

An implantable device for the treatment of drug resistant hypertension

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Hypertension is a major public health problem. Despite the increasing awareness of hypertension and its implications among patients and treating physicians, the prevalence of resistant hypertension remains high. It is not uncommon for hypertension to be resistant to the effects of medical therapy, and this poses a significant risk of adverse cardiovascular events. Many patients fail to reach their target blood pressure (BP) despite the wide availability of several antihypertensive agents and the continued recommendation of dietary and lifestyle modifications. It is estimated that at least 10% of all patients with hypertension are resistant to existing therapies [1]. These patients are at increased risk of cardiovascular events and progressive kidney disease. In the face of uncontrolled hypertension, alternative therapies are needed. A new investigational device-based baroreflex hypertension therapy has been developed to treat these patients. This therapy works by electrically activating the carotid baroreflex.

Clinical background

Physicians have long recognized the importance of the carotid sinus in modulating autonomic tone and regulating BP [2]. As early as 1958, it was demonstrated that initiation of the baroreflex through electrical stimulation of the carotid sinus produces a reduction in BP in humans [1]. Modern technology and better understanding of physiology have finally allowed the development of a technologically feasible treatment option.

In recent years, as BP goals have become more stringent [3], there has been renewed interest in electrical stimulation of the carotid sinus for the

treatment of refractory hypertension. Electrical stimulation of the carotid sinus wall has been shown to activate the baroreflex [4]. Such stimulation of the carotid sinus lowers BP by initiating the baroreflex and, in so doing, reducing sympathetic tone and increasing renal excretory function (in part, by exerting inhibitory effects on renin secretion). Recent evidence from experimental studies suggests that the baroreflex may be more important in the setting of chronic hypertension than originally believed. It appears that the baroreflex attenuates chronic hypertension, in large part by inhibiting renal sympathetic tone.

Baroreflex hypertension therapy device description

The newest carotid sinus stimulator is a device called Rheos. It is manufactured by CVRx Inc. (MN, USA) and consists of an implanted pulse generator with leads that tunnel subcutaneously and bilaterally attach to the carotid sinuses.

The device requires surgical implantation under general anesthesia, and is fully programmable after implantation to allow adjustment of stimulation parameters. The device delivers a stimulus to trigger the body's own natural blood flow regulation system to treat high BP and heart failure. The device is intended for patients with type 2 hypertension who do not respond to BP-lowering drugs. The system works in a similar fashion to a pacemaker. The activation energy is delivered from the device to the left and right carotid arteries. The Rheos device provides control and delivery of the activation energy through the Rheos carotid sinus leads. The leads conduct activation energy from the Rheos

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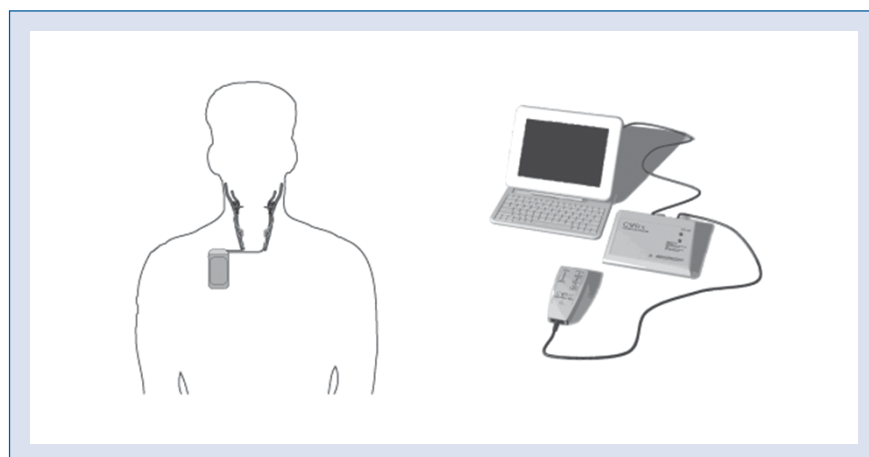


Figure 1. A schematic of the Rheos System. The system includes: implantable pulse generator, carotid sinus leads, and programmer. The leads have electrical contacts that are positioned on the carotid sinus and conduct activation energy from the pulse generator to the left and right carotid sinus. The programmer provides the ability to non-invasively program the pulse generator.

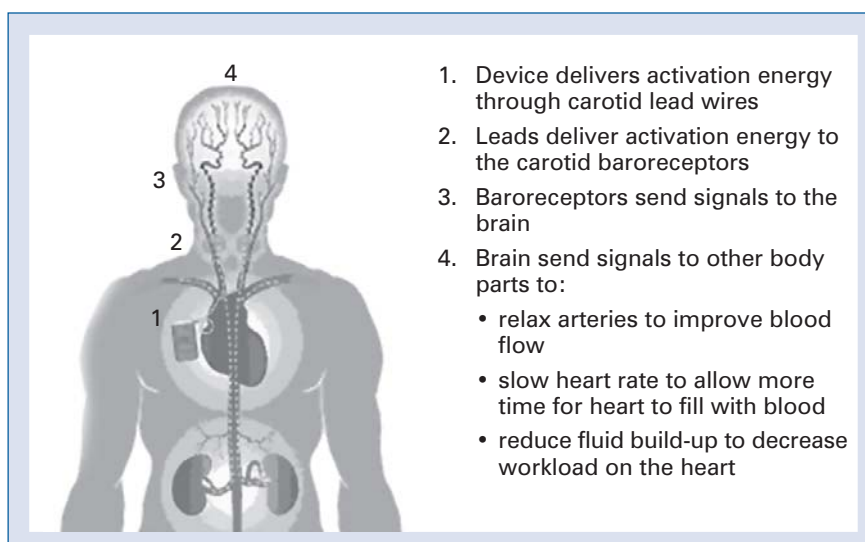


Figure 2. Summary of the system functions.

device to the left and right carotid arteries. The Rheos programmer system provides the ability to non-invasively regulate the activation energy therapy from the device to the leads. The therapy can be adjusted to meet each patient's individual needs as they change over time, providing personalized treatment (Fig. 1).

