Resistant hypertension: baroreflex stimulation as a new tool

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Abstract

Uncontrolled hypertension remains a significant public health challenge. In recent years, a new baroreflex stimulator has been used to treat these patients. Initial observations suggest that the electrical field stimulation of carotid baroreceptors acutely attenuates sympathetic activation of the vasculature, heart and kidney while augmenting cardiac vagal regulation. During the long-term treatment an average blood pressure (BP) drop of 30–40/15–25 mmHg was observed with a responder rate (>10 mmHg reduction in BP) of up to 80% after 1 year of treatment. Some of this effect can be explained by a ‘placebo’ effect as suggested by the double-blind Pivotal Trial. The complication rate with the first generation device was 20–30%. With a second generation device, these problems have been reduced to <10%. Even though additional data from controlled clinical trials will be required before more widespread use can be recommended, this treatment option is now approved in Europe for the treatment of severe resistant hypertension and is performed in selected centres with experienced vascular surgeons and hypertension specialists.

Keywords: resistant hypertension; autonomic nerve system; baroreflex activation; therapy; renal denervation

Hypertension affects 20–30% of the adult population in the Western civilization. Beside recommendations to change lifestyle, different antihypertensive drug classes are the main tools to treat this condition. Unfortunately, 10–30% of hypertensive patients—depending on the population analysed—have resistant hypertension [1]. Treatment resistant arterial hypertension is defined as blood pressure (BP) that remains above target in spite of the concurrent use of three antihypertensive agents of...
different classes and after exclusion or elimination of all treatable secondary forms of arterial hypertension. One of the three agents should be a diuretic and all agents should be prescribed at an appropriate dose. Treatment resistant arterial hypertension is associated with excessive target organ damage including left ventricular (LV) hypertrophy, increased carotid intima media thickness, retinopathy and nephropathy among others [2]. The mechanisms driving treatment resistant arterial hypertension and mediating cardiovascular and renal organ damage are not completely understood. Excessive sympathetic activity is one of the underlying pathophysiological mechanisms.

**Sympathetic activity**

Sympathetic activation is a significant predictor of a poor prognosis in various conditions including heart failure, myocardial infarction and chronic kidney failure. In patients with different levels of kidney disease severity, the level of sympathetic activation parallels the degree of renal dysfunction [3]. Moreover, patients with severe arterial hypertension show the highest sympathetic activity [4]. Finally, patients with arterial hypertension show a greater increase in the muscle sympathetic nerve activity after myocardial infarction compared with normotensive patients [5]. Sympathetic activation appears to be more than a prognostic ‘biomarker’ in cardiovascular and renal disease.

**Baroreflex in the control of sympathetic activity**

The baroreflex is a well-known regulatory reflex. The reflex is present in mammals and throughout vertebrate animals. Early civilizations became aware of the baroreflex through the practice of carotid massage which, when vigorously applied, was observed to induce drowsiness. In the 19th century, it was documented that baroreflex activation by carotid massage produced acute reductions in the heart rate and BP. Research in previous decades has elucidated the pathways involved (Figure 1). Briefly, stretch-sensitive baroreceptors exist in the area of the carotid sinus. The distention of the sinus by the arterial pulse—as higher the BP as stronger is the distension of the carotis sinus—leads to depolarization of the associated neurons, generating an afferent message. This message is relayed to the nucleus of the solitary tract (NTS) in the medulla via the carotid sinus and glossopharyngeal nerves. From this nucleus, a host of efferent pathways are modulated, the most prominent of which involve an autonomic regulation of the heart, vasculature and kidneys via parasympathetic efferent nerve fibres and sympathetic nerve fibres. Thus, an increase in the systemic BP leads to counter regulatory adjustments in peripheral vascular resistance and modulation of renin release [6].

The importance of baroreflex mechanisms in short-term BP control was always undisputed. The idea that baroreflex mechanisms are also involved in long-term control of sympathetic activity and BP was more controversial until recently [7, 8].

