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Review • DOI: 10.2478/ahem-2023-0004 • AHEM • Vol. 77 Issue 1/2023 • 27-35

Advances in Hygiene and Experimental Medicine
Postępy Higieny i Medycyny Doświadczalnej

Devices for the treatment of arterial hypertension

Review

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Received 25 March, 2022, Accepted 18 November, 2022

Abstract

Hypertension is still the cause of many cardiovascular complications and the premature death of a large number of patients despite the use of increasingly effective pharmacological drugs. Most patients with therapy-resistant hypertension show excessive activity of the sympathetic system. In the last two decades, there have been successful attempts at nonpharmacological reduction of this activity. The earliest method for this purpose is the denervation of the renal arteries by using devices specially designed for this purpose. Other methods of lowering blood pressure are the electrical activation of baroreceptors, which increases the tone of the parasympathetic system, and special pacemaker software to lower blood pressure. The paper discusses the studies assessing the effectiveness and safety of these methods, and on the basis of the current research results, predictions are made concerning which patients with arterial hypertension would be the most appropriate for these treatment methods.

Keywords

hypertension • renal denervation • baroreflex activation therapy• pacemaker-mediated programmable hypertension control therapy

1. Introduction

Despite many advances in understanding the pathophysiology of hypertension and the development of the pharmaceutical industry's several classes of effective antihypertensive drugs, it is still not possible to normalize blood pressure in many patients [1]. Approximately 10% to 20% of patients with hypertension are diagnosed with resistance to therapy, when three or more antihypertensive drugs administered at the maximum doses, including diuretics, do not cause the desired decrease in blood pressure [2].

Recently, attention has been paid to patients' nonadherence to medical recommendations and their failure to use all prescribed medications. A thorough evaluation of metabolites in urine has shown that 25% of patients miss taking at least one of their prescribed drugs [3]. Other studies show that 50% of patients do not use all the prescribed antihypertensive drugs despite intensive convincing about the need for treatment [4]. Finally, in a certain percentage of patients, despite the use of all drugs, blood pressure normalization cannot be achieved [1, 5]. Therefore, new methods of treating arterial hypertension are being searched for. In the last 20 years, methods of nonpharmacological neuromodulation have developed. In over 50% of patients with treatment-resistant hypertension, increased sympathetic system tension was found [6, 7, 8], which can be reduced by nonpharmacological methods. These methods include, first of all, renal denervation [9], electrical stimulation of baroreceptors [10], and pacemaker-based cardiac neuromodulation therapy [11].

2. Renal artery denervation

Understanding the sympathetic nerves in the renal arteries is important to develop devices to reduce blood pressure. The nervous system influences kidney function and blood pressure values by activating sympathetic fibers, narrowing the renal vessels, increasing sodium reabsorption in the renal tubules, and releasing renin from the juxtaglomerular apparatus [7]. In order to reduce the activity of the sympathetic nervous system, attempts were made to ablate the nerve fibers running in the renal arteries. The arterial vessels of the kidneys are richly innervated and relatively easily accessible through intravascular catheters. The

