical vagus nerve, as confirmed in previous studies [18]. Stimulation parameters include delivered current, pulse duration, and inter-pulse interval. Manufacturer recommendations suggest a stimulation intensity of 1.5 mA, signal frequency of 30 Hz, pulse width of 250 s, and inter-pulse interval of 12 s [19].

However, in a recent systematic study, THOMAS et al. [20] found that gradually increasing current intensity (by 0.25 mA every 1-3 weeks) and adjusting stimulation frequency from 30 Hz to 20 Hz not only achieved good therapeutic effects but also reduced adverse reactions, though this study did not explore VNS stimulation duration. Therefore, LI et al. [21] conducted short-term VNS treatment (3-7 days) in CHF rats and found that compared with the control group, the VNS group showed significant improvements in left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV), as well as improved myocardial cell arrangement disorder, confirming that VNS has certain effects on improving myocardial remodeling.

In a long-term (18-month) VNS treatment study for CHF, patients receiving different durations (6, 18 months) of VNS treatment showed improved LVEF, LVEDV, and LVESV compared with the control group, along with reduced myocardial fibrosis and remodeling. However, although longer stimulation time

improved cardiac function indices and fibrosis degree, no significant differences in therapeutic efficacy were observed with prolonged treatment duration [22]. Similarly, the Autonomic Regulation Therapy Via Left or Right Cervical Vagus Nerve Stimulation In Patients With Chronic Heart Failure (ANTHEM-HF) study confirmed these findings [6].

In summary, VNS improves cardiac function and myocardial remodeling, with therapeutic effects varying according to stimulation time and parameters. However, determining optimal VNS stimulation time and parameters remains challenging and requires further clinical validation.

3.2 VNS in CHF Inflammatory Mechanisms

Following extensive research on VNS application in CHF treatment, partial mechanisms have been revealed, particularly significant breakthroughs in inflammatory mechanisms. In 2019, ZHOU et al. [23] enrolled 48 Dahl salt-sensitive (DS) rats divided into LS (Low Salt, 0.3% NaCl diet) control group (n=12) and HS (High Salt, 4% NaCl diet) group (n=36). The HS group was further divided into LL-VNS group (n=18) and sham stimulation group (n=18). After model establishment and short-term (4 weeks) VNS treatment, left ventricular inflammatory cell infiltration was significantly lower in the LS group than in the HS group, and LL-VNS group showed significantly reduced LV inflammatory cell infiltration compared with the HS group.

At the gene expression level, IL-11, IL-18, IL-23a, secreted phosphoprotein 1, and osteopontin were upregulated in the sham stimulation group but downregulated in the LL-VNS group. Moreover, these gene expressions positively correlated with echocardiographic left ventricular measurements (circumferential strain) and systolic blood pressure. Therefore, it is reasonable to conclude that LL-VNS prevents left ventricular function deterioration by inhibiting pro-inflammatory and pro-fibrotic gene expression. However, this study could not determine the extent to which left ventricular hypertrophy regression and inflammation/fibrosis reduction contributed to diastolic dysfunction improvement. Furthermore, previous studies have shown that interferon-γ can regulate myocardial hypertrophy independent of blood pressure regulation, suggesting that diastolic dysfunction can be improved without affecting left ventricular hypertrophy. These studies collectively suggest that improved left ventricular inflammation may lead to enhanced diastolic function. Therefore, further exploration of VNS inflammatory mechanisms in CHF treatment for diastolic dysfunction improvement is warranted.

To further investigate inflammatory mechanisms, ZHAO et al. [24] conducted animal experiments in beagle dogs divided into sham operation group, CHF group, and LL-VNS group. After CHF model establishment and LL-VNS treatment, LL-VNS group showed significantly lower N-terminal pro-B-type natriuretic peptide (Nt-proBNP), C-reactive protein (CRP), and TNF-α levels compared with CHF group, with more orderly myocardial cell arrangement and

less fibrosis and inflammatory cell infiltration. Additionally, STAVRAKIS et al. [14] conducted a clinical study enrolling 52 CHF patients randomized into groups. After 3 months of treatment, the VNS group showed significant improvements in TNF-α and IL-8 levels despite no significant differences in mitral inflow Doppler velocity and early mitral annular velocity, effectively improving overall inflammatory levels. In summary, VNS can reduce inflammatory factor levels and improve myocardial function while reducing inflammation-induced damage. Recent research has made important discoveries in VNS inflammatory mechanisms for CHF treatment, necessitating further in-depth investigation of these mechanisms.

