Summary

✓ Of the 20% of Canadian adults diagnosed with hypertension, a small number have treatment-resistant hypertension — that is, their blood pressure remains above the target level despite the use of an optimal combination of at least three antihypertensive drugs, including a diuretic.

✓ Baroreflex activation therapy (BAT) is a new treatment option for individuals with resistant hypertension. It delivers electrical stimulation to baroreceptors (pressure sensors) in the carotid arteries, which acts on the sympathetic nervous system, resulting in a reduction in blood pressure.

✓ The Barostim neo system, a second-generation device for BAT, is a modified version of the earlier Rheos Baroreflex Activation Therapy system.

✓ Evidence from trials of the older Rheos system, and from a small trial of the Barostim neo device, indicates that some patients with resistant hypertension may benefit from this treatment.

✓ The Barostim neo is also being investigated as a treatment for heart failure.

Background

Blood pressure is the force of blood pumped from the heart against the walls of the arteries. Optimal adult blood pressure is considered to be below 120/80 mm Hg (the first number indicates the systolic pressure as the heart contracts, and the second the diastolic pressure as the heart relaxes).

Hypertension, or high blood pressure, is usually defined as blood pressure above 140/90 mm Hg. (For Canadians with diabetes, 130/80 mm Hg is the threshold for diagnosis.) Approximately 20% of Canadian adults have been diagnosed with hypertension.

Uncontrolled hypertension increases the risk for cardiovascular and other adverse events, including stroke, aneurysm, heart attack, heart failure, and kidney failure.

Most individuals can reduce their blood pressure through lifestyle changes such as weight loss, reduced alcohol and salt consumption, and exercise. If lifestyle changes are not made, or blood pressure cannot be adequately reduced, various antihypertensive drug therapies may be used. Even small reductions in blood pressure (e.g., 10 mm Hg systolic or 5 mm Hg diastolic) lower the risk for cardiovascular disease and stroke.

Resistant hypertension is blood pressure that remains above the target despite the optimal use of at least three different hypertensive drug therapies, including a diuretic. (According to some guidelines, patients are considered to have resistant hypertension if they need four or more medications to reach their target blood pressure.)

The incidence of resistant hypertension is likely to rise due to increasing obesity rates and an aging population.

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The Technology

Barostim neo System

The carotid arteries are major blood vessels that supply blood to the brain. Baroreceptors are sensory nerve endings in the walls of blood vessels that stimulate the afferent pathways (those that transmit signals toward the central nervous system) of the autonomic nervous system.

The Barostim neo system uses electrical stimulation of the baroreceptors in the carotid arteries to lower blood pressure by inducing carotid baroreflex.13 When the carotid baroreceptors are stimulated, afferent nerve activity increases. Ultimately, this modulates the autonomic nervous system and causes a decrease in blood pressure.13

The Barostim neo consists of a pulse generator (similar to a pacemaker) that is implanted under the skin below the collarbone.14 The carotid sinus lead from the generator is tunneled under the skin, upwards into the neck, and a single-button electrode is sutured to the carotid sinus (a widening at the branch of the internal and external carotid artery in the neck) through a small incision.6,15 The patient receives general anesthesia or conscious sedation for the procedure.16 During the procedure, mapping is used to determine optimal stimulation position. Through the use of an external programmable system, the physician can tailor the level of electrical stimulation for each patient. Accessories for the system include an implant adapter, an implant tool, a carotid sinus lead repair kit, and an external inhibit magnet (Dean Bruhn-Ding, CVRx, Inc., Minneapolis, Minnesota: personal communication, 16 Mar 2015). The device is usually activated two to four weeks after implantation to allow time for the surgical site to heal.16,17

The Barostim neo’s predecessor device, the Rheos system, used bilateral leads to both the left and right carotid sinus.13 The second-generation Barostim neo has a smaller generator and uses a unilateral lead (i.e., connected to one carotid sinus, rather than to both), and can be implanted through a smaller surgical incision. These changes are expected to improve the safety of the procedure and reduce procedural time as well as patient discomfort (the older Rheos device was larger and required surgical incisions on both sides of the neck).15

Evidence from trials of the older Rheos device has been assessed in earlier reviews. This bulletin focuses on the current-generation Barostim neo system.