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results of such proceedings (renal artery denervation) were published for the first time in 2009 in a patient with resistant arterial hypertension [9]. The blood pressure values in this patient decreased, and after a year decreased to 127/81 mmHg. In the following years, a number of studies were conducted to assess the impact of renal artery denervation (the so-called SYMPLICITY 1 and SYMPLICITY 2 studies) and confirmed the effectiveness of such a procedure in the majority of patients [12, 13]. In 2014, the results of the randomized SYMPLICITY 3 study were published: 535 patients whose blood pressure drop after renal artery denervation was comparable to the control group, in which the patients underwent a sham procedure. The results were surprising, as there was no significant difference in the pressure drop in patients undergoing renal artery denervation and in the control group [14]. Initially, the results of this study inhibited the development of this treatment method. Soon, however, a number of authors criticized the results of this study, arguing that the procedure of renal artery ablation was performed by nonskilled surgeons, often not in accordance with the procedure, patients were noncompliant with medical recommendations after randomization, and pharmacological therapy was changed for some patients during the study [15]. In 2014, Bohm et al. published a collective assessment of the available results of the Global SYMPLICITY Registry after 6 months of renal artery denervation [16]. This evaluation included 998 patients with hypertension (323 persons with severe hypertension). The initial systolic blood pressure measured in the office SBP in the latter group of patients was 179.3±16.5, and in the automatic ABPM test it was 159.0±15.6 mmHg. Six months after the renal artery denervation, the office BP dropped by 11.6 mmHg and in ABPM by 6.6 mmHg. All these changes were highly statistically significant (p <0.0001). In addition, the higher the baseline arterial pressure was, the greater was the reduction in blood pressure. There were only a few complications after the denervation of the renal arteries. One patient had more than 70% stenosis of the renal artery. In 2015, the *Lancet* published the results of the randomized DENERHTN study, in which some of the subjects had renal artery denervation and pharmacological standardized stepped-care antihypertensive treatment was performed; in the remaining patients only routine pharmacological therapy was used [17]. Unfortunately, noncompliance with medical recommendations was found in as many as 50% of all patients. In the group of patients fully adhering to medical recommendations, after 6 months, the reduction of blood pressure was 5.9 mmHg higher in the group with renal denervation than in the control group. Another pooled review of the Global SYMPLICITY Registry study on blood pressure values at 3 years after renal artery denervation showed that blood pressure drop was increased [18]. The reduction in office BP from baseline was 16.5 mmHg and in the ABPM study 8.0 mmHg. Thus, the concern raised by some authors resulting from the study of animals—that the renal arteries will re-innervate over time [19]—has not been confirmed and is unlikely to be of clinical relevance in humans [18]. Glomerular filtration rate in patients with a baseline above 60 ml/min within 3 years after renal denervation decreased from 87.7 ml/min to 79.1 ml/min, while in patients with renal damage and baseline glomerular filtration less than 60 ml/min, the GFR decreased slightly from 46.7 ml/min to 43.1 ml/min [18].

Subsequent attempts at therapy with the denervation of the renal arteries took into account the recent histological and physiological studies in which it was proved that the proximal and middle segments of the renal arteries, as well as the branches of these arteries, are the most innervated. The most distally located segments are the least innervated. Histological studies by Mompeo indicate that, apart from the main renal artery, many nervous plexuses are located just behind the branching of the artery [20]. According to Sakakura et al. mean subject-specific nerve distance to arterial lumen was greatest in proximal segments (3.40±0.78 mm), followed by middle segments (3.10±0.69 mm), and least in distal segments (2.60±0.77 mm, $p < 0.001$) [21].

Therefore, the technique of performing denervation was changed, abandoning a single electrode (Uni-electrode) and replacing it with a spiral arrangement of several electrodes (Spyral Multi Electrode). In this way, it is possible to denervate the entire circumference of the vessel more quickly and to ensure greater efficiency of the denervation. The SPYRAL HTN-OFF MED study was conducted using this method in patients with systolic-diastolic hypertension (150–179/> 90 mmHg) without pharmacological treatment. The pilot evaluation of this study showed a statistically significant greater decrease in systolic blood pressure in the ABPM method compared to the group of patients after the sham procedure of the renal arteries [22]. The pressure drop after renal artery denervation was on average 5.0/4.4 mmHg in the ABPM method and by 10/5.3 mmHg greater in the office BP than in the control group. The reduction of systolic blood pressure turned out to be highly significant both during the day and at night (p <0.0001). In a parallel study, SPYRAL HTN-ON, in 80 hypertensive patients 6 months after renal artery denervation, office BP was 6.6/4.2 mmHg lower than in patients undergoing sham surgery. In the ABPM method, the difference was also significant and was 7.0/4.3 mmHg [23].