In addition to inflammatory mechanisms, studies indicate that disruption of myocardial glucose uptake and utilization is a key feature of advanced CHF [25], associated with downregulation of fatty acid transport protein carnitine palmitoyltransferase (CPT) 1-α and glucose transporter (GLUT) 4, and upregulation of pyruvate dehydrogenase kinase (PDK) 4. Therefore, in 2020, LUO et al. [26] established a myocardial infarction (MI) model in rats through left anterior descending coronary artery (LAD) ligation. Results showed that VNS successfully alleviated typical inflammation processes triggered by MI and reduced apoptosis. Concurrently, VNS treatment increased phosphorylated protein kinase levels, decreased P53 and P16 levels, and reduced P65-nuclear factor B nuclear translocation.

Additionally, VNS significantly increased expression of myocardial sarcomeric structural genes related to myocardial contraction, such as α-actin, sarcoplasmic reticulum Ca2+ ATPase2, cardiac troponin T, and tropomyosin 1, and improved myocardial sarcomere organization. Furthermore, VNS reduced CPT1-α and GLUT4 levels and increased PDK4 expression. The study further discovered that the novel signaling pathway protein kinase (AKT)/transcription factor FOXO 3A/vascular endothelial growth factor (VEGF) activation increased major histocompatibility complex α expression, sarcomere organization, and adenosine triphosphate (ATP) production, suggesting this pathway may promote improved cardiomyocyte phenotype and energy metabolism in damaged hearts, ultimately improving cardiac sarcomere structure and function while optimizing cardiomyocyte sarcomere organization and energy metabolism, reducing myocardial inflammatory infiltration, and preventing transition from compensatory hypertrophy to decompensated heart failure. This study provides a novel and promising clinical strategy, demonstrating that VNS improves cardiomyocyte phenotype accompanied by metabolic process optimization [26].

Subsequently, SUN et al. [27] designed a special and significant practical system: a closed-loop self-powered LL-VNS system based on triboelectric nanogenerator technology. Male SD rats were randomly divided into four groups: control, sham operation, model, and treatment (LL-VNS) groups. After 4 weeks of treatment with the LL-VNS hybrid nanogenerator system (stimulation intensity 5-15 La), results showed that treatment group had significantly reduced collagen volume fraction compared with model group, with increased connexin 43 (Cx43)

and B cell lymphoma 2 (Bcl-2) expression levels and significantly reduced Bax protein expression and Cx43 lateralization. Additionally, by measuring TNF-α and IL-6 content in myocardial tissue, the study found reduced inflammatory molecules in arterial blood of the treatment group. These results indicate that LL-VNS improves myocardial fibrosis, inhibits atrial myocyte apoptosis, reduces inflammatory factor infiltration, and prevents further myocardial cell damage. Moreover, LL-VNS stimulation intensity is far lower than conventional VNS, meaning less organ impact and fewer adverse reactions. In summary, the closed-loop LL-VNS system based on nanogenerators has good antiarrhythmic and anti-inflammatory properties and may greatly improve stimulation therapy targeting. This system will help promote home health monitoring development, reduce clinical treatment costs, and provide new ideas and directions for VNS application in cardiac inflammation and apoptosis research.