Regulatory Status

The Barostim neo system (CVRx, Inc., Minneapolis, Minnesota) is not currently licensed by Health Canada. CVRx will be applying for Health Canada licensing in 2015 — first for the treatment of heart failure. After it receives licensing approval for this indication, the company will consider applying for regulatory approval for Barostim neo in the treatment of resistant hypertension (Dean Bruhn-Ding, CVRx, Inc., Minneapolis, Minnesota: personal communication, 16 Mar 2015).

In the US, the Barostim neo Legacy received Food and Drug Administration (FDA) humanitarian device exemption for use in patients with resistant hypertension who had received implantation of the earlier generation, bilateral Rheos Carotid Sinus Leads (now discontinued) during clinical trials, and who had shown a response to this intervention. The US clinical trials of the Barostim neo for resistant hypertension are being conducted under an investigational device exemption from the FDA.

Patient Group

Of individuals with hypertension, international estimates of those with treatment resistance range from 2% to 30%. Depending on the population and definition used, an estimated 4% to 12% of Canadians with hypertension may have resistant hypertension. However, if patients with non-adherence to medications and those with “white coat” effect (blood pressure that is usually normal but becomes elevated in medical settings) are excluded, the prevalence of resistant hypertension is substantially less.

Risk factors for resistant hypertension are usually multifactorial, including age (over 75 years), obesity (especially central or visceral adiposity), diabetes, kidney or cardiovascular disease, and excessive dietary sodium intake. Women and African Americans are also at higher risk for resistant hypertension.

For approximately 14% of individuals with resistant hypertension, secondary causes are responsible. These can include other medical conditions, such as pheochromocytoma, primary aldosteronism, Liddle syndrome (genetic mutations, most common in African Americans, that cause loss of potassium, and salt and
Another subgroup of patients may have pseudo-resistant hypertension due to non-compliance with their antihypertensive medications, suboptimal combinations of blood pressure medications, or poor in-office blood pressure measurement techniques. When urinary drug levels and/or metabolite levels were measured to confirm whether patients were taking their medication as prescribed, more than 50% of cases of resistant hypertension were found to be due to non-adherence.

In addition, up to 40% of those who appear to have resistant hypertension actually have the white coat effect. While white coat hypertension is not benign, it should be distinguished from resistant hypertension. So that pseudo-resistant hypertension due to the white coat effect is ruled out and more accurate blood pressure readings are obtained, 24-hour ambulatory blood pressure monitoring is preferable to office-based blood pressure measurement. Thus, most of what appears to be resistant hypertension is actually due to secondary causes, medication non-adherence, or the white coat effect.

Patients who are ultimately diagnosed with resistant hypertension benefit from referral to a hypertension specialist and from multidisciplinary management.

## The Evidence

### Rheos Trials
- The Device-Based Therapy in Hypertension Trial (DEBuT-HT) was a small, multi-centre, non-randomized trial that assessed the safety of baroreflex activation therapy (BAT). The trial included 45 patients with resistant hypertension, some of whom were followed over a period of up to two years. Compared with baseline, average office-based blood pressure was reduced at all follow-up points: in 37 patients at three months, 21 ± 4 mm Hg systolic / 12 ± 2 mm Hg diastolic (P < 0.001 for both); in 26 patients at one year, 30 ± 6 / 20 ± 4 (P < 0.001 for both); and in 17 patients at two years, 33 ± 8 / 22 ± 6 (P < 0.001 for systolic and P < 0.002 for diastolic).

