A new use of transcutaneous electrical nerve stimulation: Role of bioelectric technology in resistant hypertension (Review)

CHENGHUA WANG, PU WANG and GUOQING QI

The Third Department of Cardiology, The First Hospital of Hebei Medical University, Shijiazhuang, Hebei 050030, P.R. China

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Abstract. Hypertension is an important risk factor for cardiovascular and cerebrovascular disease-associated death. Hypertension and its complications are the main problems that have an impact on public health at present. A portion of adults with hypertension fail to meet the recommended blood pressure (BP) treatment goals, despite strict clinical management. Those individuals requiring at least three types of antihypertensive drugs to achieve their BP goal may be classified as patients with resistant hypertension (RH). Bioelectric technology is an emerging method that functions with the help of the human body's own bioelectric system. It is widely used in auxiliary examination, pain relief and organ function rehabilitation. Bioelectrical technology, as an effective treatment for RH, has developed rapidly in recent years and mainly includes renal sympathetic denervation, carotid baroreflex activation therapy, Traditional Chinese Medicine electroacupuncture and transcutaneous electrical nerve stimulation (TENS). The present review describes the pathogenesis of hypertension and provides an understanding of bioelectrical technology as a treatment. In particular, the development of the application of TENS in RH is introduced. The aim is to provide a basis for the clinical treatment of RH and a new idea for further clinical trials in this field.

Contents

1. Introduction

Hypertension is one of the most common chronic diseases in the world. It may lead to target organ damage, which is a major cause of increased morbidity and mortality from cardiovascular disease. The disease burden attributable to arterial hypertension is substantial, accounting for 62% of all strokes and 49% of all cases of heart disease. Furthermore, it culminates in an estimated 7.1 million deaths a year, equivalent to 13% of total worldwide deaths. In addition, those individuals classified as having resistant hypertension (RH) have been observed to have increased target organ damage and cardiovascular risk. Compared to those hypertensive patients with superior pharmacological treatment, the damage and above-mentioned risk are still increasing, in spite of them being treated with anti-hypertensive medications (typically an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker with a calcium channel blocker and a thiazide/thiazide-type diuretic). The prevalence of RH varies by definition from study to study, with a reported prevalence range of 5-30% in patients with treated hypertension. However, compared with the general hypertensive population, the population with RH is older and contains a high-risk sub-population with more cardiovascular complications (1). Thus, patients with RH are encouraged to adhere to intensive lifestyle-based therapy with salt restriction, aerobic exercise, smoking cessation and weight reduction in conjunction with pharmacological blood pressure (BP) control. However, medication side effects, poor adherence to treatment and difficulty in adhering to lifestyle changes limit BP control to target values in patients with RH. Due to the target organ damage and the autonomic imbalance, RH has become common and costly (2). In recent years, there has been an increasing emphasis on complementary and alternative treatments without medication. Furthermore, growing evidence has been provided for bio-electric techniques in the treatment of hypertension, with results seen in the fields of renal sympathetic denervation (RDN), carotid baroreflex activation

Correspondence to: Dr Guoqing Qi, The Third Department of Cardiology, The First Hospital of Hebei Medical University, 89 Donggang Road, Shijiazhuang, Hebei 050030, P.R. China
E-mail: q7g7q7@163.com

Abbreviations: RH, resistant hypertension; RDN, renal sympathetic denervation; CBAT, carotid baroreflex activation therapy; TENS, transcutaneous electrical nerve stimulation; RVLM, rostral ventrolateral medulla

Key words: resistant hypertension, bioelectric technology, acupuncture, transcutaneous electric nerve stimulation, therapy

therapy (CBAT) and Chinese medicine electroacupuncture for the lowering of BP. However, only a small number of studies on transcutaneous electrical nerve stimulation (TENS) applied to hypertension are currently available. This technique is gradually gaining attention due to its low side effects and high acceptability, and the application prospect is promising. In the present review, the progress, advantages and disadvantages of common bio-electric techniques for the treatment of RH were discussed in order to deepen the knowledge in this field.

2. Methodology

Search strategy and study selection. The literature search was conducted covering six important online databases (PubMed, Embase, Web of Science, Cochrane, Chinese National Knowledge Infrastructure and Wanfang) using relevant keywords for the present study on the topic of interest. For the epidemiological and pathophysiology information, the following terms were used: 'resistant hypertension', 'hypertension', 'blood pressure', 'epidemiology', 'pathophysiology' and 'mechanism'. Only research conducted on humans (double-blind, single-blind and unblinded trials) published after the year 2,000 was included. Abstract-only articles, letters to editors and studies on animal or cell models were excluded. When referring to investigations on bioelectric techniques and therapeutic options, medical subject headings terms, such as 'transcutaneous electric nerve stimulation', 'renal sympathetic denervation', 'carotid baroreflex activation therapy' and 'electroacupuncture' were used. The same study inclusion criteria as those stated above were applied (Fig. 1).