3.3 VNS in CHF Apoptosis Mechanisms

Studies have shown that inflammation and apoptosis are interdependent in CHF pathogenesis. In recent years, besides breakthroughs in CHF inflammatory mechanisms, important discoveries have also been made in apoptosis mechanisms. XUAN et al. [28] randomized 58 male Wistar rats into sham operation (SO-SS), sham stimulation (CHF-SS), and stimulation (CHF-VNS) groups, with 3 weeks of continuous treatment. Results showed that MicroRNA-205 (MIR-205) expression levels were significantly elevated in CHF-SS group but significantly reduced in CHF-VNS group, suggesting that MIR-205 expression levels can reflect myocardial apoptosis levels in CHF and that VNS treatment may improve myocardial apoptosis and delay CHF progression by reducing MIR-205 expression.

Beyond MIR-205 research, studies indicate that the most significant genes regulating cardiomyocyte apoptosis are Bcl-2 and Bcl-2-associated X protein (Bax). Bcl-2 inhibits apoptosis by reducing oxygen free radical generation and decreasing intracellular Ca2+ influx, while Bax induces apoptosis by inhibiting Bcl-2 expression and increasing intracellular Ca2+ influx [29-32]. Therefore, the Bcl/Bax ratio is commonly used to indicate apoptosis degree. BEAUMONT et al. [33] conducted experiments in 18 guinea pigs; 4 died during MI modeling, leaving 14 randomly divided into stimulation (VNS-MI) and non-stimulation (MI) groups, with age-matched non-operated animals as parallel controls. After 90 days of chronic, intermittent, low-intensity left cervical VNS treatment, VNS-MI group showed significantly lower Bax levels and higher Bcl-2 levels compared with MI group, with no significant differences compared with control group. These results indicate that VNS affects cardiomyocyte apoptosis by reducing Bax and increasing Bcl-2 levels.

To further confirm VNS effects on Bcl and Bax levels in CHF, ZHANG et al. [34] selected 40 healthy Wistar rats randomly divided into sham operation (SO), CHF, physiological ischemia training (PIT), and vagus nerve transection (VN-CUT) groups, with 8 weeks of treatment after modeling. Results showed that

Bcl-2/Bax ratio was significantly lower in CHF group compared with VN-CUT group, indicating that vagotomy downregulates Bcl-2 expression and upregulates Bax expression, increasing apoptosis degree. These findings suggest that VNS can influence myocardial cell apoptosis by reducing Bax levels. However, no studies have confirmed direct VNS effects on cardiomyocyte apoptosis, requiring further mechanistic investigation. The above studies confirm that VNS indeed plays a role in CHF apoptosis processes, affecting cardiomyocyte apoptosis and providing a foundation for subsequent research.

3.4 Clinical Research Progress in VNS for CHF

In addition to mechanistic breakthroughs, recent clinical studies have advanced VNS application in CHF. In 2021, NEARING et al. [35] conducted an ANTHEM-HF study applying low- and high-intensity VNS to CHF patients for 24 months, finding that high-intensity group showed significantly increased intrinsic heart rate recovery while low-intensity group showed only modest increase, with significant LVEF improvement in both groups, suggesting that VNS intensity may influence treatment outcomes. However, this study had a relatively homogeneous sample source and small sample size, requiring large-scale trials for further validation.

KONSTAM et al. [36] conducted a large-scale randomized controlled trial to determine VNS effects in CHF patients, finding after several months of follow-up that VNS-treated patients showed improvements in 6-minute walk test, LVEF, and quality of life compared with baseline, exceeding combined guideline-directed medical therapy effects. Additionally, KUMAR et al. [37] recently modified the ANTHEM-HF study and similarly found that after 12 months of treatment, patients showed improved New York Heart Association (NYHA) classification ($P<0.0001$), 6-minute walking distance ($P<0.05$), and quality of life ($P<0.0001$), with improved autonomic tone and reflexes. These findings demonstrate that recent VNS treatment for CHF has achieved certain success, playing a role in improving NYHA classification, 6-minute walk test, LVEF, and delaying ventricular remodeling.

4. Summary and Outlook

CHF represents the end-stage of various heart diseases with high morbidity and mortality [38]. Despite decades of research, treatment modalities remain less than ideal for CHF prognosis and clinical outcomes. This review summarizes the novel therapeutic approach of VNS, exploring its mechanisms in CHF treatment with emphasis on VNS applications in CHF inflammation and apoptosis mechanisms.

