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Review

Carotid Baroreceptor Stimulation: A Potential Solution for Resistant Hypertension

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Carotid sinus · Baroreceptor · Electrical stimulation · Resistant hypertension

Abstract
Resistant hypertension indicates that the blood pressure cannot reach the target value despite standard drug treatment, which harbors an increased risk for cardiovascular diseases. The role of the carotid sinus in regulating blood pressure has long been observed; thereby, the idea that treating resistant hypertension by stimulating carotid baroreceptors emerged. Nevertheless, this idea has been abandoned for years due to technical limitations. Recently, with the evolutions in implantable electrical devices, expectations for treating resistant hypertension with baroreceptor stimulation have increased. Positive results from several multicenter clinical trials further captured the researchers' enthusiasm for more effective baroreceptor-stimulating devices. This study reviews the recent progress in baroreceptor stimulation as a treatment alternative for resistant hypertension.

Resistant Hypertension and Carotid Baroreceptor Stimulation

Resistant hypertension is defined as blood pressure remaining above the target value in spite of the concurrent use of three antihypertensive agents of different classes. Ideally, one of the three agents should be a diuretic and all agents should be prescribed at optimal dose amounts [1, 2]. While the exact prevalence of resistant hypertension is unknown, clinical trials suggested that it is not rare, involving about 20–30% of all study participants [3].

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A carotid sinus is a dilated area located in the bifurcation of the carotid artery. It contains numerous baroreceptors, which are stretch-sensitive mechanoreceptors and innervated by the carotid sinus nerve. Carotid sinus baroreceptors are sensitive baroreceptors that can sense the intra-arterial blood pressure change and regulate the sympathetic tone towards the opposite direction (as a negative feedback) [4]. When blood pressure is elevated, carotid baroreceptors are activated to send signals to the brain stem nuclei in which inhibitory signals are delivered to attenuate the sympathetic tone and subsequently the blood pressure after a complex signal reception and conversion process [5].

The History of Carotid Baroreceptor Stimulation

The idea of stimulating carotid baroreceptors as an approach to lower blood pressure is not new [6]. More than a century ago, Cooper [7] uncovered the roles of the baroreceptor system in regulating blood pressure. It was demonstrated that in animals, the blood pressure decreased when the carotid sinus nerve was electrically stimulated, while it increased if the nerve was transected. In 1965, the pioneering work by Bilgutay and Lillehei [8] utilized a compact implantable device with two electrodes attached directly to the carotid sinus of seven hypertensive dogs. The results indicated that bilateral electrical stimulation of the baroreceptors for 2 h caused a drop in blood pressure, with a reduction in systolic blood pressure (SBP) ranging from 35 to 100 mm Hg and from 25 to 75 mm Hg in diastolic blood pressure [8]. One year later, they employed this technique in 2 patients: 1 had a blood pressure reduction from 250/160 to 130/90 mm Hg and the other from 280/160 to 140/100 mm Hg [9]. Clinical studies demonstrated that the mechanism of resetting and the insensitivity of the baroreceptor system contributed to the elevated blood pressure in hypertensive patients [10, 11]. These data indicated that the primary function of the baroreceptor system was to balance the sympathetic and vagal tone, thereby regulating blood pressure. Unfortunately, at that time, the baroreflex was regarded as a short-term regulation system with temporal effects. This recognition, together with adverse effects, discouraged further investigation of carotid baroreceptor stimulation as a potential treatment for hypertension.