Diagnostic criteria. Optimal doses (or best-tolerated doses) of an appropriate therapeutic strategy, which should include a diuretic (typically an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker with a calcium channel blocker and a thiazide/thiazide-type diuretic), fail to lower the clinical systolic BP (SBP) and diastolic BP (DBP) values to <140 and/or <90 mmHg, respectively. Inadequate control of the BP has been confirmed by ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM), and after the exclusion of various causes of pseudo-RH (particularly poor medication adherence) and secondary hypertension (3). The diagnosis of RH is becoming more clear after several international guidelines for hypertension unified their definitions, but the details require to be further explored. According to the latest 2018 European Society of Cardiology/European Society of Hypertension guidelines for the management of arterial hypertension (4), the diagnosis of RH requires detailed information regarding the following items: i) The patient's history, including lifestyle characteristics, alcohol and dietary sodium intake, interfering drugs or substances and sleep history; ii) the nature and dosing of the antihypertensive treatment; iii) a physical examination, with a particular focus on determining the presence of hypertension-mediated organ damage (HMOD) and signs of secondary hypertension; iv) confirmation of treatment resistance by out-of-office BP measurements (i.e. ABPM or HBPM); v) laboratory tests to detect electrolyte abnormalities (hypokalaemia), associated risk factors (diabetes), organ damage (advanced renal dysfunction) and secondary hypertension; vi) confirmation of adherence to BP-lowering therapy.

3. High prevalence and treatment bottleneck with RH

Due to the complexity of the diagnosis of RH, it has rarely been included in large experimental studies. In addition, definitive epidemiological data are not available internationally. However, the importance of RH cannot be ignored. Over the past decade, RH has appeared to account for a larger proportion of all hypertensive patients receiving treatment. The findings of a meta-analysis indicated that the prevalence of RH among patients with treated hypertension ranged between 13.72 and 16.32% (5). This data suggests that the prevalence of RH is significant. Furthermore, the ReHOT study recruited patients with hypertension stage 2 (never treated or under previous antihypertensive treatment) at 26 sites in Brazil. A more precise assessment indicated that the prevalence of RH using a 12-week open-label forced-titration regimen of 3 antihypertensive drugs was 11.7%. Patients with true RH were then randomized into 2 treatment groups comparing the 2 drugs spironolactone vs. clonidine as a fourth-drug therapy (fourth drug to be added to the commonly prescribed triple antihypertension regimen) for RH. The results indicated that clonidine was not superior to spironolactone as a fourth-drug therapy in patients with RH (6). No ideal medication or treatment adherence technique is available. Furthermore, the 2017 American College of Cardiology/American Heart Association hypertension guidelines suggest that the treatment goal for RH should be a BP <130/80 mmHg (7). A more simple definition of RH and more aggressive anti-hypertensive goals would lead to a substantial increase in the prevalence of RH among those who have already received medication. RH is likely to be <10% of treated patients, even if the optimal drug treatment of RH has been poorly studied. However, patients with RH are at higher risk of HMOD, chronic kidney disease and premature cardiovascular events. Diabetes mellitus or BP ≥180/100 mmHg at study entry was independently associated with an RH diagnosis (6). The increased prevalence and the magnitude of the risk of its coexisting conditions have led to a further focus on the importance of RH in the field of hypertension. In the case of resistance to existing drugs, it is worth paying attention to the improvement of the treatment of RH through the pathophysiological mechanisms of RH, which are complex. In the study of new anti-hypertensive drugs that may treat hypertension in different ways, whether they are able to cooperate with other auxiliary methods to treat RH or whether they may increase the medical compliance of patients or increase the antihypertensive efficacy requires to be investigated.

4. Pathophysiology by which mechanisms promote RH

Multifactorial stimulation. The pathogenesis of RH is the persistence of multiple factors that influence the abnormal activation of the central integration system. Studies have indicated that continuously activated sympathetic as well as renin-angiotensin-aldosterone system (RAAS) activity are among the important pathogenic mechanisms of RH (8). RH tends to have sustained stimulation by longer-term risk

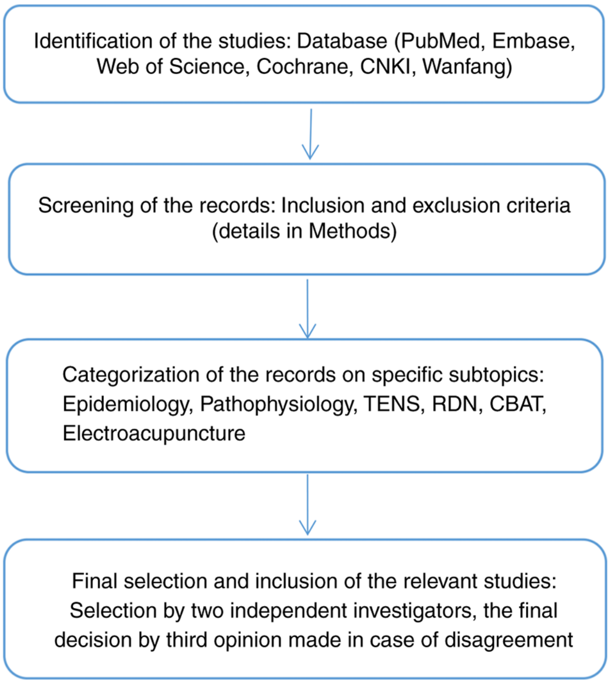

Figure 1. Detailed protocol of the search strategy and study selection. RDN, renal sympathetic denervation; CBAT, carotid baroreflex activation therapy; TENS, transcutaneous electrical nerve stimulation; CNKI, Chinese National Knowledge Infrastructure.