The Rheos System works by electrically activating the baroreceptors, the body's natural blood flow regulation sensors, sensors that regulate cardiovascular function (Fig. 2). These baroreceptors are located on the carotid artery and in the carotid

sinus. When activated by the Rheos System, signals are sent through neural pathways to the brain. The brain responds by modulating autonomic nervous activity and thereby lowering BP. The brain sends signals to other parts of the body to treat high BP and heart failure, as shown below.

Surgical implantation

Surgical implantation is used to place the device under the skin near the collarbone [5]. The electrodes are placed on the carotid arteries and the leads run

under the skin and are connected to the device. Meticulous implantation is crucial to avoid damage to baroreceptors and sinus nerves, and essential to achieve adequate BP responses to testing. Generous tissue dissection may cause damage to the carotid sinus, making an implantation of the device ineffective.

The successful implantation and testing of the Rheos System is critically dependent on the use of agents that preserve the carotid sinus baroreceptor sensitivity during electrode placement and subsequent testing. Sevoflurane and Propofol are known to effectively block the carotid baroreflex. Isoflurane, however, produces only a dose-dependent reduction in the response to electrical activation of the baroreflex. Anti-hypertensive and pressor medications routinely used in the operating room also affect the baroreceptor and are not recommended.

Dedicated vascular surgeons, trained in operating in the carotid bifurcation region, are qualified for such implantations [6]. The importance of the surgical implantation technique for therapeutic success should not be underestimated.

This therapy works by electrically activating the carotid baroreflex [7]. The device generates signals that are centrally interpreted as a rise in BP. The brain responds by modulating autonomic nervous activity, and thereby lowering BP. Initial study results suggest that electrical activation of the carotid baroreflex results in sustained, dose-dependent reduction in BP.

Early clinical results

Baroreflex hypertension therapy was initially studied in canines. Currently, it is being evaluated in ongoing clinical trials. Early data suggests BP can be reduced with this device in patients with otherwise resistant hypertension as defined by a BP of ≥ 160 mm Hg systolic while receiving three or more drugs (one being a diuretic) at maximal doses for at least two months [8].

As of today, more than 300 people in the US and Europe have been implanted with the Rheos Hypertension Therapy System [9].

Results published on a group of 13 patients from one early trial reported an average systolic BP reduction of 29 mm Hg (from 189 to 160) after three months of treatment and 39 mm Hg (from 189 to 150) after 12 months [9].

Ongoing trials are finding significant and sustained reductions in BP, a good safety profile, and tolerable side-effects.

The early results from the multicenter phase II Rheos feasibility trial [4] are very encouraging. Ten

patients with resistant hypertension (taking a median of six antihypertensive medications) underwent implantation. All ten were successful, with no significant morbidity. The mean procedure time was 198 minutes. There were no adverse events attributable to the device. Predischarge dose-response testing revealed consistent ($r = 0.88$) reductions in systolic BP of 41 mm Hg (mean fall from 180–139 mm Hg), with a peak response at 4.8 V ($p < 0.001$) and without significant bradycardia or bothersome symptoms.

In another study, [10] the outcomes of the multicenter trial of Rheos technology were presented.

Bilateral perivascular carotid sinus electrodes (CSL) and a pulse generator (IPG) were permanently implanted in 17 patients enrolled in a multicenter study. Prior to implant, mean BP of the cohort was $189.6 \pm 27.5/110.7 \pm 15.3$ mm Hg despite stable therapy (5.2 ± 1.8 antihypertensive drugs). The mean procedure time was 202 ± 43 minutes. No perioperative strokes or deaths occurred. System tests performed one or up to three days post-operatively resulted in significant (all $p \leq 0.0001$) mean maximum reduction, with standard deviations and 95% confidence limits for systolic BP, diastolic BP and heart rate of 28 ± 22 (17, 39) mm Hg, 16 ± 11 (10, 22) mm Hg and 8 ± 4 (6, 11) mean BP, respectively. Repeated testing during three months of therapeutic electrical activation demonstrated a durable response.

The outcomes of the US-European clinical trial [11, 12] are even more encouraging: 33 subjects (18 male, 15 female, age 52.4 ± 10.4 years, body mass index 33.0 ± 7.3 kg/m²) were implanted at five centers. The Rheos System improved cardiac structure and function while reducing BP. Although change in arterial compliance was correlated ($r = -0.53$, $p < 0.01$) with change in systolic BP at month three, no other relationships were observed between changes in cardiac structure and BP, suggesting alternative mechanisms for these effects. Reduced mitral A-wave velocity, coupled with decreased left atrial dimension and left ventricular mass index, suggests that the therapy reduces left ventricular diastolic filling pressure. No unanticipated adverse events occurred.

These promising results indicate that this has the potential to become a useful tool in the treatment of drug resistant hypertension.

Conclusions

Preliminary data suggests an acceptably safe procedure with a low rate of adverse events and

supports further clinical development of baroreflex activation as a new concept to treat resistant hypertension. Reduction in BP is associated with a reduction in the risk of death, stroke, heart attack, heart failure and kidney disease. In addition to sustained BP reduction, chronic Rheos therapy in early-stage heart failure patients remodels left atrial and ventricular chambers and improves systolic function. Benefits are incremental to those achieved with aggressive medical therapy. A feasibility study is now under way to assess the potential benefit of Rheos therapy in patients with more advanced heart failure [11, 13].

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