Recent Technical Progress in Carotid Baroreceptor Stimulation

Recently, with the accumulation of knowledge on baroreflex and technical progress, treating resistant hypertension with carotid baroreceptor stimulation has emerged and been popularized. Results from recent studies have suggested that the baroreflex also exerts a long-time control on the sympathetic output and participates in the balance of body fluid volume regulated by kidney, and is thus involved in the long-term regulation of blood pressure [12, 13]. In 2004, Lohmeier et al. [14] showed that prolonged bilateral stimulation of carotid baroreceptors in conscious dogs could reduce blood pressure and heart rate significantly for 7 days. Thereafter, they confirmed these results in both normotensive and hypertensive dogs [15, 16]. The first clinical study evaluating the efficacy and safety of carotid baroreceptor stimulation for long-term treatment of hypertension was performed in 2004. A hypertensive patient with end-organ damage underwent carotid baroreceptor stimulation. Blood pressure decreased by 38/8 mm Hg and remained well for 1 month [17].

Several implantable devices for carotid baroreceptor stimulation have been developed, which facilitates research in this field [18]. The Rheos Baroreflex Hypertension Therapy System (CVRx, Minneapolis, Minn., USA) consists of an implantable pulse generator, two electrode leads attached to the carotid sinus and an external programming system. The pulse

generator delivers activation energy (voltage range 1–7.5 V) through electrode leads to stimulate the carotid sinus, and then the triggered baroreceptors send signals to the brain, which are interpreted as a rise in blood pressure. The brain initiates the body's own control mechanisms to counteract this perceived rise in blood pressure by delivering signals to other parts of the body to reduce blood pressure. In their study, Heusser et al. [19] have shown that the depressor response was achieved through sympathetic inhibition, together with a decrease of the heart rate. However, there were no negative effects on the physiological regulation of the baroreflex. Moreover, there was a correlation between depressor response and the reduction of muscle sympathetic nerve activity. After implantation, the device should not be switched on until the patients recover for 1 month. Then, they should undergo a dose-response test and parameter settings (typically 100 Hz of continuous bilateral stimulation, <7 V) to obtain an optimal antihypertensive efficacy.

Several influential studies have evaluated the efficacy and safety of carotid baroreceptor stimulation in the short-time and long-time control of blood pressure. In a phase II feasibility trial [20], 10 patients with resistant hypertension (SBP ≥160 mm Hg) were enrolled and successfully underwent bilateral implantation of the Rheos system. As the voltage increased, the mean SBP decreased from 170 to 133 mm Hg in an intraoperative test and from 180 to 139 mm Hg before hospital discharge. Moreover, it revealed a linear relationship between voltage value and hemodynamic response (r = 0.88), with the maximal response observed at around 4.8 V. There were no unanticipated serious adverse events (SAEs) throughout the trial process. The Rheos system has proven to be safe and effective in the treatment of resistant hypertension.

The DEBuT-HT (Device Based Therapy in Hypertension Trial) was a multicenter, prospective, nonrandomized feasibility study [21]. The study aimed to evaluate the safety and efficacy of the Rheos system over 3 months or longer in patients with resistant hypertension. The trial enrolled 45 patients with a blood pressure of ≥160/90 mm Hg. After device implantation, 37 patients were evaluated in the first 3 months. Compared to the baseline mean blood pressure (179/105 mm Hg), there was a mean reduction of 21/12 mm Hg. During the 1-year and 2-year follow-ups, the mean blood pressure was reduced by 30/20 and 33/22 mm Hg, respectively. In terms of safety, 7 subjects experienced procedure-related SAEs, and 1 subject experienced device-related SAEs. Most SAEs were related to the individual risks and comorbidities. None of the patients suffered carotid artery stenosis during the follow-up period. During the trial, a substudy of voltage-dependent blood pressure response was conducted at the same time. The voltage response test was performed at 1, 4, and 13 months after implantation. By comparing the index of the baroreflex sensitivity, there were no significant differences between 1, 4, and 13 months. This indicated that the baroreflex function was preserved 1 year after the stimulation, and there was no response adaption or nerve fatigue [22].