In exploring VNS inflammatory mechanisms in CHF, ZHOU et al. [23] found reduced inflammatory cells, inflammatory factors, and inflammatory gene expression in myocardium of DS rats after VNS treatment. Subsequent studies by ZHAO et al. [14] and STAVRAKIS et al. [24] in large animals and clinical

settings confirmed that VNS treatment effectively reduces heart failure markers and inflammatory factor indices. LUO et al. [26] and SUN et al. [27] further explained VNS mechanisms in CHF inflammation, demonstrating that VNS improves cardiomyocyte phenotype and energy metabolism, increases Bcl-2/Bax ratio, reduces typical inflammatory processes and inflammatory factor infiltration, and prevents further inflammatory damage to myocardial cells through ACh-m/nAChR-FOXO 3A-VEGF-A/B integrated signaling and improved Cx43 expression. In addressing CHF-induced adverse injury, VNS treatment effectively reduces myocardial cell apoptosis. XUAN et al. [28] found that VNS treatment improves CHF-induced myocardial apoptosis through MIR-205, while studies by BEAUMONT et al. [29] and ZHANG et al. [34] confirmed that significantly downregulated Bcl-2/Bax ratio reduces myocardial cell apoptosis in close relation to VNS treatment. These studies provide helpful insights for further understanding VNS application mechanisms in CHF treatment, offering novel and promising clinical strategies for clinicians while providing new ideas and directions for VNS application in cardiac inflammation and apoptosis research.

Despite significant progress in VNS application for CHF and elucidation of various therapeutic mechanisms [39-40], certain limitations remain. Related studies indicate that selecting optimal VNS dosage and stimulation parameters represents a major challenge. Intervention dosage is fundamental to treatment success; however, no clear measurement standard currently exists, which may hinder VNS development. Furthermore, large clinical trials Neural Cardiac Therapy for Heart Failure (NECTAR-HF) and ANTHEM-HF did not achieve expected results [32-33], requiring further exploration of VNS mechanisms in CHF. Although recent research in inflammation and apoptosis mechanisms has partially explained mechanisms through cytokines and inflammatory pathways, research protocols in this field still need improvement, including setting different stimulation parameter gradients and clarifying the relative contributions of glycolysis and oxidative phosphorylation to ATP generation and related mechanisms in VNS treatment.

Beyond inflammation and apoptosis mechanisms, exploration of the "gut-heart axis" mechanism [41-42] may further enhance understanding of VNS mechanisms in CHF and yield promising therapeutic targets. This review summarizes VNS research in CHF inflammation and apoptosis mechanisms, discussing new findings in this field. VNS can improve myocardial function and CHF by reducing inflammatory factor and related protein expression and apoptosis-related protein expression. This article discusses VNS mechanisms and limitations in anti-inflammatory and anti-apoptotic aspects of CHF, providing new ideas and methods for VNS research in CHF and identifying potential therapeutic targets. However, VNS application in CHF still requires extensive research. Therefore, to better apply VNS clinically, further mechanism exploration is needed.

Author Contributions: HU Yuchi and DAI Songyuan were responsible for conception and design, literature collection and organization, and manuscript writing; ZHAO Lulu and ZHAO Ling were responsible for manuscript revision,

quality control and review, and overall supervision.

Conflict of Interest: The authors declare no conflict of interest.

HU Yuchi: https://orcid.org/0009-0007-1703-9904

ZHAO Ling: https://orcid.org/0009-0002-9588-0751

References

[1] ZHANG Yongzhen, FAN Yuanyuan. Interpretation of the universal definition and classification of heart failure [J]. Chinese Journal of Cardiovascular Medicine, 2021, 26(5): 409-412. DOI:10.3969/j.issn.1007-5410.2021.05.001.

[2] MARTIN N, MANOHARAN K, DAVIES C, et al. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction [J]. Cochrane Database Syst Rev, 2021, 5(5): CD012721. DOI:10.1002/14651858.CD012721.pub3.

