

# Exploring the Mechanism of Auricular Vagus Nerve Stimulation for the Treatment of Post-Stroke Dyskinesia in Conjunction with Traditional Chinese Medicine Auricular Acupuncture Points

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**Abstract:** Stroke is an important disease leading to death and disability of our nationals, causing a great economic burden to society and families. Limb motor dysfunction is a common complication after stroke, which seriously affects the recovery process of patients, and more effective treatments are still being searched for in clinical practice. Vagus nerve stimulation (VNS), as a well-established neuromodulation technique, has been mainly applied to the treatment of refractory epilepsy, refractory depression and other brain diseases. In recent years, it has been found that VNS can be applied to limb movement rehabilitation in stroke patients. Percutaneous auricular vagus nerve stimulation (t-VNS) is more easily accepted by patients because of its non-invasiveness and economy, therefore, clinical trials and basic research on t-VNS for limb movement disorders after stroke have been gradually carried out at home and abroad. Although percutaneous vagus nerve stimulation and traditional Chinese medicine auricular acupoint therapy belong to different systems, they have similarities in the treatment of stroke, and the theory of vagus nerve stimulation may provide a new idea for traditional auricular acupoints. In this study, we will summarise the clinical studies on percutaneous vagus nerve stimulation for the treatment of post-stroke limb disorders in the past few years, and combine it with the theory of traditional Chinese medicine auricular acupoints to explore its therapeutic mechanism.

**Keywords:** auricular acupuncture points; auricular vagus nerve stimulation; limb movement disorders; mechanism; review

## 1. Introduction

### 1.1. Perceptions of Chinese Medicine

The first relevant description of post-stroke limb movement disorders and hemiplegia appeared in the Nei Jing, "Deficiency evil partial capacity in the body half, ..... Rongwei slightly weakened, then the true qi to go, the evil qi alone to stay, hair for the partial blight". Ming Medical Miscellaneous Writings: "The ancients on stroke paralysis, numbness, aches and pains, not lifting the symptoms, to blood deficiency, dead blood, phlegm and drink as the words, is on the root cause of the disease ..... Evil into the blood veins, meridians, the hands, feet, fingers, palms, shoulders, back, waist and knees heavy hardness, hard to flexion, extension and lifting". It can be seen that the important pathogenesis of limb movement disorders is the deficiency of positive qi, and the disease enters the blood vessels and meridians. In "Suwen zhongjing lian", "hand flexion but not extension, the disease is in the tendon", "medical Guan zhongfeng lian", "qi and blood movement disorder, meridians can't be blocked, meridian contracture and loss of meridian", all indicate that the lesion site is in the tendon. Disorders of qi and blood movement and blockage of the meridians lead to the occurrence of movement disorders.

Another theory is that yin and yang imbalance is an important mechanism for the occurrence of post-stroke limb movement disorders, and "Suwen - Anger and Tongtian Theory" has the following words: "Yang qi, essence nourishes the spirit, and softness nourishes the tendons". Once the body of yin and yang imbalance, yin deficiency and hyperactivity of yang is easy to cause heat phenomenon, heat leads to limb tendon relaxation, decreased muscle tone, unable to complete the limbs should be functional movement. And yin and yang deficiency is easy to trigger cold, cold is collected, limb tendon contracture,

limb flexion and extension is unfavourable. As the "spiritual centre - meridian tendon" said: "meridian tendon disease, cold is reflexive tendon anxious, hot tendon relaxation and vertical not to close". Yin and yang imbalance, limb tendons out of control is also an important mechanism.

"Stroke disease" is the traditional medicine for the stroke of the general term, Chinese medicine believes that the stroke of the disease in the brain, after the stroke of the spasm of the limbs of the disease in the meridians, various reasons lead to qi and blood yin and yang imbalance, blood stasis, phlegm and drink, and other evils in the limbs meridians to the operation of the qi and blood fluid run smoothly is an important mechanism of the disease, meridians paralysis, the limbs do not get qi, blood and fluid moistening, therefore Muscle atrophy, joint contracture, impaired mobility symptoms. Traditional Chinese medicine therapies such as acupuncture, massage, herbal fumigation, acupressure, and auricular acupuncture point therapy play a very important role in the recovery process of the patient, and can be used to treat both soft and hard paralysis.