Currently, other methods of renal artery denervation, apart from the use of radiofrequency current, are also being attempted in the studies discussed so far. In the multicenter, randomized RADIANCE-HTN study, renal artery denervation was performed using ultrasound generated by the ReCor Medical device (Palo Alto, CA, USA) [24]. The patients were not administered antihypertensive drugs for one month before the renal denervation. After 2 months, the systolic blood pressure in patients with renal denervation was statistically significantly lower by 6.3 mmHg than in patients who underwent only sham surgery. After 2 months, administration of antihypertensive drugs was also start-

ed in both study groups in those patients whose blood pressure in home measurements was equal to or higher than 135/85 mmHg. It was found then that the amount of antihypertensive drugs necessary to normalize blood pressure was lower in the renal denervation group of patients. In the RADIANCE-HTN SOLO study, renal denervation was performed in 65 patients, sham procedure in 67 patients. Renal denervation reduced daytime ambulatory systolic blood pressure more than the sham procedure (–8·0 mmHg) and this remained stable at 12 months [25]. In nonrandomized studies of TIVUS II including 39 patients, ultrasound denervation caused a significant decrease in systolic blood pressure by 30 mmHg in office BP and 6.8 mmHg in 24-hour ABPM [26]. In another WAWA IV study, renal artery denervation did not significantly reduce blood pressure compared to the control group [27].

Another technique of renal denervation is to administer alcohol through a Peregrine catheter containing 3 microneedles that puncture the renal wall. In a multicenter study using this method in 45 patients, systolic blood pressure dropped by 11 mmHg, and diastolic blood pressure by 7 mmHg 6 months after denervation [28]. Two other studies, TARGET BP and TARGET-OFF-MED, are currently underway.

In the Bullfrog-Infusion-Catheter-Mercator MedSystems method, quanethidine monosulfate administered directly to the renal arteries was used instead of alcohol. In this method the microneedle is enclosed within an uninflated balloon catheter, and upon inflation with saline and contrast agent, the microneedles are pushed through the vessel wall into the adventitia and the perivascular tissue [29].

Already in 2020, over 6,000 patients had been treated with renal denervation; this number is constantly increasing. The greatest interest in the results of this treatment concern patients with resistant or uncontrolled hypertension. Numerous meta-analyses assessing the effectiveness of renal denervation for reducing hypertension have already been published. Most of them have shown success, [30–36] but not all [37].

The meta-analysis of Stavropoulos et al. did not show a reduction in pressure after the use of the first generation of renal denervation devices, while the use of the second generation of these devices resulted in a significant decrease in pressure compared to sham procedures [35]. The greatest drop in blood pressure was observed in patients whose renal denervation was related to the main renal artery and its branches [34]. Irrespective of the pressure reduction, renal denervation reduces the variability of blood pressure, which was confirmed by the meta-analysis of Vogiaztzakis et al. [36]. A greater reduction of resistant hypertension than after renal denervation is observed after the administration of spironolactone. This drug also lowers blood pressure in patients with renal denervation [38].

European Society of Hypertension in its last position paper on renal denervation in 2021 stated that this procedure reduced blood pressure both in the presence and absence of concomitant antihypertensive pharmacotherapy and the antihypertensive effect is durable, although reliable follow-up data are only available for up to 3 years [39].

3. Future renal denervation devices

One of these approaches uses the cryoablation of the renal arteries [29]. Evaluation of this method is being carried out in an ongoing clinical trial (SMART). Three other methods were developed by Chinese companies. The use of one of these methods in 15 hypertensive patients lowered the mean-24-h ambulatory systolic and diastolic blood pressure by 7.5 and 3.3 mmHg, and office BP decreased by 11.5 and 6.9 mmHg, respectively [29].

Subsequent methods of renal artery denervation are characterized by an increasing degree of effectiveness, but they do not reach 100% effectiveness. In experimental studies on animals, Baik et al., using a laparoscopic procedure, introduced flexible electrodes with which they wrapped the renal arteries and caused denervation from the outer membrane of the vessel [40]. According to the cited authors, it is a method that effectively reduces blood pressure, is safe and independent of the anatomical differences in the distribution of nerve endings in the walls of the renal vessels.

The noninvasive method of renal artery denervation was presented by Cai et al. and Mahfound et al. also in an animal model [41, 42]. In order to effect denervation of the renal arteries, they used an x-ray beam directed stereotactically towards the area of the renal arteries. The dose of 25 gray turned out to be sufficient to significantly reduce the secretion of norepinephrine, which indicated effective denervation. Three months after the aforementioned dose of X-rays, the concentration of BUN in the blood increased by 26.7% and creatinine by 28.7%, which, unfortunately, may indicate kidney damage.

