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Interventional Treatment in Hypertension

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Abstract

Hypertension is a systemic disease that can cause serious complications and its frequency is increasing day by day in the society. Various pharmacological agents are used in hypertension. Various interventional treatments have been tried in resistant hypertension that cannot be regulated with pharmacological agents. Interventional approaches such as reducing the activity of the sympathetic nervous system with renal denervation, stimulation of baroreceptors, and creation of a peripheral arterial venous anastomosis are the main treatments. In this article, we presented interventional treatment in hypertension.

Keywords: Resistant hypertension; interventional therapy; renal denervation; baroresptor; anastomosis.

Introduction

Hypertension is associated with 62% of all strokes and 49% of all heart disease cases. It is the most common controllable disease in developed countries, affecting 20-50% of the adult population. It is estimated that only 5-30% of hypertensive patients achieve adequate blood pressure control. Difficulties in achieving target values are underdiagnosis, ineffective treatment, or poor patient adherence to lifelong medical treatment. However, once these challenges are overcome and even if patients are taking three or more antihypertensive medications, about 20-30% will continue to present with resistant hypertension. Considering these results, it is clear that the introduction of alternative treatment options in clinical practice, rather than just appropriate patients, will be a promising approach in the treatment of hypertension [1, 5].

Lowering blood pressure in hypertensive patients is one of the cornerstones of primary and secondary prevention of cardiovascular events. Therefore, treatment-resistant hypertension poses a clinical problem [6,7]. In particular, treatment-resistant hypertensive patients showed a higher prevalence of target organ damage. Therefore, poor cardiovascular outcomes occur most commonly in treatment-resistant hypertensive patients [8, 11].

A retrospective analysis by Dagerty et al. showed that in a large cohort of hypertensive patients receiving antihypertensive therapy, 1.9% of patients developed resistant hypertension within a mean of 1.5 years after the first treatment. Patients with resistant hypertension are almost 50% more likely to experience a cardiovascular event over an average follow-up of 3.8 years than patients without resistant hypertension [12].

Much data on the role of interventional approaches in the treatment of resistant hypertension are eagerly awaited in the near future. Studies on reducing the activity of the sympathetic nervous system, stimulating baroreceptors, and creating a peripheral arterial venous anastomosis with renal nerve ablation are important.

The Role of the Sympathetic Nervous System in Hypertension

The concept of managing therapy-resistant hypertension by reducing sympathetic nerve activity is based on the important role of the sympathetic nervous system in the regulation of blood pressure. The cardiovascular system is regulated by both sympathetic and parasympathetic (vagal) neurons. Parasympathetic neurons show their effects largely in the control of heart function by innervating the heart and a small number of blood vessels. In contrast, sympathetic neurons stimulate the heart, blood vessels, adrenal glands and kidneys, providing direct and indirect control of heart and vascular function [7].

Activation of the sympathetic nervous system can raise blood pressure by causing vasoconstriction, increased cardiac pumping capacity, and increased heart rate. Conversely, its inhibition can quickly lower blood pressure. Consequently, various reflex mechanisms may affect the sympathetic nervous system, causing changes in blood pressure [7]

Sympathetic nervous system is also involved in the pathogenesis of hypertension. The sympathetic nervous system plays an important role in the long-term control of blood pressure by activation of the renal sympathetic nerves. Sympathetic innervation of the kidneys plays an important role in blood pressure regulation through modulation of renin secretion, glomerular filtration rate and renal absorption of sodium [13-15]. Studies for the role of renal nerves in hypertension indicate that renal denervation reduces blood pressure in some models of experimental hypertension. Complete renal denervation spontaneously reduced the development of hypertension in hypertensive rats and obese hypertensive dogs [7].