factors. Specifically, there may be four major pathways, including sodium overload, sympathetic nervous system activation, endothelial dysfunction and atherosclerosis. These co-stimulations cause vascular remodeling and volume expansion, leading to the development of RH. On the basis of multiple risk factors, excessive activation of the RAAS *in vivo* increases sympathetic activity in central or local tissues and activates inflammatory factors. The resulting state of inflammation initiates oxidative stress processes and promotes the progression of arterial calcification and atherosclerosis, exacerbating abnormalities in vascular structure and function and causing systemic vascular remodeling. Thus, the series of changes make the BP, which had already reached beyond the limit, more difficult to control. Under pathological conditions, reactive oxygen species production may cause oxidative stress, leading to endoplasmic reticulum stress and autophagy, resulting in vascular endothelial dysfunction, vascular remodeling and reduced compliance (9). The renal sympathetic nerve is composed of afferent and efferent fibers. Excessive activation of renal sympathetic afferent fibers enhances central sympathetic nervous system activity, resulting in systemic sympathetic hyperactivity and increased adrenaline release, which causes structural and functional changes in target organs such as the kidney, heart and blood vessels. Eventually, the maintenance and progression of hypertension are established. Excessive excitation of renal sympathetic efferent fibers leads to the production and excessive secretion of norepinephrine. Thereby, renal vasoconstriction and decreased renal blood flow occur, activating the renal and systemic RAAS systems; norepinephrine also causes the small inlet arteries to constrict more than the small outlet arteries, resulting in a decreased glomerular filtration rate and increased sodium reabsorption; at the same time, the stimulated granulosa cells release renin, which also further activates the RAAS. The above pathophysiological processes exacerbate the elevated BP levels and participate in the maintenance and progression of RH (10-12).

Central integration. The role of central integration has received increasing attention in the study of pathogenesis in hypertension. The central nervous system (CNS) controls peripheral vasodilation and vasoconstriction mainly through the vegetative nerves. The regulatory centers are mainly in the medulla oblongata, pons, hypothalamus and other parts of certain nerve clusters. In recent years, rostral ventrolateral medulla (RVLM) has been considered to be closely related to the occurrence and development of hypertension. The RVLM is the final pathway of the CNS in the regulation of cardiovascular activity and is indispensable in maintaining BP homeostasis (13). The nucleus tractus solitarius (NTS) is located in the RVLM. The NTS is the main central relay station that integrates multiple inhibitory and excitatory sensory inputs from the viscera, as well as downstream cortical inputs. Carotid pressure receptors send axons via the glossopharyngeal and vagus nerves. Aortic pressure receptors send axons via the aortic inhibitory nerves to the cell bodies in nodal ganglia. Then both ways assemble in the NTS (14). Over-regulation by the center after receiving abnormally activated peripheral signals is significantly associated with RH. If the body is subjected to a sustained increase in arterial pressure, the pressure reflex adapts to the new 'normal' and the receptors are reset to respond to the higher pressure with reduced sensitivity. The increase in intravascular volume leads to activation of stretch-sensitive nerve fibers in pressure receptors located in the carotid sinus, aortic arch and thoracic great vessels. As arterial pressure increases, the rate of firing through the glossopharyngeal and vagus nerves into the medullary dorsal solitary bundle nuclei also increases. The brain interprets the increased signal as an increase in BP and attempts to counteract the perceived increase by transmitting the signal to various end organs (15). The lateral ventral lateral medullary region and the medullary questioning nucleus result in decreased sympathetic outflow (inhibitory effect) and increased parasympathetic outflow (excitatory effect). The practical effect is a decrease in heart rate, myocardial contractility and vascular tone, sodium benefit and hypotension (Fig. 2).