[3] ANAND I S, KONSTAM M A, KLEIN H U, et al. Comparison of symptomatic and functional responses to vagus nerve stimulation in ANTHEM-HF, INOVATE-HF, and NECTAR-HF [J]. ESC Heart Fail, 2020, 7(1): 75-83. DOI:10.1002/ehf2.12592.

[4] ARIMURA T, SAKU K, KAKINO T, et al. Intravenous electrical vagal nerve stimulation prior to coronary reperfusion in a canine ischemia-reperfusion model markedly reduces infarct size and prevents subsequent heart failure [J]. Int J Cardiol, 2017, 227: 704-710. DOI:10.1016/j.ijcard.2016.10.074.

[5] DICARLO L A, LIBBUS I, KUMAR H U, et al. Autonomic regulation therapy to enhance myocardial function in heart failure patients: the ANTHEM-HFpEF study [J]. ESC Heart Fail, 2018, 5(1): 95-100. DOI:10.1002/ehf2.12241.

[6] SANT' ANNA L B, COUCEIRO S L M, FERREIRA E A, et al. Vagal neuromodulation in chronic heart failure with reduced ejection fraction: a systematic review and meta-analysis [J]. Front Cardiovasc Med, 2021, 8: 766676. DOI:10.3389/fcvm.2021.766676.

[7] HADAYA J, ARDELL J L. Autonomic modulation for cardiovascular disease [J]. Front Physiol, 2020, 11: 617459. DOI:10.3389/fphys.2020.617459.

[8] SHARMA K, PREMCHAND R K, MITTAL S, et al. Long-term follow-up of patients with heart failure and reduced ejection fraction receiving autonomic regulation therapy in the ANTHEM-HF pilot study [J]. Int J Cardiol, 2021, 323: 175-178. DOI:10.1016/j.ijcard.2020.09.072.

[9] OTTAVIANI M M, MACEFIELD V G. Structure and functions of the vagus nerve in mammals [J]. Compr Physiol, 2022, 12(4): 3989-4037. DOI:10.1002/cphy.c210042.

[10] SHAFFER C, BARRETT L F, QUIGLEY K S. Signal processing in the vagus nerve: hypotheses based on new genetic and anatomical evidence [J]. Biol

Psychol, 2023, 182: 108626. DOI:10.1016/j.biopsycho.2023.108626.

[11] XUE Songwei. Non-pharmacological treatment of heart failure: non-invasive vagus nerve stimulation (55) [J]. Chinese Journal of Rural Medicine and Pharmacy, 2019, 26(17): 27-28. DOI:10.19542/j.cnki.1006-5180.003199.

[12] DOLPHIN H, DUKELOW T, FINUCANE C, et al. "The wandering nerve linking heart and mind" -the complementary role of transcutaneous vagus nerve stimulation in modulating neuro-cardiovascular and cognitive performance [J]. Front Neurosci, 2022, 16: 897303. DOI:10.3389/fnins.2022.897303.

[13] CARAVACA A S, GALLINA A L, TARNAWSKI L, et al. Vagus nerve stimulation promotes resolution of inflammation by a mechanism that involves Alox15 and requires the $ $7nAChR subunit [J]. Proc Natl Acad Sci USA, 2022, 119(22): e2023285119. DOI:10.1073/pnas.2023285119.

[14] STAVRAKIS S, ELKHOLEY K, MORRIS L, et al. Neuromodulation of inflammation to treat heart failure with preserved ejection fraction: a pilot randomized clinical trial [J]. J Am Heart Assoc, 2022, 11(3): e023582. DOI:10.1161/JAHA.121.023582.

[15] SABBAH H N, ILSAR I, ZARETSKY A, et al. Vagus nerve stimulation in experimental heart failure [J]. Heart Fail Rev, 2011, 16(2): 171-178. DOI:10.1007/s10741-010-9209-z.

