REVIEW

Baroreceptor stimulation for resistant hypertension: First implantation in France and literature review

Stimulation des barorécepteurs carotidiens comme traitement de l’hypertension artérielle : premier cas en France et revue de la littérature

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Summary Despite a wide choice of effective antihypertensive treatments, blood pressure (BP) in roughly half of hypertensive subjects is not controlled. Resistant hypertension is defined as an uncontrolled BP despite optimal doses of three antihypertensive treatments, including a diuretic. After confirmation of resistant BP using home BP measurement or 24-hour ambulatory BP monitoring (ABPM), patients usually go through a work-up to rule out secondary hypertension. If secondary hypertension is ruled out, the recent European guidelines on hypertension consider baroreceptor stimulation or renal denervation to be possible options. The prevalence of resistant primary hypertension may reach up to 10% in specialized centres. The two proposed non-pharmacological therapeutic strategies have been developed recently to inhibit

\textit{Abbreviations}: ABPM, ambulatory blood pressure monitoring; BAT, baroreceptor activation therapy; BP, blood pressure; CT, computed tomography; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

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sympathetic overactivity in resistant hypertension. Among them, baroreceptor activation therapy (BAT) is an innovative approach that interferes with baroreflex function. The first-generation BAT device (Rheos®; CVRx, Inc., Minneapolis, MN, USA) demonstrated good efficacy in lowering office BP and ABPM, but had an insufficient safety profile due to complex surgery. The second-generation BAT device (Barostim neo® system; CVRx, Inc.) seems to share the same BP-lowering efficacy but has a better safety profile. We report the first French case of baroreceptor stimulation for hypertension using the Barostim neo® system. We also discuss the pathophysiological features of and current levels of evidence for this technique.

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### Background

Despite a wide number of antihypertensive treatments, roughly half of hypertensive subjects are not controlled [1]. The therapeutic strategy for managing resistant hypertension has been simplified recently in the latest French guidelines [2]. Resistant hypertension is defined as an uncontrolled blood pressure (BP) despite optimal doses of three antihypertensive treatments, including a diuretic. Resistant office BP must be confirmed using home BP measurement or 24-hour ambulatory BP monitoring (ABPM). When resistant hypertension is confirmed, patients undergo a work-up to rule out secondary hypertension. This may leave up to 10% of true resistant primary hypertension in dedicated centers accustomed to the management of hypertension in France [3–5]. These patients may be considered for a non-pharmacological approach (i.e. renal denervation). While this technique appeared very promising after the SYMPLICITY HTN-1 and HTN-2 trials, the publication of the SYMPLICITY HTN-3 trial has cast some doubt on its real efficacy [6–8]. In addition, there are some limitations related to renal function (estimated glomerular filtration rate < 45 mL/min) and renal artery anatomy (length and diameter before bifurcation, accessary renal arteries) that preclude its use in every resistant patient. Thus, there is still room for other approaches in this currently unsettled field.

One alternative (or additional) approach could be baroreceptor stimulation—a novel technique targeting the baroreflex via stimulation of the carotid sinus wall [9]. The recent European guidelines on hypertension made the following recommendations: to consider baroreceptor stimulation or renal denervation in case of ineffectiveness of drug treatment in patients with resistant hypertension (class IIb, level C) and, until more evidence is available on the long-term efficacy and safety of renal denervation and baroreceptor stimulation, to restrict these procedures to hypertension centers (class I, level C) [10].

We report here on the first French implantation of a baroreceptor stimulator for hypertension, and we discuss the pathophysiological features of and current levels of evidence for this technique.