5. What is bioelectricity technology?

Bioelectricity is a technical method for diagnosis and treatment of human diseases using electrical stimulation and biofeedback that collects electrical signals from living organisms (human body). Bioelectric technology may be divided into electrophysiological examination and electrophysiological treatment. Common electrophysiological examinations include electrocardiogram and electromyogram, and treatments include electroshock defibrillation, cardiac pacing, pulsed radiofrequency techniques and other clinically common modalities. What is being described in the present study is mainly the electrical stimulation therapy in electrophysiological treatment, i.e., the application of electric current without producing significant heat consists of electrical stimulation of nerves or muscles, the passage of electric currents

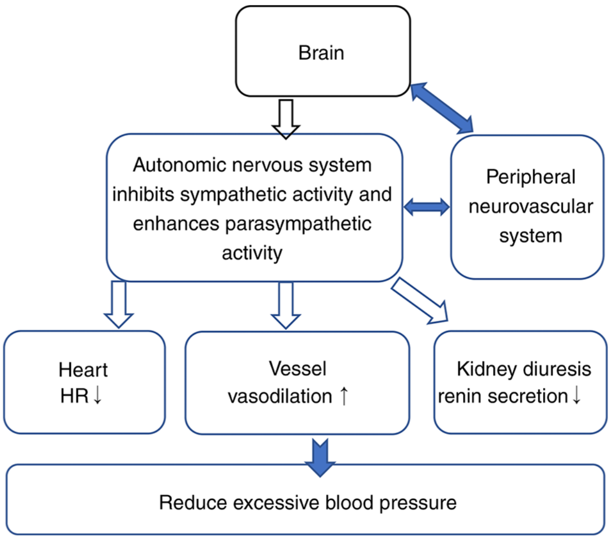

Figure 2. Mechanism of excessive blood pressure regulation. HR, heart rate.

into the body or the use of low-intensity interrupted currents to raise the skin's threshold for pain detection. Electrical stimulation therapies include artificial pacemakers (cardiac resynchronization therapy), deep brain stimulation, electroshock, electroacupuncture, pulsed radiofrequency therapy, spinal cord stimulation, intracranial direct current stimulation, TENS and vagus nerve stimulation. Electrical stimulation therapy is now widely used in fields such as sports rehabilitation and postoperative analgesia. It may indicate a normal or abnormal muscle activity state through biofeedback and guide patients to carry out correct muscle rehabilitation training. It is used to stimulate nerve reflexes or neuromuscles by means of electrical pulses of different frequencies, which may awaken the proprioceptors, make the muscles stretch passively, have an analgesic effect and promote blood circulation.

Electrical stimulation in rehabilitation therapy can not only improve motor deficits at individual sites, but also connect systems to create functional multi-joint movements. TENS, originally designed as an electrophysiological technique to overcome painful impulses, is a form of low-frequency stimulation that acts on smaller afferent sensory fibres. Low-frequency TENS does not cause site muscle contraction because it only acts on sensory nerve fibers and does not activate motor fibers (16). Low-frequency high-intensity TENS enhances ongoing alpha oscillations in the primary sensorimotor cortex and increasing functional connectivity between the brains, leading to long-term changes in ongoing brain activity. This TENS-induced regulation of sustained brain states allows for a wider range of analgesic effects of low-frequency and high-intensity TENS (17). There is moderate-quality evidence that TENS reduces pain and has no serious adverse events compared to placebo (18). TENS may also be applied in the treatment of neurological disorders. TENS may improve cognition and behavior in patients with early and mid-stage Alzheimer's disease. This is evidenced by improvements in long-term and short-term memory, verbal fluency, circadian rest activity rhythms, as well as physical, social and emotional functioning of patients (16). A study indicated that proprioceptive neuromuscular facilitation (PNF) stretch combined with TENS on the triceps gastrocnemius muscle triggered muscle contraction during the muscle contraction phase of PNF stretch, significantly improved ankle function in subjects after ankle sprain and was a good adjunctive rehabilitation technique (19). In most countries, TENS devices and accessories are available without prescription, and the running costs and follow-up clinical support for TENS are not expensive. These conditions allow for self-administration of the treatment without risk of harm, thus potentially relieving patients' symptoms throughout the day (Fig. 3).

6. Role of bioelectric technology in RH

Renal sympathetic denervation for RH. RDN mainly includes radiofrequency, ultrasound, chemical ablation and cryoablation. The persistent increase in the activity of the renal sympathetic-associated RAAS system is one of the important pathogenic mechanisms of RH, which has been confirmed by numerous basic experiments (20). The emergence of RDN based on these mechanisms is considered to be a superior means of lowering BP in the future, in addition to the possibility of renal protection (21). The widely studied and effective first-generation radiofrequency RDN catheter has problems such as being affected by respiration, difficult operation and inadequate ablation, but related trials have also obtained significant antihypertensive efficacy with the advantage of sustained pressure reduction (22-24). The second-generation catheter currently used is able to better achieve combined ablation of the renal aorta and branches than the first-generation catheter, which overcomes certain technical difficulties of the first-generation catheter and improves the ablation effect (25,26). SPYRAL HTN-OFF MED is an international multicenter randomized single-blind sham-operated controlled study that included patients with mild to moderate hypertension (non-RH), with up to 1 antihypertensive drug applied. The patients were randomized into either the RDN group or the sham-operated group. The study used a second-generation standard spiral spherical catheter, which may reach branch arteries of 3-8 mm in diameter, to perform a combined ablation of the distal renal artery and branch vessels in the RDN group, and found that the 24-h ABP decreased better in the RDN group than in the sham-operated group at 3 months after the procedure, and there were no adverse effects in either group (26,27). The RADIANCE-HTN SOLO study indicated that intravascular ultrasound RDN was significantly more effective in lowering BP than intracatheter ablation of RDN (28); however, further evidence is required to confirm this. Numerous existing studies have demonstrated good results of RDN application in mild to moderate hypertension (22,28,29). However, based on the obvious correlation between the mechanism of RDN in lowering BP and the pathophysiological mechanism of RH, the application of RDN in RH still cannot be ignored. The effect of RDN treatment on RH is also significant. The SPYRAL HTN-ON MED study of patients with RH based on ABPM and evaluation at 6 months indicated reduced RDN in the main renal arteries and branches compared to sham controls without any major safety event (25). The current clinical trials of RDN for RH have problems of patient population selection and a lesser amount of data, and a short follow-up time. One study found a more pronounced decrease in BP in patients with RH