However, much smaller reductions were reported for ambulatory blood pressure measurements at the same follow-up intervals (fewer patients were included due to technical difficulties with ambulatory measurements): in 26 patients at three months, 6 ± 3 mm Hg systolic / 4 ± 2 mm Hg diastolic (P = 0.102 for systolic and P = 0.041 for diastolic); in 15 patients at one year, 13 ± 3 / 8 ± 2 (P ≤ 0.001 for both); and in 8 patients at two years, 24 ± 8 / 13 ± 5 (P = 0.017 for systolic and P = 0.049 for diastolic).

- The Rheos Pivotal Trial was a double-blind, randomized controlled trial that included 265 patients with resistant hypertension (and an additional 57 patients in a non-randomized, open-label group). Participants were randomized in a 2:1 ratio: Group A (n = 181) received immediate activation (one month after implant) while Group B (n = 84) received delayed activation (at seven months post-implant). At six months, the percentage of patients with systolic blood pressure of less than 140 mm Hg was 42% in Group A and 24% in Group B (using office-based blood pressure measurement; actual numbers of patients not reported). At one year, when both groups had received activated BAT for either 12 or six months, 50% of patients had systolic blood pressure at or below 140 mm Hg, and 81% of patients had a decrease in systolic blood pressure of at least 10 mm Hg. Most of the participants (approximately 75%) received unilateral, rather than bilateral, carotid stimulation.
• After completion of the Rheos Pivotal Trial, patients continued to be monitored in a follow-up study. Of the 322 patients implanted with the device (including patients in the open-label group), 276 patients participated in the long-term follow-up. Most of these patients (n = 244, or 88%) had a clinically significant response to BAT treatment. This was defined as sustained systolic blood pressure reduction to below 140 mm Hg (below 130 mm Hg in patients with diabetes or renal disease), or a reduction of 20 mm Hg or more following at least six months of BAT. Alternately, a patient could be deemed to have had a clinically significant response if, at least a week after device deactivation, the patient’s blood pressure increased by 20 mm Hg or more. Blood pressure was determined by office-based blood pressure measurement. At the most recent follow-up, average blood pressure measurements were reduced in all three patient groups (an average of 35/16 mm Hg in the responder group [n = 239], 19/10 mm Hg in the indeterminate group [n = 32], and 33/14 mm Hg in the withdrawn group [n = 29]; P < 0.001 for all reductions). Of patients who experienced a clinical response, 55% achieved their target blood pressure reduction, and blood pressure reductions were maintained throughout an average of 28 months of follow-up.

A recent conference presentation reported ongoing follow-up of participants from the earlier Rheos Pivotal trial. Forty participants who had the device for five years experienced a sustained reduction of 32.9 (± 4.5) mm Hg in systolic blood pressure from a baseline measure of 176.8 (± 21.2), and a reduction in diastolic blood pressure of 17.1 (± 2.6) mm Hg from a baseline measure of 101.3 (±14.4) mm Hg (P < 0.001).

The manufacturer of the Barostim neo has established a European patient registry to continue to monitor patients who receive the device for hypertension.

Barostim neo Trials

• The Barostim neo trial (XR-1 Verification Study) was a single-group, open-label trial to explore the safety and efficacy of the Barostim neo device. (At the time, the Barostim neo device was known as XR-1.) The trial included 30 patients and was conducted at seven centres — six in Europe (20 patients) and one in Canada (one patient). Resistant hypertension was defined as resting systolic blood pressure over 140 mm Hg despite taking at least three antihypertensive drugs, including at least one diuretic. The participants included both male (n = 14) and female patients (n = 16), most of whom were middle-aged (average age 57) and obese, and who were taking an average of six medications for hypertension. Six participants had previously undergone renal denervation. The average baseline blood pressure was 171.7 (± 20.2) mm Hg systolic /99.5 (± 13.9) mm Hg diastolic. The Barostim neo device was activated two weeks post-implantation and blood pressure was measured using an office-based device (rather than ambulatory measurement). At the six-month follow-up, average blood pressure reduction was 26.0 (± 4.4) mm Hg systolic / 12.4 (± 2.5) mm Hg diastolic (P < 0.001), and 43% of patients (actual number not reported) had systolic blood pressure of less than 140 mm Hg.