### ***1.2. Western Medicine's Perceptions***

Limb dyskinesia is the most common complication after stroke and the most important factor affecting the quality of daily life of patients, which can lead to limb pain, deformity, muscle atrophy, and even severe disability. Limb dyskinesia is divided into flaccid and spastic, flaccid dyskinesia is manifested as loss of random movement, low muscle tone, and weakened or disappeared tendon reflexes, which usually occurs in the early stage of acute brain injury, at this time, the pyramidal fasciculus is in a state of shock, and the low centre has not yet shown its effect, and it can be recovered by itself after a few days or a few weeks, and the main goal of this stage is to avoid dislocation of the joints and muscle atrophy, and to prevent the occurrence of various complications. The main goal of this stage is to avoid joint dislocation and muscle atrophy, and to prevent various complications. Early intervention in the flaccid stage is very important for the recovery of limb function. Spasmodic dyskinesia, which manifests as increased muscle tone, hyperreflexia, and difficulty in limb movement, is defined as a dyskinesia characterised by velocity-dependent hyperreflexia due to increased excitability of the detachment reflexes, and is mainly attributed to a decrease in the inhibitory effect of the higher central nervous system on the lower central nervous system, over-release of the function of the lower motor neurons, and abnormalities of the sympathetic nerves, as well as a decrease in the excitatory and inhibitory neurotransmitters of the brain. Imbalance of excitatory and inhibitory neurotransmitters in the brain, etc. Spasmodic dyskinesia is longer in duration, has a greater probability of occurrence, and is a priority in treatment.

The widely used Brunnstrom staging method divides the recovery process of patients' limb function into six stages, and the staged, targeted and comprehensive rehabilitation treatment is of great significance for the recovery of patients' movement disorders. At present, there is no specific drug for limb movement disorder, oral drugs to muscle relaxation, analgesia, nutritive nerve-based, modern medical treatment methods mainly include drug therapy, physiotherapy, exercise therapy, surgical treatment, extracorporeal shockwave therapy, supportive orthosis and other therapies. Spasmodic dyskinesia may be accompanied by the patient throughout the course of the disease, is an important factor affecting the recovery of the patient, Chinese and Western medicine a variety of therapies combined with comprehensive rehabilitation treatment can avoid the single therapy on the cerebral cortex stimulation is small, the effect of a short period of time, the shortness of the required course of treatment, in the clinic has shown great advantages.

## **2. Auricular acupoints in Chinese medicine and post-stroke movement disorders**

Auricular acupoint therapy is a traditional Chinese medicine treatment method that stimulates the ear points through acupuncture, buried needles, electroacupuncture, acupoint pressure pills, bloodletting and other means to treat diseases. As a green therapy with no obvious adverse effects, little pain, convenient operation and continuous stimulation of local acupuncture points, it has become an indispensable part of rehabilitation treatment for stroke patients.

Chinese medicine theory of the ear and meridian circulation has a close relationship with the "Nei Jing" records "the ear, the clan pulse of the gathering also". The six yang meridians either enter the ear directly or are spread around the ear, while the six yin meridians are connected to the ear through the collaterals, or indirectly through the meridians and the yang meridians. "Twelve meridians, three hundred and sixty-five channels, their gas and blood are on the face and go to the empty orifices, ..... its other gas to go to the ear and listen to", it can be seen that the twelve main meridians have a close relationship with

the ear. "Danxi Xinfu" "cover twelve meridians, on the complex in the ear" "Health Baojian" that "the five viscera and six bowels, twelve meridians, there is a complex in the ear", also shows that the ear and the five viscera and six, meridians are closely related. Li Shizhen's "Examination of the Eight Meridians" points out that the Yang Wei and Yang Stilt Meridians both enter the ear or circulate around the ear. According to the connection between auricular acupoints and internal organs and meridians of the body, when the body undergoes dysfunctions that cause blockage or malfunction of the meridians, corresponding auricular acupoints will also produce various positive reaction points, and stimulate the corresponding positive reaction points in order to prevent and treat the corresponding diseases. In addition, the holographic theory is also an important mechanism of auricular acupoint therapy, the holographic theory that any one of the relatively independent part of the organism in the function and structure of the whole is not only a constituent unit of the whole, but also a holographic response to the overall biological characteristics, which coincides with the traditional Chinese medicine, "there are all internal must be shaped in the external", "the ear, the collection of the zongqi This coincides with the Chinese medicine, "what is inside must be shaped outside" and "the ear is the gathering of the veins".