**Electrical carotid baroreceptor stimulation**

Electrical stimulation of baroreflex afferent nerves could simulate a BP increase to the brain, which will be counteracted by a reduction in the sympathetic activity, thus, lowering BP [9]. Electrical stimulators directly activating afferent baroreflex nerves were developed as early as in the 1950s. Initially, electrical stimulation was used as a tool in physiology and basic science experiments. By the 1960s, interest had turned to using carotid sinus nerve stimulation (CSNS) as a treatment for angina pectoris and later on for arterial hypertension but failed for technical reasons [9]. Recently, a novel implantable device (Rheos System; CVRx Inc.) was developed that may overcome some of these problems (Figure 2) [10]. The device produces an electrical field stimulation of the carotid sinus wall. In dogs, the electrical carotid baroreflex stimulation with the device elicited sustained reductions in sympathetic nervous system activity and BP [11]. Moreover, in normotensive patients undergoing elective carotid surgery, short-term electrical carotid baroreceptor stimulation lowered BP.

Heusser et al. [12] applied microneurography to monitor acute changes in centrally generated sympathetic activity with electrical carotid sinus stimulation in patients with treatment resistant arterial hypertension. The method determines motor sympathetic nerve activity (MSNA) in human subjects. Electrical baroreflex stimulation rapidly decreased MSNA and BP. The stimulation resulted in concomitant reductions in sympathetic nerve activity and BP strongly suggesting a centrally mediated response (Figure 3).

The hypothesis that BP reduction is mediated through the central nervous system is further supported by the
Figure 2. X-ray of patients with the first generation (Rheos System, CVRx) and second generation device (neo™ System, CVRx).

Figure 3. (A) Original recordings showing the electrocardiogram tracing, arterial BP and motor sympathetic nerve activity (MSNA) recordings. When the stimulator was switched on (upper panel) the heart rate, BP and MSNA acutely decreased and returned to the baseline level when the stimulator was switched off (lower panel). (B) The result in a different patient with the device turned on and off for 9-min intervals. A strong sustained decline in the heart rate, BP and MSNA can be observed during stimulation phases (modified from ref. [12]).
time course of the response (Figure 3). Normally, BP reduction elicits baroreflex-mediated tachycardia and renin–angiotensin system activation. The latter response is mediated mainly through renal sympathetic activation. Instead, Heusser et al. [12] observed reductions in the heart rate and the suppression of renin release with electrical carotid baroreflex stimulation. Others observed chronic reductions in BP and favourable effects on heart rate variability (HRV) with electrical carotid sinus stimulation.

Wustmann et al. [13] reported on chronic changes in the HRV in 21 patients treated with the Rheos system. Twenty-four hour ambulatory electrocardiogram recordings were conducted the day prior to device activation and after 3 months of treatment. Measurements were made of power in the low-frequency (LF) band (variation due to both sympathetic and parasympathetic activity), power in the high-frequency (HF) band (variation due to parasympathetic activity) and the ratio of LF power to HF power. Baroreflex activation therapy significantly decreased the median LF power (150–117 ms²), increased the median HF power (42–67 ms²) and decreased the median LF/HF ratio (2.78–2.24), all P < 0.001. Time-domain measures of HRV changed in a parallel fashion. These changes in HRV are consistent with chronic changes in autonomic heart rate regulation. The change in the LF/HF ratio was also found to correlate (r = 0.47, P = 0.006) with the change in the systolic BP (SBP), consistent with baroreflex activation therapy as a common causal mechanism [13].

Together, these observations suggest that the electrical field stimulation of carotid baroreceptors acutely attenuates sympathetic activation of the vasculature, heart and kidney while augmenting cardiac vagal regulation.

Clinical efficacy–first generation system

To date, around 400 patients have received baroreflex activation therapy with the Rheos System (CVRx Inc, Minnesota, USA) worldwide. Longitudinal data with up to 5 years of follow-up on effects of baroreflex activation therapy are currently available from feasibility studies conducted in the European Union and USA. The DEBuT-HT/HET (European) and US Feasibility trials were single-arm, open-label designs [14]. A total of 61 patients were enrolled in the studies (45 EU, 16 US). In each study, the device was activated 1 month after implantation. The inclusion criteria required that study participants have drug-resistant hypertension, defined as systolic BP >160 mmHg and/or diastolic BP (DBP) >90 mmHg despite intensive and stable treatment with three or more antihypertensive medications including a diuretic in an adequate dose. Patients were excluded if their hypertension was secondary to a treatable cause, were experiencing bradyarrhythmias/atrial fibrillation or if the carotid sinus region was unsuitable for implant (>50% stenosis or ‘instable’ atherosclerotic plaques).