4. Baroreflex activation therapy

An entirely different method of lowering blood pressure is to activate the baroreceptors. Already in the 1960s and 1970s, the possibility of lowering blood pressure by this means was observed. The technique involves stimulating electrodes wrapped around the carotid sinus nerve [43]. As this approach was improved, the Rheos system was developed to stimulate the right and left baroreceptors simultaneously. Electrodes placed near the carotid bulbs were connected to a pulse generator implanted in a pocket in the anterior chest wall. The stimulation of baroreceptors by the sinus nerve (a branch of the IX cranial nerve) reaches the medulla prolongata, and then through efferent pathways it affects the work of the heart, the tone of blood vessels, and the function of the kidneys. Baroreflex activation therapy acutely reduces sympathetic nervous activity and increased parasympathetic activity [10,44]. Moreover, it has been shown that baroreceptor stimulation lowers blood pressure also

in patients without increased sympathetic system activity, that is, in patients after denervation of the renal arteries [44].

The first multicenter treatment by baroreceptor stimulation was the nonrandomized DEBuT-HT study, which included 45 patients with blood pressure above 160/90 mmHg [45]. After 3 months of baroreceptor stimulation, despite the fact that the dosage of antihypertensive drugs was not changed, the systolic blood pressure decreased by 21 mmHg and the heart rate decreased by 8 beats per minute. In 17 patients, this method of treatment was extended for a further 2 years and an even greater reduction in blood pressure, a reduction of 33/22 mmHg, was found. In the Rheos Pivotal Trial the authors of this study extended the follow-up observation to 53 months, and consistently noted favorable reductions in blood pressure [46]. An improved method of activating baroreceptors is called Barostim Neo. This method uses a miniature electrode only on one side placed on the surface of the carotid sinus, which makes the surgery safer and much less invasive. In the first nonrandomized open-label study (the Barostim Neo Trial), the effect of baroreceptor stimulation was assessed within 3 months and a decrease in systolic blood pressure by 26 mmHg was observed, and after 6 months, 43% of hypertensive patients showed a normalization of systolic blood pressure (<140 mmHg) [47]. An alternative method of activating baroreceptors is to use a self-expanding nitinol stent, implanted in the internal carotid artery, which changes the vessel's geometry, increases the effective radius, and thereby passively increases pulsatile wall stretch [48]. This method, using the MobiuHD Device for Baroreflex Amplification, was used in an open, nonrandomized study and proved to be effective and safe [48, 49, 50].

In 2020, the results of a randomized trial (CLM_FIM) were published involving 30 patients with hypertension [50]. After switching on the described baroreceptor stimulation, blood pressure dropped by 24/12 mmHg in the office BP; after 6 months, 24-hour ambulatory BP decreased by 21/12 mmHg (p <0.001).

The CALM-2 study (Controlling and Lowering Blood Pressure with the MobiusHD) is ongoing randomized, sham-controlled multicenter trial evaluating the effect of EVBA on blood pressure. It will study 300 patients enrolled at 40 centers throughout Europe and the US [51]. The partial results of this study were published in 2022 [51]. This analysis included 47 patients with resistant hypertension (despite a stable regiment of >3 antihypertensive medications including a diuretic agent). After 3 years of endovascular baroreflex amplification therapy, blood pressure was decreased by 30/12 mmHg. Data from randomized sham-controlled trials are needed to further the risk-benefit profile.

Baroreceptor activation therapy showed a significantly reduced number of hospitalizations over 2 years in 22 patients with refractory arterial hypertension [52].

Walbach and Koziolek developed a meta-analysis concerning the influence of baroreceptor activation on blood pressure values. The authors showed that in 444 assessed patients in 7 observational and 2 randomized studies, electrical activation of baroreceptors caused a significant decrease in systolic blood pressure: 36 mmHg [53]. In another meta-analysis activation of baroreceptors reduced systolic hypertension by 24 mmHg and diastolic hypertension by 12 mmHg [54].