### Case report

A 74-year-old man was referred to our department for an arterial hypertension work-up. His medical history included
peripheral artery disease (bypass graft and angioplasty), single-vessel coronary artery disease treated with a bare-metal stent on the left anterior descending artery, with a left ventricular ejection fraction (LVEF) of 55% and obstructive sleep apnea syndrome treated with continuous positive airways pressure. After withdrawal of antihypertensive treatment interfering with hormonal status, we ruled out secondary endocrine forms of hypertension (mainly primary aldosteronism, Cushing’s syndrome and pheochromocytoma). Duplex ultrasound did not demonstrate any significant renal artery stenosis. Target organ damage was observed at the level of the heart (left ventricular mass index 155 g/m²), vessels (pulse wave velocity 16 m/s) and kidney (estimated glomerular filtration rate 49 mL/min and microalbuminuria 280 mg/24 hours). Antihypertensive treatment was gradually optimized and a low dose of spironolactone was not tolerated because of hyperkalemia. Finally, the patient received daily: indapamide 1.5 mg, amlodipine 10 mg, valsartan 160 mg, nebivolol 5 mg, rilmenidine 1 mg and prazosin 5 mg. ABPM was uncontrolled on supervised intake of drugs: 172/75 mmHg, 24 hours; 172/76 mmHg, daytime; and 172/72 mmHg, nighttime (non-dipper status). Long-term non-compliance with antihypertensive treatment was unlikely using questionnaires and home BP measurement. The patient was first screened for renal denervation. A computed tomography scan demonstrated mild atherosclerotic stenosis of around 40% on both renal arteries and a right inferior accessory renal artery. Moreover, we observed an occlusion of the superficial right femoral artery and an occlusion of the left bypass. Renal denervation was not possible because of two exclusion criteria: renal artery atheroma and severe peripheral artery disease.

Carotid ultrasonography ruled out significant atherosclerosis (> 50% reduction in diameter). Baroreceptor stimulator implantation was indicated. Twenty-four hours before surgery, antihypertensive treatments that interfere with the sympathetic nervous system were withdrawn (angiotensin receptor blocker, diuretics and beta-blockers) and replaced with a continuous intravenous infusion of nicardipine. The level of the right carotid bifurcation was marked using ultrasound guidance. General analgesia was performed with specific drugs (etomidate, midazolam, fentanyl and rocuronium) known for their limited interaction with the sympathetic nervous system. A catheter was placed in the left radial artery for continuous BP monitoring. The implantation procedure consisted of a right carotid sinus exposure via a 4 cm incision (Fig. 1A). The electrode was positioned around the bifurcation in the area of the carotid sinus (Fig. 1B). The electrode and lead were connected to the battery impulse generator and briefly activated with impulses of 3 V, 100 Hz and a pulse width of 480 micros, once blood pressure and heart rhythm were stable. The hemodynamic response was tested and the electrode was repositioned in different locations to identify the site of optimal response. A marked acute reduction in BP was observed from 171/64 to 119/45 mmHg (Fig. 1C). Once the optimal location was confirmed, the electrode was sutured in place; then, a subcutaneous pocket was made inferior to the right clavicle for the battery impulse generator (Barostim neo™ system; CVRx, Inc.). The lead was advanced under the skin and connected to the battery (Fig. 2). The battery impulse generator was sutured in place with a permanent suture, and the two incisions were closed in layers with absorbable sutures. All antihypertensive treatments were started 24 hours after surgery, and the patient was discharged from hospital on the third day after device implantation.

Baroreflex activation therapy (BAT) was initiated only 2 weeks after implantation. Programmed variables (pulse amplitude, pulse width and frequency) were titrated for optimal response over the first few months. Trained CVRx field staff performed device programming under the
direction of the clinician. Prazosin was withdrawn after initiation of the therapy because of orthostatic hypotension. BAT was well tolerated, with only a transient episode of cough and hoarseness when a high intensity of stimulation was used. After 9 months of follow-up, we observed a reduction of 15 mmHg in SBP and a reduction of 8 mmHg in DBP on 24-hour ABPM (157/67 mmHg, 24 hours; 158/67 mmHg, daytime; and 155/66 mmHg, night-time), with five antihypertensive drugs: indapamide 1.5 mg; amlodipine 10 mg; valsartan 160 mg; nebivolol 5 mg; and rilmenidine 1 mg.