[16] ALLEN E, PONGPAOPATTANAKUL P, CHAUHAN R A, et al. The effects of vagus nerve stimulation on ventricular electrophysiology and nitric oxide release in the rabbit heart [J]. Front Physiol, 2022, 13: 867705. DOI:10.3389/fphys.2022.867705.

[17] YANCY C W, JESSUP M, BOZKURT B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America [J]. Circulation, 2017, 136(6): e137-161. DOI:10.1161/CIR.0000000000000509.

[18] COOPER C M, FARRAND A Q, ANDRESEN M C, et al. Vagus nerve stimulation activates nucleus of solitary tract neurons via supramedullary pathways [J]. J Physiol, 2021, 599(23): 5261-5279. DOI:10.1113/JP282064.

[19] MARTLÉ V, VAN HAM L M, BOON P, et al. Vagus nerve stimulator placement in dogs: surgical implantation technique, complications, long-term follow-up, and practical considerations [J]. Vet Surg, 2016, 45(1): 71-78. DOI:10.1111/vsu.12427.

[20] HARCOURT-BROWN T R, CARTER M. Implantable vagus nerve stimulator settings and short-term adverse effects in epileptic dogs [J]. J Vet Intern Med, 2021, 35(5): 2350-2358. DOI:10.1111/jvim.16226.

[21] LI Y, XUAN Y H, LIU S S, et al. Short-term vagal nerve stimulation

improves left ventricular function following chronic heart failure in rats [J]. Mol Med Rep, 2015, 12(2): 1709-1716. DOI:10.3892/mmr.2015.3597.

[22] DE FERRARI G M, STOLEN C, TUINENBURG A E, et al. Long-term vagal stimulation for heart failure: eighteen month results from the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) trial [J]. Int J Cardiol, 2017, 244: 229-234. DOI:10.1016/j.ijcard.2017.06.036.

[23] ZHOU L P, FILIBERTI A, HUMPHREY M B, et al. Low-level transcutaneous vagus nerve stimulation attenuates cardiac remodelling in a rat model of heart failure with preserved ejection fraction [J]. Exp Physiol, 2019, 104(1): 28-38. DOI:10.1113/EP087351.

[24] ZHAO Li, SU Wei, WANG Kun, et al. Study on improving cardiac function in heart failure dogs by transcutaneous auricular vagus nerve stimulation [J]. Medical Information, 2020, 33(11): 58-60, 71. DOI:10.3969/j.issn.1006-1959.2020.11.018.

[25] HOU B, WANG D D, QIU Y H, et al. Boosting NAD level suppresses inflammatory activation of PBMCs in heart failure [J]. J Clin Invest, 2020, 130(11): 6054-6063. DOI:10.1172/JCI138538.

[26] LUO B, WU Y, LIU S L, et al. Vagus nerve stimulation optimized cardiomyocyte phenotype, sarcomere organization and energy metabolism in infarcted heart through FoxO3A-VEGF signaling [J]. Cell Death Dis, 2020, 11(11): 971. DOI:10.1038/s41419-020-03142-0.

[27] SUN Y, CHAO S Y, OUYANG H, et al. Hybrid nanogenerator based closed-loop self-powered low-level vagus nerve stimulation system for atrial fibrillation treatment [J]. Sci Bull, 2022, 67(12): 1284-1294. DOI:10.1016/j.scib.2022.04.002.

[28] XUAN Y H, LIU S S, LI Y, et al. Short-term vagus nerve stimulation reduces myocardial apoptosis by downregulating microRNA-205 in rats with chronic heart failure [J]. Mol Med Rep, 2017, 16(5): 5847-5854. DOI:10.3892/mmr.2017.7344.

[29] WANG Y, ZHANG Y. LncRNA CAIF suppresses LPS-induced inflammation and apoptosis of cardiomyocytes through regulating miR-16 demethylation [J]. Immun Inflamm Dis, 2021, 9(4): 1468-1478. DOI:10.1002/iid3.498.