• A small observational study in Germany reported on 25 of 30 patients who received the Barostim neo, and examined the effect of BAT therapy on central hemodynamics. The study included 11 men and 14 women, with an average age of 61. Nine of the participants had previously undergone renal denervation and most participants were obese. After six months of BAT therapy, as measured in office, the average peripheral blood pressure was reduced from 109.9 (± 20.4) mm Hg to 97.3 (± 18.5) mm Hg (P < 0.01). Central aortic systolic blood pressure was reduced from 147.2 (± 27.8) mm Hg to 130.2 (± 25.2) mm Hg (P < 0.01).

• The Barostim neo Pivotal trial, a multi-centre, randomized controlled trial, has been undertaken to demonstrate the safety and efficacy of the Barostim neo system in resistant hypertension treatment. It will include approximately 310 patients in the US. The primary efficacy end point is an office-based systolic blood pressure reduction of 12.5 mm Hg, with a superiority margin of 5 mm Hg for the Barostim neo treatment group (BAT plus optimal medical management) compared with patients in the control group (optimal medical management only). The trial is expected to be completed in July 2015.

Whether the Barostim neo treatment will reduce morbidity or mortality has not yet been demonstrated.
Adverse Effects

In the earlier Rheos trials, adverse events included infection, nerve damage (e.g., tongue paresis, probably due to injury to the hypoglossal nerve during the procedure), surgical complications, respiratory complications, pain in the glossopharyngeal nerve area, and shifting of the implanted generator that required further surgery.22,43 One patient in the Rheos DEBuT-HT trial died from angioneurotic edema six days post-implantation, likely due to a drug reaction.18,43 Another patient in this trial had a serious infection that required surgical removal of the device.18

Five of the 265 patients in the Rheos Pivotal trial had their devices removed. Although no patient deaths during the trial and follow-up were attributed to the device or the procedure, the trial did not meet its pre-specified short-term safety end point of 82% adverse–event-free procedures.12 Most adverse events (n = 68; 25.5%) reported in the Pivotal trial were procedure-related events: surgical complications (n = 13; 4.8%), permanent nerve injury (n = 13; 4.8%), temporary nerve injury (n = 12; 4.4%), and respiratory and wound complications (n = 7; 2.6% for each). A few patients in both groups experienced BAT-related hypertensive crises, and six patients (2.3%) had hypertension-related strokes.12

In the Barostim neo trial of 30 patients, three adverse events were reported within 30 days of implantation, all of which were resolved: bruising around the generator implant, a complication from a self-inflicted wound, and intermittent pain near the implant site.39 One patient reported discomfort around the site of the implant beyond 30 days. Patients may experience some sensation of tingling in the neck, which is reportedly tolerable and lessens over time.44 In an Italian study of Barostim neo in 11 patients with heart failure, one patient required a blood transfusion due to anemia at the time of implantation.45

The impact of long-term BAT on kidney function was examined in an analysis of data from the Rheos Pivotal Trial.21 Kidney function at one year post-BAT showed a slight increase in serum creatinine and a slight decrease in estimated glomerular filtration rate — believed to be due to the decrease in blood pressure — indicating the procedure does not appear to adversely affect kidney function.21

Administration and Costs

The implantation procedure requires surgical skill, and correct placement of the electrode is important.46 The surgical procedure is more complicated than cardiac pacemaker implantation and has been compared with carotid endarterectomy.6,12

During the surgical implantation procedure, the administration of anesthetic agents that affect the baroreflex should be avoided.37

In the Barostim neo trial, the implantation procedure took an average of 107 minutes (± 28 minutes), of which approximately 44 minutes (± 28 minutes) were needed to map the target stimulation.39 When the first two procedures at each centre were not included (considered part of the learning curve), the average procedure time was 97 minutes (± 29 minutes).39

A German cost-effectiveness model of BAT, funded by CVRx and based on data from both the Rheos and Barostim neo trials, estimated a two-day hospital stay for the implant procedure.48