Pathophysiological effects of sympathetic activity in hypertension

Different mechanisms are involved in the pathogenesis of hypertension and particularly in resistant hypertension: the renin-angiotensin-aldosterone system, the kidneys, and the sympathetic nervous system. Sympathetic overactivity has been associated with increased BP and also with a high incidence of target organ damage: left ventricular hypertrophy, renal failure, and hypertensive retinopathy [11,12]. Pharmacological agents (beta-blockers, alpha-blockers, centrally acting drugs) and, more recently, non-pharmacological therapeutics (renal denervation, baroreceptor stimulation) have been developed to inhibit sympathetic overactivity in hypertension (Fig. 3). Baroreflex regulation originates from baroreceptors located in the aortic arch and carotid sinuses. Baroreceptors are mechanoreceptors that are activated by pressure-induced stretch on the vessel wall. Baroreceptor afferents from the carotid sinus travel in the carotid sinus nerve before joining the glossopharyngeal nerve (IX), while those from the aortic arch travel in the vagus nerve (X). All baroreceptor afferents terminate in the nucleus of the tractus solitarius in the medulla of the brain. Efferents of the central nervous system are represented by sympathetic fibres for the heart and vessels, but also by parasympathetic fibres only for the heart. The sympathetic and parasympathetic tones allow tight control of BP in the short-term (Fig. 4).

Alteration of the baroreflex is a common phenomenon in chronic hypertension. Indeed, a sustained BP elevation implies a diminished baroreflex response; this is known as baroreflex resetting and corresponds to a new threshold of baroreceptor activation [13]. Baroreceptor stimulation seems to be an innovative approach to restore this pathophysiological feature in hypertensive subjects.

Current level of evidence for baroreceptor stimulation

Resistant hypertension

The original implantable active medical BAT device (Rheos®; CVRx, Inc., Minneapolis, MN, USA) activates the carotid baroreflex through electrical stimulation of the walls of both carotid sinuses (Fig. 5). Both electrodes implanted on the exterior surface of the carotid sinus wall are connected to a battery-powered impulse generator. This concept was initially validated in animal studies. In conscious dogs, 7 days of baroreflex activation demonstrated a sustained reduction in heart rate, mean arterial BP and norepinephrine concentration [14]. In the same animal model, a high continuous infusion of angiotensin II was associated with a lower effect of baroreflex activation on BP [15]. In a dog model of obesity-induced hypertension with a fatty diet, the same team observed that baroreflex activation chronically suppressed the sympathoexcitatory associated with obesity and abolished the attendant hypertension [16].

The first-in-man feasibility of BAT was described in 2007 in 17 patients with drug-resistant hypertension (5.2 ± 1.8 antihypertensive drugs) enrolled in a European multicentre study [9]. These preliminary data suggested that the procedure had an acceptable safety level, with a low rate of adverse events: one hypoglossal nerve injury (symptoms of hoarseness and eating disturbances), which improved during follow-up, and one infection requiring complete removal of the device. Overall, office blood BP fell by 28/16 mmHg. Three years later, Device Based Therapy in Hypertension Trial (DEBuT-HT) – a multicentre prospective non-randomized feasibility study to assess the safety and efficacy of the Rheos® system over 3 months – was published [17]. Forty-five patients with systolic BP (SBP) ≥ 160 mmHg or diastolic BP (DBP) ≥ 90 mmHg despite at least three antihypertensive drugs were enrolled, and were followed up for as long as 2 years. After 3 months of BAT, the mean office BP was reduced by 21/12 mmHg (P < 0.001) and ABPM was reduced by 6/4 mmHg (P = 0.102). After 1 and 2 years of follow-up, the office BP fell by 30/20 mmHg and 33/22 mmHg respectively (P < 0.002 for both). The same trend was observed with ABPM, which decreased by 13/8 mmHg at 1 year and 24/13 mmHg at 2 years (P < 0.05 for all). Some serious adverse events were reported: three infections requiring the device to be explanted; one perioperative stroke, probably due to intraoperative injury to the hypoglossal nerve (tongue paresis without abnormalities on
Figure 3. Therapeutic targets of the sympathetic nervous system in hypertension.

brain magnetic resonance imaging); and one movement of the implantable pulse generator, resulting in the need for further surgery to reposition the implantable pulse generator.

In 2012, a double-blind randomized trial of 265 subjects with resistant hypertension was performed [18]. All patients were implanted and subsequently randomized (2:1) either to group A with BAT for the first 6 months or to group B with delayed BAT initiation following the 6-month visit. The trial showed significant benefits for three of the five co-primary endpoints: sustained efficacy (reduction in SBP of at least 10 mmHg at 12 months, 88% responders), BAT safety (40% rate of reduction in hypertensive events in Group A), and device safety (2.3% hypertension-related stroke). The two other co-primary endpoints did not show significant benefit: acute SBP responders at 6 months (achievement of 10 mmHg fall in SBP compared with month 0, Group A 54%, Group B 46%; P = 0.97); and procedure safety (4.4% transient nerve injury, 4.8% permanent nerve injury, 4.8% general surgical complications and 2.8% respiratory complaint). The authors concluded that significant and sustained reductions in SBP were observed, but that new technology for delivering BAT, which involves a less invasive implantation procedure, was needed. Long-term follow-up of 22–53 months confirmed the maintenance of the BP reduction [13].