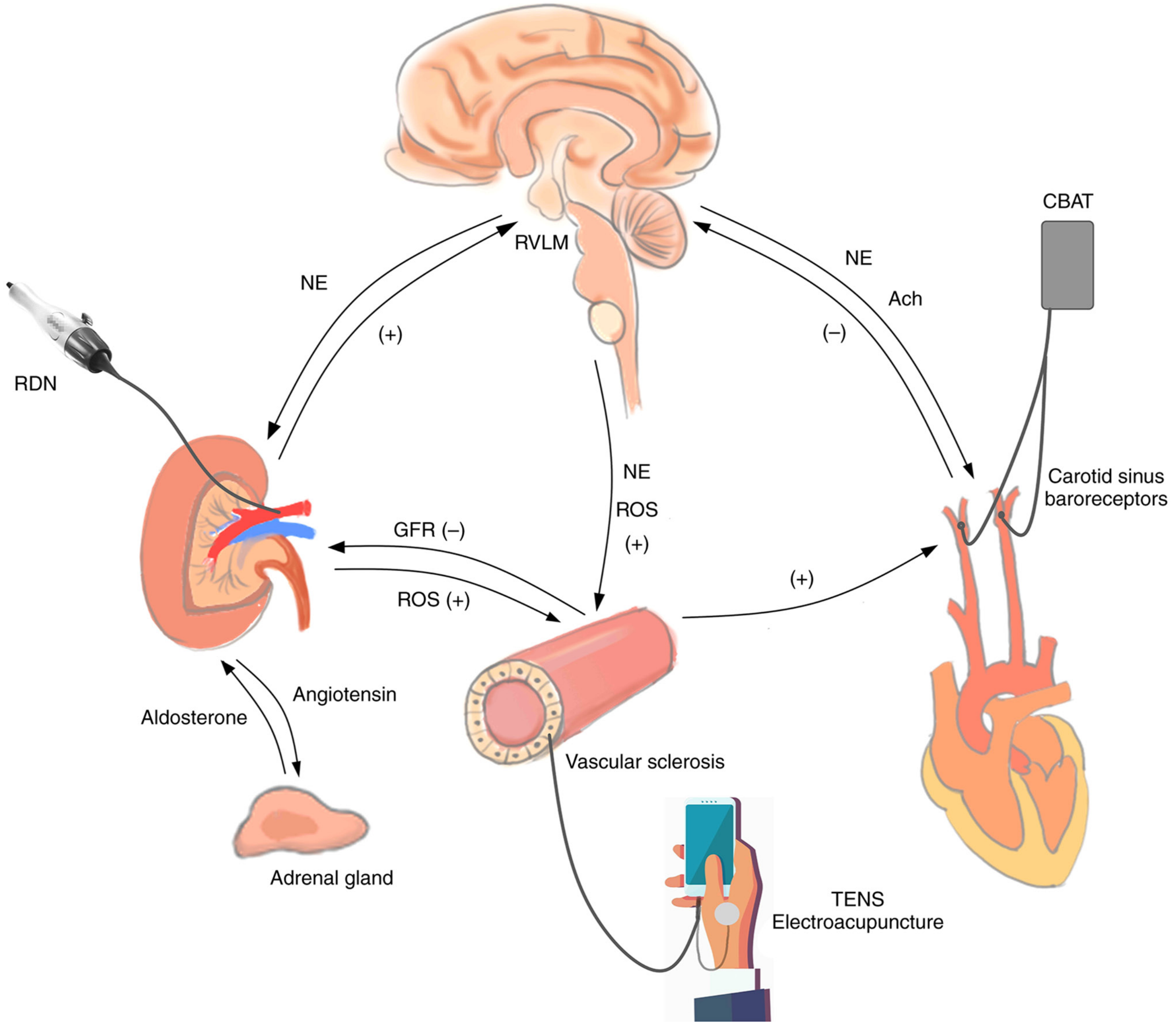

Figure 3. Mechanism of central integration and bioelectric technology. RDN, renal sympathetic denervation; CBAT, carotid baroreflex activation therapy; TENS, transcutaneous electrical nerve stimulation; RVLM, rostral ventrolateral medulla; NE, noradrenaline; Ach, acetylcholine; ROS, reactive oxygen species; GFR, glomerular filtration rate; (+), promotion; (-), restraint.