Based on studies on dogs, Lohmir and Hall suggested that the use of baroreceptor activation decreases the level of sympathetic activity and increases heart rate variability (HRV). Observation of the latter may reduce the tendency to cardiac arrhythmias. In the Abraham et al. study, after 6 months of baroreflex activation therapy in 76 patients with heart failure with class III NYHA, there was a significant increase in the distance walked in 6 minutes, improvements of class NYHA and a decrease in the concentration of N-terminal pro-brain natriuretic peptide in the blood serum (p = 0.02) [55]. This year Coat et al. confirmed in their meta-analysis the reduction of symptoms of heart failure in patients treated with baroreceptor activation [56].

5. Pacemaker-mediated programmable hypertension control therapy

Neuzil et al. developed an innovative method of lowering blood pressure in hypertensive patients who, for various cardiac reasons, had a pacemaker (with electrodes in the atrium and ventricle) [57]. These authors reduced arterial hypertension by changing (shortening) the conduction time through the atrioventricular junction. The blood pressure generated by the heart depends on the amount of blood flowing into the left ventricle (preload). This parameter is to some extent dependent on the amount of blood flowing from the atrium to the left ventricle. Shortening the conduction time in the atrioventricular junction reduces blood inflow from the atrium to the ventricle, which results in a reduction in blood pressure. However, experimental studies have shown that after 5–7 minutes, the stimulation of the autonomic system increases the contraction of blood vessels and blood pressure returns to the baseline values [58]. The cited authors further demonstrated that if the atrioventricular conduction interval is extended to 100-180 ms after 8–13 heartbeats with a shortened atrioventricular time, after only 1–3 heartbeats, the stimulation of the sympathetic system is inhibited, and the pressure values are lowered. Thus, alternating the length of atrioventricular time at well-defined times is an effective method of reducing hypertension. A remotely located programmer allows for precise control of the amount of blood flowing into the left ventricle and accordingly modifies the pressure values throughout the day. In order to test this method of therapy, using pacemaker-based Programmable Hypertension Control (PHC), the MODERATO study was undertaken, which eventually included 27 patients with arterial hypertension, whose blood

pressure was not controlled despite the simultaneous use of 2 or 3 antihypertensive drugs. Among others, patients with atrial fibrillation and severe heart failure were excluded from the study [57]. After a one-month baseline period (pressure values in the ABPM test exceeded 140 mmHg), the programmer was turned on. After 3 months of operation of the PHC programmer, the mean systolic blood pressure in the ABPM study decreased by 16±15 mmHg (systolic blood pressure values decreased from 157±11.3 to 141±14.2 mmHg, p <0.001) despite the fact that in 2 patients blood pressure increased slightly. The diastolic blood pressure values did not change significantly. The heart rate in all patients slightly accelerated after switching on the programmer, and decelerated to the baseline values after 3 months of such treatment. Echocardiography showed no significant changes in left ventricular ejection fraction (LVEF 61.4% vs. 59.7%, NS). During the period of PHC treatment, glomerular filtration did not change significantly (GFR 72 ml/min at baseline and 71 ml/min after 3 months of treatment). Last year, the results of the multicenter randomized trial MODERATO II, which included 68 persons with uncontrolled hypertension, were announced, but 47 patients met criteria for study continuation and were randomized [11]. Additionally, these patients had indications for implantation or replacement of a dual-chamber pacemaker due to second- and third-degree atrioventricular block. After a 3 week run-in phase patients were divided into two subgroups. In the first subgroup of 26 patients, programming of atrioventricular conduction time PHC was included; in the remaining subgroup of 21 patients this procedure was not included. Twenty-four hours following randomization, SBP decreased by 15.6 mmHg in the treatment group, compared with a 1.5 mmHg decrease in the control group (a net SBP reduction of 14.1±10 mmHg, p <0.001). At 6 months following randomization a SBP was 11.1 mmHg lower than pre-randomization in the treatment group (p <0.001) compared to 3.1 mmHg lower in control patients. A net treatment effect of an 8.1±10.1 mmHg (p = 0.012). Additionally, no patient reported symptoms related to hypotension. Cardiac complications and echocardiographic changes turned out to be comparable in both subgroups after 6 months of the study. There was a non-significant trend to a drop in LV ejection. This method of therapy is therefore indicated in patients with isolated systolic hypertension, that is, in the elderly, who often need a pacemaker for other reasons. However, large studies with longer follow-up are needed to confirm the long-term safety of the technique before any thought can be given to the device`s role in clinical practice [58].