Sun Weiyan <sup>[1]</sup> selected auricular acupuncture points "heart, shenmen, kidney, sympathetic, subcortical", and observed patients in the acute stage of stroke, and the results showed that auricular acupoints burying beans combined with rehabilitation training can better promote the recovery of patients' limb function than simple rehabilitation training. Xu Yiqiang <sup>[2]</sup> took the auricular points "shoulder, wrist, finger, spleen, brain point, thalamus, sympathetic points" and observed the changes of blood flow rate of ulnar artery, ulnar vein, radial artery, radial vein, and interphalangeal artery of the middle finger of the affected limb, and the results showed that auricular acupuncture can promote the venous blood flow of the upper limb of the patients with post-stroke shoulder-hand syndrome, improve microcirculation, alleviate the patients' symptoms of pain and oedema, and then improve the motor function of the affected limb significantly. Zhang Jinling <sup>[3]</sup> divided 60 patients with stage I shoulder-hand syndrome after cerebral infarction into 2 groups, and found that auricular shovel needling combined with conventional needling could improve patients' motor function better than conventional needling alone. Cao Liping <sup>[4]</sup> selected auricular acupuncture points "brainstem, subcortical, and Shenmen" as the main points, and "shoulder, elbow, knee, ankle, and positive sensitive points" as the matching points, and observed the efficacy of auricular acupoint shovel acupuncture combined with stilt-vein acupuncture on 72 patients, and found that auricular acupoints combined with stilt-vein acupuncture can improve the motor function of patients better than routine acupuncture alone in the case of post-stroke spastic paraplegia. It was found that auricular acupressure with stilt pulse acupuncture had better efficacy than conventional antagonist muscle acupuncture for spastic hemiplegia after stroke. As a therapeutic method with Chinese medicine characteristics, the efficacy of auricular acupoint therapy is indisputable, and it can treat a variety of pain, insomnia, anxiety, depression and other diseases, and it is widely used in clinical practice because of its convenient, economical and effective operation, but at present, auricular acupoints are often used as a combined treatment method in the treatment of post-stroke limb disorders, and there is a lack of separate effective research.

### 3. Ear Vagus Nerve Stimulation and Poststroke Limb Disorders

In 2017 Capone <sup>[5]</sup> divided 14 patients with a disease duration of more than 1 year into 2 groups, which included patients with both haemorrhagic and ischemic strokes, and after 10 days of treatment (frequency 20hz, pulse width 0. 3ms) found that there was a significant improvement in limb function in the t-VNS combined with rehabilitation robotics group compared to patients treated with robot-assisted rehabilitation alone. In 2020 Wu <sup>[6]</sup> recruited 21 patients with subacute ischaemic stroke, and limb function was more significantly improved in the t-VNS combined rehabilitation training group after 15 days of treatment. Wei <sup>[7]</sup>, for subacute ischaemic stroke patients, found that t-VNS combined functional training had better efficacy than upper limb functional training alone after 4 weeks of treatment (frequency 25hz, pulse width 0. 1ms) and studied the improvement of brain plasticity and found that t-VNS may improve the recovery of upper limb motor function in stroke patients by modulating the levels of norepinephrine, acetylcholine and dopamine in the cortex. Function. In 2021 Chang <sup>[8]</sup> recruited 36 stroke patients with a disease duration greater than 6 months, this study triggered the t-VNS visually during rehabilitation robot training, and the EMG changes on the surface of the biceps and triceps muscles were measured before and after the treatment (frequency 30hz, pulse width 0. 3ms), the results suggested that there was a significant improvement in the function of the upper limbs and the degree of spasticity of the patients. In 2022, Li <sup>[9]</sup> recruited 60 patients with acute ischaemic or haemorrhagic stroke and after 4 weeks of treatment found that the patients' movement, sensation and mood were improved and well tolerated. Zhang <sup>[10]</sup> recruited 65 patients with shoulder-hand syndrome stage I. After 8 weeks

of treatment (frequency 4/20hz, pulse width 0.2ms), the test group showed superior improvement in HLA-DR levels in peripheral blood, temperature difference in ROIs of both upper limbs, FMA-U scores, and degree of swelling in the affected hand after treatment compared to the control group.