The procedure is performed in specialist centres by vascular surgeons, cardiothoracic surgeons, or neurosurgeons.12,49 Continued patient follow-up will be needed to monitor the device settings and manage antihypertensive drug therapies.49

The Barostim neo is not currently commercially available in Canada or the US, and the cost in these countries has not been determined. The German study estimated the cost of the Barostim neo system at €21,000 and the replacement battery cost at €15,000.48 Because of the lifespan of the battery at optimal therapy settings, the implanted generator will require surgical replacement every three years.39 Patients will still need antihypertensive drug therapies. Consequently, BAT will be an added cost for the treatment of resistant hypertension.13 However, if it can prevent serious complications due to hypertension, such as stroke or chronic kidney disease, it may it reduce overall treatment costs.22

Concurrent Developments

Newer antihypertensive drugs that affect different physiological processes, such as arterial stiffness, are currently under investigation. Some of these may become options for some patients with resistant hypertension.4
Renal denervation is another device-based treatment for resistant hypertension. This involves catheter-based ablation of both afferent nerves and efferent nerves (those that transmit signals away from the central nervous system to parts of the body) in the renal arteries. The treatment initially looked promising, but in 2014, when one of the major randomized controlled trials of renal denervation failed to meet its primary end points, several manufacturers halted development of their devices.\textsuperscript{22,27} Subsequent analysis of patient registry data for approximately 1,000 patients suggests that those with more severe hypertension may benefit most from renal denervation.\textsuperscript{50} Recent news reports indicate that at least two manufacturers of renal denervation systems (Medtronic and Boston Scientific) are planning to start new trials using modified renal denervation catheters in 2015.\textsuperscript{51}

The ROX Coupler (ROX Medical, San Clemente, California) is another new device-based intervention for resistant hypertension. The Coupler is surgically implanted between a vein and artery in the upper thigh, in a procedure called arteriovenous anastomosis (surgically connecting the blood vessels). As with renal denervation, the Coupler device acts on a different biological process (“arterial compliance and vascular resistance”) to reduce blood pressure.\textsuperscript{52}

Baroreflex activation therapy is also being investigated as a treatment for heart failure.\textsuperscript{44,45,53} A conference report on preliminary results from a randomized trial of the Barostim neo device in patients with heart failure (n = 146) found that it improved the ejection fraction, patient quality of life, exercise capability and NYHA functional classification; moreover, it did not interfere with other implanted devices, such as cardiac pacemakers or implantable cardioverter-defibrillators.\textsuperscript{44} Larger trials of BAT in heart failure are under way.\textsuperscript{44}

In some countries, renal denervation diffused rapidly — before good-quality evidence of its effectiveness was available.\textsuperscript{5} If the Barostim neo receives regulatory approval for heart failure treatment, as anticipated, the potential patient group will expand and the costs associated with this technology will increase.

**Implementation Issues**

Collaboration between clinical specialties (i.e., vascular surgeons and hypertension specialists) will be needed to appropriately identify patients who may benefit from this procedure and to ensure they are monitored post-implantation.\textsuperscript{49}

Based on early evidence from the Barostim neo trials and older evidence from the Rheos device trials, not all individuals with resistant hypertension will reach their target blood pressure reduction with BAT. Further evidence is needed on how best to identify individuals who will benefit from this procedure.

Patients still require antihypertensive drug therapies, and no noteworthy reduction in antihypertensive drug use was reported in the trials to date.

**References**


**Rate of Technology Diffusion**

CVRx anticipates receiving Health Canada licensing of the Barostim neo in 2015 for the treatment of heart failure, after which the company will consider submitting it for regulatory approval for resistant hypertension (Dean Bruhn-Ding, CVRx, Inc., Minneapolis, Minnesota: personal communication, 16 Mar 2015).

According to the ECRI Institute, once the results of the phase 3 trials of the Barostim neo are available, US FDA approval of the Barostim neo device may take another year or more.\textsuperscript{22}