Renal Nerve Denervation

The first randomized trial, the Symplicity HTN trial, documented that the catheter-based renal nerve ablation technique actually lowers blood pressure with sympathetic nerve activity in some patients with resistant hypertension. These studies also documented the rare occurrence of intraprosedural complications, including renal artery dissection and femoral pseudoaneurysms. The first large-scale prospective controlled randomized trial was conducted in a large population (Symplicity HTN-3). The study included 535 patients with resistant hypertension followed for 6 months, randomly allocated 2: 1 to renal radiofrequency denervation or placebo procedure. Treatment-refractory hypertension was defined as office systolic blood pressure 160 mmHg or 24-hour mean systolic blood pressure 135 mmHg (ambulatory blood pressure monitoring) under maximum tolerated doses of three or more antihypertensive drugs, one of which was an appropriate dose of diuretic. The primary safety endpoint of the Symplicity HTN-3 study was met, but did not meet the primary and secondary efficacy endpoints without observed a significant decrease in office or ambulatory blood pressure between the denervated and placebo groups.

Should catheter-based renal nerve ablation be abandoned due to ineffectiveness? It seems premature to come to such a conclusion. Many aspects of the Symplicity HTN-3 study need to be critically analyzed. For example, concerns arose about the quality of procedural performance, as the majority of operators were unfamiliar with the procedure and had only performed 1-2 procedures previously. No further instructions were given by the protocol, except for the recommendation to perform 4-6 ablations to each renal artery, starting at the distal end of the artery and rotating in a spiral pattern. Not only the number of effective ablations is important, but also the portion of the artery from which they are made. A recent anatomical evaluation of sympathetic peri-arterial renal nerves in humans showed that the highest mean nerve count was observed in the proximal middle segments of the renal artery and the lowest in the distal segments. However, the average distance from the lumen to the nerves is the longest in the proximal segments and the shortest in the distal segments, respectively. The peripheral distribution of the nerves was also most pronounced in the central and least in the dorsal regions. Another concern of the Symplicity HTN-3 study is that the stability of the antihypertensive therapy used is not optimal [16-21].

The recent DENERHTN study demonstrated that in patients with well-defined refractory hypertension, a standardized step antihypertensive therapy alongside sympathetic renal denervation reduced ambulatory blood pressure at 6 months more than pharmacological therapy alone. The DENERHTN study showed that in patients with resistant hypertension, renal denervation combined with standardized stepwise antihypertensive therapy reduced 6-month daytime (primary endpoint) nighttime and 24-hour ambulatory systolic blood pressure by approximately 6 mmHg more than pharmacological therapy alone. This study also confirmed that the short- and long-term side effects of sympathetic renal denervation were minimal [21-23].
Important information provided by Symplicity HTN-3 and DENERHTN studies will guide the design of future research on renal denervation.

In the first studies of renal denervation in Chronic Kidney Disease (CKD), patients with renal insufficiency and a glomerular filtration rate of less than 45 mL / min were excluded for safety reasons. More recent studies support that kidney denervation may be safe and effective in these patients as well. Hering et al. Reported that bilateral renal nerve ablation was safe and effective in 15 patients with resistant hypertensive stage 3-4 CKD. A study by Schlaich et al. Showed that renal nerve ablation reduced blood pressure and sympathetic nerve activity in patients with end-stage kidney disease without major complications or changes in renal function [24].

Carotid Baroreceptor Activation Therapy (BAT)

Arterial baroreceptors are mechanically sensitive sensory nerve endings located in the carotid sinus and the aortic arch that controls arterial blood pressure fluctuations. Arterial baroreceptors increase arousal rates when blood pressure rises, causing an increase in parasympathetic stimulation and a decrease in sympathetic arousal.
To prevent an acute increase in blood pressure, peripheral vasodilation and bradycardia follow. Conversely, baroreceptors decrease arousal rates when blood pressure drops. This causes reflex tachycardia and vasoconstriction that counteract acute hypotension. Hypertensive patients are characterized by particularly treatment-resistant hypertension and baroreflex dysfunction [25].
About 10 years ago, preclinical data first used the bilateral Rheos carotid pacemaker system (CVRx Inc., Minneapolis, MN). Subsequently, the miniaturized second generation unilateral Barostim system revived interest in BAT in clinical practice and