The above clinical studies confirmed that t-VNS for stroke patients in the acute, subacute, and recovery phases improved upper limb mobility to varying degrees and was effective in patients with ischaemic or haemorrhagic stroke, although the treatment parameters and treatment cycles were not consistent. In the current study, the stimulation intensity of t-VNS was mostly limited to the patient's pain domain, and the optimal treatment parameters for limb dyskinesia after stroke have not yet been determined, with a lack of controlled trials between the treatment parameters and a large sample size of clinical trials. Since the efficacy and intensity of electrical stimulation vary from person to person, the stimulation parameters may be optimised according to the patient's characteristics, the degree of injury and the site of injury in order to achieve the best therapeutic effect. If a biomarker is identified to indicate the degree of vagal activation, the optimal stimulation parameters can be formulated for each patient with stroke, and the patients can be better served.

#### **4. Mechanisms of vagus nerve stimulation for the treatment of post-stroke limb impairment**

According to anatomical studies <sup>[11]</sup>, the ear branch of the vagus nerve (Arnold's nerve) is the only branch of the vagus nerve on the surface of the body, and it is mainly distributed in the auricular boat and the auricular cavity, while it is almost undistributed in the earlobe and the auricular portion of the ear, and some studies have confirmed the distribution of the ear branch of the vagus nerve by observing the state of vagus nerve conduction path activation, and they also have confirmed that stimulation of the ear branch of the vagus nerve can cause vagus nerve conduction path Activation of the vagus nerve conduction pathway. The vagus auricular branch transmits to the nucleus tractus solitarius and then projects to other parts of the brain through a variety of structures to regulate the neural functions in these parts of the brain. Several studies have confirmed <sup>[12,13]</sup> that auricular vagus nerve stimulation and implantable vagus nerve stimulation can produce the same effect in the brain and both have very good efficacy. t-VNS <sup>[14]</sup> may have the same efficacy and mechanism as VNS, and has the potential to be an alternative to or even a replacement for VNS.

##### **4.1. Reduction of glutamate excitotoxicity**

Glutamate is the most abundant amino acid neurotransmitter in the nervous system of mammals and is the predominant neuroexcitatory transmitter. After damage to brain cells in stroke, extracellular glutamate concentrations increase abnormally and overstimulate its receptors, resulting in excitotoxicity that damages the central nervous system. Glutamate receptors are divided into two main categories, pro-ionic and metabotropic, and pro-ionic receptors are divided into three categories based on the pharmacological specificity of exogenous agonists, of which NMDA (N-methyl-D-aspartate) receptors are one. It was found <sup>[15]</sup> that vagus nerve stimulation antagonises excitotoxicity by prompting the release of NE (norepinephrine) from the nucleus of the bluish pallidus, which acts on 5-HT neurons in the dorsal nucleus of the median sulcus, causing them to release 5-HT and activate 5-hydroxytryptophan 1A receptor, which inhibits the function of the NMDA receptor and inhibits the release of glutamate, thus acting as a protective agent for the neuronal cells after stroke.

##### **4.2. Suppression of the inflammatory response**

Strong inflammatory response is triggered after brain cell injury, especially in the acute phase of brain injury, and the occurrence of inflammatory response is an important factor affecting the recovery of brain function, and it has been shown <sup>[16]</sup> that VNS might reduce the level of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6, etc., decrease inflammatory response in the brain, and reduce cell apoptosis. By observing the effect of t-VNS on rats with acute traumatic craniocerebral injury, Zheng <sup>[14]</sup> found that the expression of TNF- $\alpha$  in the brain tissue of t-VNS group was lower than that of the model group, and the expression of  $\alpha 7nAChR$  was higher than that of the model group, which suggests that t-VNS may attenuate the inflammatory response of the brain tissue in traumatic craniocerebral injury through the upregulation of the expression of  $\alpha 7nAChR$  and inhibition of the release of inflammatory factors, such as TNF- $\alpha$ . On the other hand <sup>[17]</sup> VNS may achieve anti-inflammatory effects by prompting the release of NE from the nucleus accumbens and inhibiting the expression of IP-10, RANTES chemokines, and VCAM-1, ICAM-1 cell adhesion molecules. Inflammatory response usually occurs in the acute or early phase of stroke, so inhibition of inflammatory response is the main mechanism in treating patients in the acute phase.