with high renin after RDN therapy (30). In addition, young and middle-aged patients with high renin activity and high DBP and SBP are more suitable for RDN (30,31). There are also a small number of trials demonstrating the safety of RDN for RH, but the current paucity of evidence also poses limitations for the use of RDN. Thus, regarding RDN treatment for RH, further exploration of the efficacy and safety, further improvement of the procedure and devices, selection of the patients who are most likely to benefit from the treatment and more accurate detection methods are required.

CBAT for RH. CBAT is one of the bioelectrical applications based on the carotid baroreflex and is central integration-related. Animal studies have indicated that stimulation of the carotid baroreceptors in dogs results in a significant decrease in BP and prolonged activation of the pressure reflex, leading to a sustained increase in arterial pressure and sustained sympathetic excitation (32). A US company, CVRx®, has developed a carotid pressure receptor electrical stimulation device and the second generations of the current device have been tested in clinical trials. The first-generation Rheos™ system consists of a pulse generator and two carotid sinus electrodes. Clinical trials related to the system have confirmed certain hypotensive efficacy in lowering BP, but safety appears to be lacking. In the Rheos pivotal trial, 86,265 patients with RH with a mean baseline BP 169/101 mmHg received bilateral implantation of the Rheos™ device. All patients received pressure receptor modulation for an additional 6 months for various periods, with 50% achieving intra-month systolic BP control at 12 months, but 9% experienced transient or permanent facial nerve injury (33). It was indicated that after 6 months of CBAT, the greatest reduction in systolic BP was achieved with unilateral right carotid stimulation, intermediate values of pressure reduction with bilateral stimulation, and the smallest reduction in systolic BP with unilateral left stimulation, which is consistent with animal studies demonstrating the superiority of the right carotid pressure reflex (34,35). The second-generation device, Barostim neo™, based on the Rheos™, requires only unilateral carotid sinus electrode implantation, is smaller and lighter, has a longer battery life, improved surgical implantation procedures and safety, and has no clear difference in efficacy from the first generation. In a phase I and IIa trial involving 30 patients with RH in Europe and Canada, no major adverse events were observed 6 months after implantation of the Barostim neo™ device. Of note, no temporary or permanent facial nerve palsy were observed in the patients. Furthermore, the antihypertensive efficacy of this trial was similar to that of the phase II and III trials of the Rheos™ system (14,36). CVRx received Food and Drug Administration approval for Barostim neo™ implantation in US patients considered to be responders in the Rheos™ trial. In addition, the advantage of CBAT is that it not only reduces BP by counteracting sympathetic activation through the carotid reflex, but also serves to improve cardiac function, renal function and insulin sensitivity through sympathetic axis-related pathways (37). However, there are also issues that cannot be ignored, including the invasiveness of the implantation and the definition of the applicable population of CBAT. It is required to further optimize the device efficacy and trial design to obtain better antihypertensive efficacy on the basis of safe use and to select a more suitable population of patients for CBAT.

Electroacupuncture for RH. Electroacupuncture is a form of acupuncture that applies electrical impulses to stimulate nerve tissue through needles, which may be used for analgesia, anesthesia, rehabilitation and treatment of diseases. Acupuncture has been widely accepted in China as a traditional modality for the treatment of diseases. However, its international promotion is limited by the fact that its mechanism is more complex and not yet well-defined. It is currently thought that the antihypertensive mechanism of acupuncture is related to RAAS system inhibition, regulation of oxidative stress, modulation of peripheral nerves and inhibition of central sympathetic excitation (38-42). Tjen-A-Looi *et al* (41) indicated that acupuncture may cause a decrease in sympathetic excitability in the RVLM region by modulating the projections from the paraventricular nucleus to the RVLM and the expression of opioid receptors and γ-aminobutyric acid receptors, which in turn causes a decrease in BP, and a significant decrease in renal vascular resistance was found by Doppler ultrasound measurement of renal artery vascular resistance after at least three sessions of moxibustion treatment at bilateral dorsal acupoints. The efficacy of acupuncture in the treatment of hypertension has been initially recognized, and a randomized controlled clinical trial has indicated that acupuncture may reduce the BP by 3-5 mmHg in patients with hypertension (43). It also reduces the risk of cardiovascular disease and mortality (44). A systematic review compared several sham acupuncture-controlled trials of acupuncture to lower the BP, revealing that the acupuncture group was effective in lowering both SBP and DBP. A systematic review comparing acupuncture-controlled trials of RAAS inhibitors suggested that acupuncture was more beneficial than RAAS inhibitors for lowering BP (45). Electroacupuncture also has good antihypertensive efficacy, but superiority over non-current acupuncture for lowering BP has not been demonstrated. Certain systematic analyses have indicated that acupuncture combined with ACEI therapy and acupuncture combined therapy are more effective than acupuncture alone in the treatment of hypertension (46). In conclusion, electroacupuncture has good prospects as an adjunctive treatment for hypertension in the future, and on the basis of further refinement of pathophysiological mechanisms, future clinical studies may be considered in terms of adjunctive treatment of RH.