[30] ZHANG X Y, GAO Y K, WU H Y, et al. LncRNA HOX transcript antisense RNA mitigates cardiac function injury in chronic heart failure via regulating microRNA-30a-5p to target KDM3A [J]. J Cell Mol Med, 2022, 26(5): 1473-1485. DOI:10.1111/jcmm.17160.

[31] FENG Y L, YAN B, CHENG H J, et al. Knockdown circ_{0040414} inhibits inflammation, apoptosis and promotes the proliferation of cardiomyocytes via miR-186-5p/PTEN/AKT axis in chronic heart failure [J]. Cell Biol Int, 2021, 45(11): 2304-2315. DOI:10.1002/cbin.11678.

[32] LI T, QIAN D, GUOYAN J, et al. Downregulated long noncoding RNA LUCAT1 inhibited proliferation and promoted apoptosis of cardiomyocyte via miR-612/HOXA13 pathway in chronic heart failure [J]. Eur Rev Med Pharmacol Sci, 2020, 24(1): 385-395. DOI:10.26355/eurrev_{{{202001}}_{{19937}}}.

[33] BEAUMONT E, SOUTHERLAND E M, HARDWICK J C, et al. Vagus nerve stimulation mitigates intrinsic cardiac neuronal and adverse myocyte remodeling postmyocardial infarction [J]. Am J Physiol Heart Circ Physiol, 2015, 309(7): H1198-1206. DOI:10.1152/ajpheart.00393.2015.

[34] ZHANG Xiu, CHENG Yihui, ZHANG Xintong, et al. Neural mechanism of physiological ischemia training improving cardiac function and ventricular remodeling in rats with chronic heart failure after myocardial infarction [J]. Chinese Journal of Rehabilitation Medicine, 2021, 36(8): 915-922. DOI:10.3969/j.issn.1001-1242.2021.08.003.

[35] NEARING B D, LIBBUS I, CARLSON G M, et al. Chronic vagus nerve stimulation is associated with multi-year improvement in intrinsic heart rate recovery and left ventricular ejection fraction in ANTHEM-HF [J]. Clin Auton Res, 2021, 31(3): 453-462. DOI:10.1007/s10286-021-00780-y.

[36] KONSTAM M A, MANN D L, UDELSON J J E, et al. Advances in our clinical understanding of autonomic regulation therapy using vagal nerve stimulation in patients living with heart failure [J]. Front Physiol, 2022, 13: 857538. DOI:10.3389/fphys.2022.857538.

[37] KUMAR H U, NEARING B D, MITTAL S, et al. Autonomic regulation therapy in chronic heart failure with preserved/mildly reduced ejection fraction: anthem-HFpEF study results [J]. Int J Cardiol, 2023, 381: 37-44. DOI:10.1016/j.ijcard.2023.03.030.

[38] WANG H, SHI J J, SHI S Q, et al. Bibliometric analysis on the progress of chronic heart failure [J]. Curr Probl Cardiol, 2022, 47(9): 101213. DOI:10.1016/j.cpcardiol.2022.101213.

[39] VERRIER R L, LIBBUS I, NEARING B D, et al. Multifactorial benefits of chronic vagus nerve stimulation on autonomic function and cardiac electrical stability in heart failure patients with reduced ejection fraction [J]. Front Physiol, 2022, 13: 855756. DOI:10.3389/fphys.2022.855756.

[40] ELAMIN A B A, FORSAT K, SENOK S S, et al. Vagus nerve stimulation and its cardioprotective abilities: a systematic review [J]. J Clin Med, 2023, 12(5): 1717. DOI:10.3390/jcm12051717.

[41] DU Z Y, WANG J L, LU Y Y, et al. The cardiac protection of Baoyuan Decoction via gut-heart axis metabolic pathway [J]. Phytomedicine, 2021, 85: 153322. DOI:10.1016/j.phymed.2020.153322.

[42] SUN W J, DU D B, FU T Z, et al. Alterations of the gut microbiota in patients with severe chronic heart failure [J]. Front Microbiol, 2022, 12: 813289. DOI:10.3389/fmicb.2021.813289.