#### **4.3. Enhancement of neuroplasticity**

Neuroplasticity refers to the ability of the brain to change and rewire itself in response to stimuli from learning and experience, including changes in the strength of mature synaptic connections, as well as synapse formation and elimination in the brain, and also the regeneration of new synaptic connections after CNS injury. Increased neuroplasticity is considered to be a key mechanism for functional recovery after brain injury. bDNF and bFGF are important substances that promote nerve regeneration and neuronal remodelling in the cerebral cortex, and it has been found that VNS<sup>[18]</sup> accelerates CNS remodelling by increasing the expression of neurotrophic factors (BDNF and bFGF) and promoting the release of some neurotransmitters to promote the reorganisation of the patients' motor cortex and improve motor function. In addition to the above neurotrophic factors, Ach and NE are also important in the enhancement of neuroplasticity. VNS can stimulate the release of NE from the nucleus accumbens in the brain, and stimulate the cholinergic neurons to release Ach. Both of them are important substances to promote the restoration of neuroplasticity, and VNS enhances the release of these substances to enhance the neuroplasticity of the brain and promote the restoration of limb functions. Neural remodelling is always present after brain injury. Based on the fact that t-VNS can improve the motor function of patients in all periods of stroke, it proves that VNS can promote central neural remodelling in all periods after brain injury, and also lays the foundation for t-VNS in the treatment of other neurological injurious diseases.

#### **4.4. Reduce cerebral oedema and protect the blood-brain barrier**

VNS can reduce brain cell injury and promote patient recovery by reducing cerebral oedema, lowering intracranial pressure, and protecting the blood-brain barrier. Kitchen<sup>[19]</sup> et al. 's study found that the expression of aquaporin-4 (AQP4), a water channel protein, increased significantly after craniocerebral injury, and that cerebral oedema could be significantly reduced by targeting and inhibiting the expression of AQP4. Lopez<sup>[20]</sup>, through his study found that VNS could regulate the expression of AQP4 in brain tissues, protect the blood-brain barrier and reduce cerebral oedema. In China, Zheng<sup>[14]</sup> also confirmed that t-VNS can reduce AQP4 expression in brain tissue and reduce cerebral oedema, thus improving brain injury and clinical symptoms.

### **5. Chinese Medicine Auricular Acupuncture Points and Ear Vagus Nerve Stimulation**

Traditional auricular acupoints are based on meridian theory, holographic theory, through acupuncture, electroacupuncture acupoint pressure and other methods to play a therapeutic effect of a Chinese medicine treatment means. In recent years, research on vagus nerve stimulation theory has led to the formation of modern auricular acupoints. t-VNS provides a theoretical basis for nerve conduction and anatomy for auricular acupoint therapy. t-VNS works through electrical stimulation, which is based on a different approach but has similarities in the treatment of post-stroke limb movement disorders. Clinical studies have confirmed that it is when the auricular vagus nerve is used in conjunction with specific rehabilitation training that neurotransmitters in the brain are triggered, resulting in a significant therapeutic effect, so perhaps auricular vagus nerve stimulation is more suitable for patients who still have residual motor function. Linking TCM auricular acupoint theory with VNS theory will stimulate more potential.

### **6. Summary**

Previous studies have confirmed that auricular vagus nerve stimulation can achieve almost the same efficacy as traditional implantable vagus nerve stimulation, but it needs to be combined with rehabilitation training or specific functional training to be effective<sup>[21]</sup>, but it is not clear whether the above mechanism can only be effective when combined with exercise training to promote the reorganisation of the cerebral motor cortex, or whether the stimulation is insufficient to be effective, which is yet to be explored. The efficacy of auricular vagus nerve stimulation combined with rehabilitation training has been confirmed many times, but the stimulation parameters and pairing patterns of the studies are different and there is no uniform standard, so it is worthwhile to further explore the optimal parameters when the efficacy is certain, so as to form a systematic programme for the rehabilitation of stroke patients. In conclusion, although auricular vagus nerve stimulation is different from traditional implantable vagus nerve stimulation, it has the same therapeutic mechanism, and the theory of auricular vagus nerve stimulation provides a new theoretical support for the auricular acupoint therapy of traditional Chinese medicine. Clinical studies have shown that t-VNS has a significant effect on the recovery of limb function from the acute stage to the sequelae stage. At present, most of the studies are validity studies, and there is a lack of cross-sectional comparisons of the differences in efficacy of

different parameters, or different treatment parameters and protocols can be formulated according to the different stages of the patient's recovery. The auricular vagus nerve stimulation device is easy to operate, safe, and economically priced. In today's environment of a large stroke patient population and gradually increasing pressure on rehabilitation therapy, t-VNS may be used to facilitate the formation of a home rehabilitation therapy programme for patients in tertiary rehabilitation after instructing the patients to operate it to provide more benefits to the patients.

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