industry-sponsored clinical trials.
The Rheos system is a bilateral carotid baroreceptor pacemaker that can be surgically implanted. Under general anesthesia, lead wires are implanted into the outer surface of both carotid sinus walls. It is connected to a pacemaker generator placed in a subcutaneous pocket in the chest. There was no difference between the groups in the primary endpoint of the percentage of patients with a 10 mmHg decrease in systolic blood pressure at six-month follow-up. In general, systolic blood pressure decreased by 25 mmHg in the device group, while 9 mmHg in the control group. Temporary or permanent facial nerve damage developed in 9% of all patients. Four years after the implantation of the Rheos device, the blood pressure of 182 of the 216 first responders was very similar to that recorded during the 12-month follow-up period. Importantly, the prevalence of carotid stenosis remained low in this cohort [26,27].

Compared to the first generation Rheos pacemaker system, the second generation Barostim neo device has a much smaller electrode that requires a smaller (55 cm) incision for implantation. Provides shorter recovery time. A simpler and less invasive surgery is required. A smaller single-sided generator with longer battery life using less electrical current was produced. Typically right-sided implantation is performed [28].

The Phase III Rheos Pivotal Trial using first-generation baroreceptor pacemaker and continuous carotid baroreceptor pacing for resistant hypertension showed questionable data on efficacy, unacceptable side effects. A miniaturized, second-generation, single-sided pacing electrode can overcome the safety concern. In early stage clinical trials, a phase III trial is currently underway testing this new device for resistant hypertension [26]. Preliminary data in humans have shown evidence of the blood pressure lowering efficacy of this new approach, but future data from ongoing randomized controlled trials are needed to definitively understand its longer-term efficacy and safety [35-48]:

Central Iliac Arteriovenous Anastomosis

The ROX Coupler (ROX Coupler, ROX Medical, San Clemente, CA) is a device that can be inserted between the iliac artery and vein using a minimally invasive catheter procedure to provide an arteriovenous anastomosis. The procedure can be completely reversed by placing a closed stent in the iliac artery at the anastomosis site. The ROXCoupler is designed for use in patients with treatment-resistant hypertension. Appears to lower blood pressure by reducing peripheral vascular resistance and improving vascular compliance [29].
Implantation of the arteriovenous coupler was associated with late ipsilateral venous stenosis in 29% of patients and could be treated with venoplasty or stenting. This preliminary study suggests that arteriovenous anastomosis may be a useful adjunct therapy for uncontrolled hypertensive patients. Future studies will be needed to assess the mechanisms of action and long-term safety of the ROX Connector [29]:

Other Devices

The carotid body is located in the bifurcation region of the carotid communis. The cervical ganglion and carotid sinus nerve are innervated by nerve fibers from the vagus nerve. Stimulation of the carotid body stimulates sympathetic tone, resulting in an increase in blood pressure and minute ventilation. Surgical resection of the carotid body is associated with a decrease in blood pressure and sympathetic overactivity in patients with heart failure. Devices for endovascular carotid body modification by ultrasound-guided ablation have been developed and their effectiveness is being investigated [30-32].

Conclusion

Various device-based approaches are being explored. Recent renal nerve denervation studies have revived interest in the interventional treatment of resistant hypertension. The few studies applying carotid baroreceptor stimulation have shown that safety concerns need to be adequately addressed. These studies have shown positive results that should be confirmed by controlled studies. Iliac anastomosis devices are no longer among our therapeutic options. In general, we live in exciting times in the field of resistant hypertension. A lot of data on the role of interventional approaches in the treatment of resistant hypertension are eagerly awaited in the near future [48].
In the ESC 2018 Hypertension Guidelines, the use of device-based therapies is not recommended for the routine treatment of hypertension, unless it is for clinical trials and randomized controlled trials, until more evidence is obtained regarding their safety and efficacy.
In summary, device-based therapy for hypertension is a rapidly evolving field. Further clinical studies are needed before device-based therapies can be recommended for the routine treatment of hypertension outside the framework of clinical trials.

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