The Rheos Pivotal Trial was a prospective, double-blind, randomized, multicenter, placebo-controlled phase III clinical trial to evaluate the efficacy and safety of the Rheos device in patients with resistant hypertension [23]. A total of 265 subjects implanted with the device were randomized (2:1) into two groups. Group A (n = 181) initiated the therapy immediately (the device was activated 1 month after implantation) and group B (n = 84) received the therapy 6 months later (the device was activated 7 months after implantation). The trial was designed to demonstrate five primary end points during 12 months of follow-up. The results indicated that the trial did not reach two of the five end points in procedure safety and short-time efficacy. Procedure safety was evaluated by the incidence of adverse events related to the implantation procedure itself within the first 30 days. It showed an event-free rate of 74.8%, which was less than the prespecified target value of 82%. The acute efficacy end point was judged by measuring the proportion of subjects in the two groups that obtained a drop of SBP by at least 10 mm Hg within the first 6 months. The results indicated that 54% of

subjects in group A and 46% in group B reached the level. With a superiority margin of 20% that was set for this end point, the target was not reached either. Apart from these, the other three end points were successfully reached in this study, including 12-month efficacy, carotid baroreceptor stimulation safety and device safety. A secondary analysis indicated that 42% of patients in group A achieved the target blood pressure (SBP ≤140 mm Hg) at the 6-month evaluation, while only 22% of patients in group B achieved this level (p = 0.005). There were no significant differences between the two groups at the 12-month evaluation. This study showed that 63% of subjects reached the target SBP of ≤140 mm Hg, and 81% of subjects achieved a minimum of 10 mm Hg reduction after implantation. Thereafter, the subjects consented to participate in a longer, nonrandomized follow-up lasting from 22 to 53 months. During the follow-up, the mean blood pressure was reduced by 35/16 mm Hg, and 55% of subjects achieved the target blood pressure. The results have revealed an even longer control of blood pressure through carotid baroreceptor stimulation [24].

To facilitate the operational process of the device implantation, the Barostim *neo*™ system, a second-generation system for carotid baroreceptor stimulation has been developed [25]. Compared to the previously developed Rheos system, the Barostim *neo* system consists of one pulse generator, one lead electrode directly sutured to the unilateral carotid sinus and a laptop computer-based programming system. The carotid sinus electrode serves as cathode (6 mm in diameter), while the pulse generator acts as anode. In an open-label, nonrandomized study of 30 resistant hypertensive patients implanted with the Barostim *neo* system, blood pressure averagely decreased by 26/12 mm Hg during the 6-month follow-up. The results were comparable to those in the DEBuT-HT [21] and Rheos Pivotal Trial using the Rheos system [23]. The percentage of patients achieving an SBP of <140 mm Hg reached 43%, consistent with that in the Rheos Pivotal Trial (42%). Therefore, the second-generation system can significantly lower blood pressure, with similar efficacy compared to the Rheos system. In terms of safety, up to 90% of patients were free from system- or procedure-related adverse events within the first 30 days after implantation. A similar result (88%) was achieved in a study on short-time cardiac pacemaker implantation [26]. During long-time observation (>180 months), 97% of the patients remained event-free. Furthermore, implantation process time decreased from 198 min with the Rheos system to 107 min with the second-generation system due to the unilateral exposure of the carotid sinus. The second-generation, minimally invasive system has preliminarily demonstrated its safety and efficacy in the treatment of resistant hypertension, and a large, randomized controlled trial is currently being planned in full swing in North America for further study [27].

Limitations and Future Directions

Carotid baroreceptor stimulation has been demonstrated to have great potential for treating resistant hypertension. However, this therapy is not suitable for all types of hypertension (e.g. angiotensin II-induced hypertension). In some previous trials, hypertensive patients were treated simultaneously by carotid baroreceptor stimulation and antihypertensive drugs. A case report showed that blood pressure increased when stimulating the carotid baroreceptor alone. Therefore, at present, it is still not possible to free patients completely from medication treatment by the carotid baroreceptor stimulation. All present devices depend on an external computer-controlled system rather than an in vivo closed-loop feedback system. Thus, further studies are warranted to probe the mechanism of blood pressure regulation and to develop self-regulating devices with a closed-loop feedback.

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