TENS for RH. TENS uses small, specially placed electrodes to deliver electrical impulses across the skin. Its use generally involves less anesthesia. TENS is now widely used in pain and rehabilitation and its safety has been validated by more advanced evidence. TENS has a similar mechanism of action to electroacupuncture for RH, with joint hypotension lowering by afferent nerves and their central regulation through electrical pulse stimulation of acupuncture points or ganglion areas. Low-frequency TENS is able to modulate the autonomic nervous system by releasing endogenous opioids. TENS lacks the invasiveness of traditional acupuncture therapy and has a certified safety profile. It leads to higher patient acceptance and helps to improve BP compliance. However, there is less evidence to analyze both in terms of pathophysiological mechanisms and clinical studies. The lack of clinical evidence is the main problem with TENS for RH. In a trial of non-invasive vagus nerve stimulation to prevent cerebral vascular rupture and improve intracranial aneurysm models in mice, TENS was indicated to rapidly reduce BP in mice by activating the vagus nerve mechanism (47). The study suggested that TENS rapidly reduced BP in mice by activating the vagus nerve. Human trials have also indicated that TENS is effective in reducing sympathetic nerve activity in healthy subjects and patients with cardiovascular disease (48). The effective stimulation point remains elusive. The effective stimulation sites remain to be clearly defined, but the commonly used electrode placement sites are on the thumb abductor muscle between the first and second metacarpal bones (Hegu point), between the palmaris longus tendon and the radial flexor tendon (Neiguan point), part of the sympathetic ganglion area (paravertebral ganglion) and the stellate ganglion. The control group exhibited a significant reduction in SBP. The available research reports have generated information regarding the effectiveness of TENS treatment. Jacobsson *et al* (49) administered 28 days of TENS to 12 hypertensive patients and observed a significant reduction in office BP after treatment. Silverdal *et al* (50) applied different frequencies of TENS to treat hypertensive patients taking ≤1 antihypertensive drug and demonstrated a significant reduction in BP in the low-frequency TENS compared to the sham stimulation group. However, neither of these studies was blinded. the effectiveness of TENS remains to be standardized. Do Amaral Sartori *et al* (51) designed a double-blinded trial, indicating that low-frequency TENS decreased sympathetic nervous system activity and increased parasympathetic nervous system activity compared to the placebo group, but there was no change in BP. The available evidence for the use of TENS in the treatment of RH indicates that the approach is not promising. It is related to the imperfect clinical design and small amount of data (Table I), but more and more patients with RH are in urgent need of a safer adjunctive therapy to increase BP lowering. More attention needs to be paid to the study of TENS in RH. A more comprehensive clinical trial design has been registered with the US Clinical Trials Center (52).

Table I. Studies examining transcutaneous electrical nerve stimulation vs. sham denervation.

First author, year	Type of study	Duration of single stimulation and total course	Types of enrolled patients	Electrode position	Cases (intervention vs. sham)	Type of BP measured at study endpoint (ABPM/office BP) and the difference between groups (post-vs. pre-treatment: mean ± standard deviation)	P-value	Lowering of BP	(Refs.)
Do Amaral Sartori, 2018	Double blind	30 min, single test	Patients with hypertension	Bilateral paravertebral region (from T1 to L2)	18 (8/10)	Office BP, ΔSBP: -2.68 (129.37±15.48 vs. 126.69±15.21)	<0.490	Not significant	(51)
Silverdal, 2012	Single blind	30 min a.m., 30 min p.m., daily for 28±4 d	Patients with hypertension taking ≥1 antihypertensive medication	On the hand over musculus abductor pollicis between the first and second metacarpal bone and over musculus extensor carpiradialis two finger breadths distal to the radial part of the bend of the arm	32 (16/16)	Office BP, ΔSBP: -4.7 (152.7±8.9 vs. 148.0±12.1)	<0.01	Significant	(50)
Jacobsson, 2000	Single blind	30 min a.m., 30 min p.m., daily for 28 d	Patients with hypertension taking ≥1 antihypertensive medication	Dorsal web between the first and second metacarpal bones and at the proximal portion of the brachioradial muscle bilaterally	56 (28/28)	ABPM, ΔSBP: -6.3 (161.9±22.1 vs. 155.6±19.9)	<0.05	Significant	(49)
Chen, 2022	Single blind	65 min, single test	Patients with controlled hypertension	Hegu and Neiguan acupoints	91 (45/45)	Office BP, ΔSBP: -2.6 (105.2±8.9 vs. 102.6±9.0)	0.172	Not significant	(53)

SBP, systolic blood pressure; d, days; ABPM, ambulatory BP monitoring.