A second-generation system for delivering BAT (Barostim neo™ system; CVRx, Inc., Minneapolis, MN, USA) [Fig. 5], with a simpler device and implantation procedure, has been evaluated in a single-arm open-label study [19]. The electrode portion of the lead consists of a single platinum-iridium disc coated with iridium oxide and attached concentrically to a circular insulative backer that is directly sutured to the carotid sinus. The miniaturized electrode and unilateral system design facilitate a minimally invasive implantation procedure. Thirty patients with resistant hypertension were enrolled. With stable antihypertensive treatment, office BP fell by 26/12 mmHg at 6 months and the safety profile was similar to that for a pacemaker. During the perioperative period of 30 days after surgery, three complications occurred: a self-inflicted wound complication; a pulse generator pocket hematoma; and discomfort in the pulse generator pocket, requiring device repositioning. A major limitation of this study was the absence of ABPM.

Thus, in resistant hypertension, BAT seems an option, although the only randomized study did not reach its efficacy endpoint; no comparable study with the second-generation device is currently available. Many more data with this technology are thus required to validate its use. In addition, some physiological features are far from being understood, including the fact that the BP response can be sustained while the baroreflex is mainly involved in short-term BP regulation. Another feature relates to the apparent lack of baroreceptor downregulation—a common phenomenon observed in case of chronic stimulation [20]. This new technique opens the way for future research. Concerning clinical aspects, a multicentre French randomized trial is about to start; it will
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Figure 4. Regulation of blood pressure via the baroreflex.

Figure 5. First-generation and second-generation baroreceptor stimulators.

evaluate the Barostim neo™ system compared with medical treatment alone, with special attention paid to safety, benefit on ABPM and cost-effectiveness.

Perspectives

Baroreceptor stimulation and renal denervation are new ways of treating hypertension. While these techniques are extremely appealing, one has to recognize that their real effects on BP—and, even more, on adverse cardiovascular events—are unknown. Sticking to the BP effect, the results of SYMPLECTIC HTN-3 trial on renal denervation have been rather disappointing compared with previous SYMPLECTIC trials [6–8,21]. The major information from this trial is the placebo effect of this therapy, which was neglected in early trials; this has to be taken into account in the same way as for any medical treatment. Extensive use of ABPM, which is less affected by the placebo effect than conventional BP measurement, is highly desirable to assess the real effect of these techniques. Another limitation is adherence to treatment; an advantage of the French DENER HTN study is that it monitored this factor precisely. Obviously, when designing future trials on the Barostim neo™ system, these two factors should be carefully considered.

Other potential cardiovascular applications

Heart failure could be another application for BAT. Chronic BAT has demonstrated enhancement of survival in dogs with rapid pacing-induced heart failure [22]. In dogs with coronary microembolization-induced heart failure, BAT demonstrated an increase in LVEF and a partial reversal of LV remodeling compared with a control group [23]. A randomized heart failure study involving 140 subjects is currently underway. Patients were included with an LVEF < 35% and a New York Heart Association Class III under optimal stable heart failure therapy for at least 4 weeks, including cardiac resynchronization therapy if indicated.
The effect of BAT on arrhythmias can be speculated upon, given the major effect of beta-blockers. Further application needs to be tested in this setting, such as severe ventricular arrhythmia despite optimal treatment.

**Conclusion**

BAT is an innovative approach for treating resistant hypertension via modulation of the baroreflex. The first-generation BAT device (Rheos®) showed some effect on BP in resistant hypertension, but its safety profile was not satisfactory due to the complexity of the surgery. The second-generation BAT device (Barostim neo® system), although it only applies stimulation to one carotid, has similar efficacy in terms of BP-lowering, with a good safety profile, offering interesting perspectives. Further study is needed to evaluate this latest device, and a French randomized trial will soon be launched.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

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