6. Deep brain stimulation

Deep brain stimulation is already widely used in medicine to treat tremor caused by Parkinson's disease. It is estimated that 160,000 patients have already been treated with this method [15]. The hypotensive effect of this method was noticed in patients treated with deep brain stimulation due to chronic pain. Research is ongoing to shed light on which regions of the brain would be most useful for inserting an electrode to effectively lower blood pressure. It seems, however, that this method of treating arterial hypertension will not be soon (if ever) introduced to the standard antihypertensive therapy.

7. What patients should get what device?

Reduction of arterial hypertension after renal artery denervation or baroreceptor stimulation is not observed in all patients. Which patient with arterial hypertension, then, is the best candidate for treatment with the described devices?

First of all, patients with severe hypertension or hypertension refractory to antihypertensive therapy can be referred to this treatment [5]. Pressure reduction during treatment with the described devices depends on the level of initial hypertension [10, 16]. About 40% to 50% of patients, for various reasons, do not fully comply with medical recommendations, including the use of all antihypertensive drugs [4]. It may be suspected that these patients will still not fully cooperate with the doctor, and then high blood pressure will result in more frequent cardiovascular complications. Such patients may be good candidates for the surgical treatment described.

In the SPYRAL HTN-OFF MED it has been noticed that the reduction of arterial hypertension is greater in patients with heart rate above 73.5 bpm. [22]. This was to be expected since the denervation of the renal arteries reduces the activity of the sympathetic system. Contrary to previous assumptions, the global SYMPLICITY registry showed no differences in the effectiveness of treatment in patients with isolated systolic hypertension compared to other patients with arterial hypertension [18]. Isolated arterial hypertension responds well to baroreceptor stimulation [10] and pacemaker-based cardiac neuromodulation therapy [11]. Renal artery denervation and baroreceptor activation is usually effective in patients with hypertension and obesity, but it does not reduce angiotensin-induced hypertension [30]. Reducing the tone of the sympathetic system may directly benefit heart failure and arrhythmias [59,60]. Interesting are the results of the ERADICATE-AF study, which described the prolonged duration of sinus rhythm in patients treated for atrial fibrillation [61.] The beneficial effect of renal artery denervation was also shown in subsequent reviews and meta-analyses [62, 63].

Patients with obstructive sleep apnea in whom CPAP has not achieved the desired results for blood pressure may also be candidates for treatment with these devices. The results of the study by Warchoł-Celińska et al. indicate that the denervation of the renal arteries not only significantly lowered blood pressure but also reduced the number of apnea episodes during the night [64]. Patients with high overnight high blood pressure (>136 mmHg) and high blood pressure variability most often respond well to renal denervation therapy. It has also been suggested

that patients treated with calcium antagonists and diuretics exhibit a greater drop in pressure after the denervation of the renal arteries, and patients treated with angiotensin converting enzyme (ACE) inhibitors and sartans respond less to this method of therapy [10]. The first two drugs increase the activity of the sympathetic system, while the last two drugs reduce sodium reabsorption in the kidney, reduce the renin secretion, and inhibit the sympathetic system [10]. However, it seems that good therapeutic effects respond to higher degrees of renal denervation, and this depends on the equipment and the experience of the person performing this procedure.

Due to technological progress and miniaturization of devices, their applications in the treatment of arterial hypertension have been developing rapidly in the last decade. It can be expected that in future more and more patients will be able to benefit from this form of nonpharmacological treatment, but before these methods can be used routinely, many further pathophysiological studies will need to be performed to answer the question of which patients are the best candidates for such therapy. We have to wait for the results of large, randomized clinical trials that will finally assess the effectiveness and safety of these methods.

Authors' contribution

Jerzy Głuszek – Research concept and design, original draft preparation, approval of the version for publication.
Teresa Kosicka – Literature review, writing–original draft.

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Conflict of interest

The authors have no potential conflicts of interest to declare.

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