Table II. Influencing factors and evaluation indexes of clinical trials in resistant hypertension.

Factors to be excluded	Evaluation indexes to be considered
• Patients with recent diabetes mellitus, congestive heart failure, myocardial infarction, cardiac pacemaker, obesity, ECG changes, cigarette smoking and beta receptor blocker treatment • Congenital renal vascular malformation and chronic kidney disease • Abnormal skin conditions at the stimulation site • Pregnancy and lactation in peri-test period	• Systolic and diastolic blood pressure in multiple different patient positions (sitting or standing) • Heart rate variability • Body mass index and abdominal circumference • Inflammatory factors, natriuretic peptide • Renal vascular resistance, glomerular filtration rate • Plasma norepinephrine, epinephrine, renin activity, plasma aldosterone or cortisol concentration • Vascular endothelial function and volume load

Future research and development are needed to evaluate the mechanism and effectiveness of TENS in the treatment of RH.

7. Biolectricity technology has great potential for RH

In recent years, increasing attention has been paid to bioelectric technology. For RDN or CBAT, improved device safety and better clinical trials are needed. With the help of TENS, the treatment and rehabilitation of a variety of neurological, skeletal and muscle-related diseases have been markedly enhanced. However, whether it may be better used to assist in the treatment of resistant hypertension still requires to be further explored. In the current review, relevant articles have been analyzed and the effectiveness and application prospects of TENS for RH have been demonstrated. However, there is only a small number of trials of TENS performed to date and the randomized clinical trials with available results have the disadvantages of lack of blinded design, inability to avoid the generation of bias and short duration of certain comparisons. Due to these weaknesses, the durability of its antihypertensive efficacy cannot be proven. A future systematic review and meta-analysis on the efficacy of TENS on hypertension is encouraged. More attention should be paid to the following in future scientific studies: i) Further improvement of the anti-hypertensive mechanisms of TENS; ii) overcoming the shortcomings of the design of existing clinical trials, increase of the sample size, design of sham stimulation control groups, use of superior stimulation sites, observation of long-term antihypertensive efficacy and selection of high-quality monitoring indicators; iii) development of a sensitive and responsive closed-loop feedback system based on the existing TENS instrument, which calculates data on BP and heart rate to automatically adjust the amount of transcutaneous current stimulation within a safe range (Table II).

8. Conclusions

The epidemiological survey (54-56) of cardiovascular disease and hypertension in recent years indicated that the level of awareness and control of hypertension are low, and the overall prevention and treatment of hypertension still require further improvement. The public awareness of hypertension vigilance, treatment and control requires to be enhanced. Therefore, patients are encouraged to focus on BP control and to discover more scientific and suitable treatments to manage hypertension internationally. In particular, attention should be paid to complementary alternative treatment options. The present review aimed to provide the current knowledge on the role of bioelectric techniques for the treatment of RH. The results from epidemiological studies, although with significant heterogeneity, demonstrate a clear increase in the prevalence of RH. Both RDN and CABT have significant anti-hypertensive efficacy and are currently supported by sufficient clinical evidence. The continuous improvement of the design of subsequent clinical trials, which allows them to improve safety in the update, allows for them to be gradually applied in the clinic. The use of electroacupuncture is associated with a certain degree of pain, which may make it difficult to accept for certain patients with RH. However, its long-term efficacy and domestic popularity make it more widely used in China.

To overcome this, a gentle stimulation treatment called TENS has been implemented. It is applied for treating the corresponding disease by placing double electrodes on the surface of the respective part of the body and feeding specific low-voltage and low-frequency pulsed currents into the body. In TENS, the afferent nerve electrodes are stimulated by the low-voltage electric pulse delivered by the skin electrodes. This method has few side effects and offers the possibility of patient self-treatment and full treatment at home, which may markedly reduce the impact of poor medical compliance to the treatment. To date, TENS has been in use in the fields of pain relief and rehabilitation. It also has the advantages of non-invasiveness, low cost, high safety and ease of use. However, compared with RDN/CABT/electroacupuncture, the mechanism of TENS for RH is not perfect. Existing studies indicated that its antihypertensive efficacy fluctuates in a small range and it may be considered separately for the treatment of mild to moderate hypertension alone. Furthermore, the treatment of RH requires to be combined with other techniques to achieve the BP target. Therefore, TENS is considered a better adjunctive treatment for RH in the future.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

GQ conceived and designed the direction of the manuscript. CW and PW performed the literature search and GQ made the final decision regarding study inclusion. CW prepared the original manuscript, as well as figures and tables. CW and PW provided help and advice regarding the manuscript. CW and GQ reviewed and proofread the manuscript. All authors contributed to editorial changes in the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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