In the European cohort 58% were male, 100% Caucasian, with a mean age of 54 ± 9 years, a body mass index (BMI) of 32 ± 6 kg/m² [14]. The baseline heart rate was 80 ± 13 b.p.m. The average baseline pressure was high (179 ± 29/105 ± 22 mmHg) despite intensive antihypertensive medical therapy. The median number of drugs was 5 (range 3–9). Both first-line (100% diuretic, 91% angiotensin converting enzyme inhibitor/angiotensin receptor blocker, 76% calcium-channel blocker and 82% beta blocker) and second-line (47% α-blocker, 38% sympathetic, 11% direct vasodilator) medications were used. Patients had a significant percentage of comorbidities, including diabetes (31%) and cardiovascular disease (76%).

Two-year follow-up data were published by Scheffers et al. [14]. The main results are shown in Figure 4. Electrical stimulation led to sustained reduction in SBP and DBP by >30 and 15 mmHg below the baseline measurement, respectively. Eighteen European patients with a follow-up of 4 years of therapy have been presented at an EDH meeting, suggesting that the BP reduction is also sustained after 4 years. Importantly, these BP reductions
were achieved even though the average number of antihypertensive drugs were reduced by 0.5–1 drug. Twenty-four-hour BP readings showed a moderate improvement after 3 months (−6/−4 mmHg) and a significant improvement after 1 (−13/−8 mmHg) and 2 years (−24/−13 mmHg). Given the lack of a control group, the true treatment effect cannot be discerned.

The randomized, double-blind Rheos Pivotal Trial was conducted in the USA and Europe [15]. In these patients the Rheos System was implanted. The inclusion and exclusion criteria were similar to the criteria used in the DeBut-HT trial. Fifty-five patients were roll-in (training) patients in centres with no previous experience with the device in whom the device was turned on 1 month after the surgery. One hundred and eighty-one patients were randomized to start treatment 1 month after the surgery (Month 0) and 84 patients were randomized to start treatment at Month 6 (7 months after the surgery). The patients and treating physicians were blinded to treatment. The baseline characteristics were similar to the feasibility studies with the exception that 18% were black [15]. The baseline BP pre-implantation was nearly 180 mmHg, but pre-activation (month 0) the average BP had dropped by nearly 10 mmHg (Figure 4). Whether this change is due to the surgery, better patient supervision, improved adherence to antihypertensive therapy or simply regression to the mean cannot be answered with certainty. The mean number of drugs was 5.2 ± 1.6 with 60% taking five or more antihypertensive drugs [15]. Aldosterone antagonists were used by 18% and direct vasodilators by 31%. 30–35% had diabetes and cardiovascular disease at the baseline. At Month 6 a significantly higher proportion of patients had achieved the BP target of SBP ≤140 mmHg (43 versus 24%, P = 0.005) [15]. Additionally the BP reduction was higher (26 ± 30 versus 17 ± 29 mmHg; P = 0.03) (Figure 4). However, at Month 6 the responder rate (defined as a BP drop of at least 10 mmHg) was not significantly different (54 versus 46%) between the treated and the non-treated patient group.

Clinical efficacy: second generation system

In 2011 a second generation device (neo™ System; CVRx) was introduced. This device has several important improvements. The battery is smaller, even though the battery life is longer and only one unipolar lead with a 2 mm tip is used (Figures 1 and 2). To decrease the invasiveness of the implantation procedure and to further increase battery life, unilateral stimulation was used. In fact, previous studies had suggested that unilateral stimulation—often on the right side—might be sufficient to achieve a chronic BP response. In February 2011, an open label study was started and 30 patients participated [16]. The inclusion and exclusion criteria were the same as in the previous study with the exception that patients also with a BP between 140 and 160 mmHg could participate in the study. In the cohort 53% were females, 100% Caucasian, with a mean age of 57 ± 12 years, and a BMI of 30 ± 4 kg/m². The baseline heart rate was 75 ± 12 b.p.m. The average baseline pressure was high (172 ± 20/100 ± 14 mmHg). The BP response (−26/−13 mmHg) at Months 3 and 6 is comparable to the results obtained with the Rheos system [16].

Operation time was decreased from an average of 3 h for the Rheos system to 97 ± 29 min with an average mapping time of 44 ± 28 min [16]. As the electrical field is small, mapping is crucial for the success of the procedure. Furthermore, the required neck incision was reduced to 2–3 cm.

Safety profile

In the two feasibility studies and the Pivotal Trial, no unanticipated adverse events occurred. However, 20–30% of patients had adverse events related to the surgical procedure [14, 15, 17]. The majority of these adverse effects was minor to moderate (e.g. haematoma or pain in the area of the pacemaker) and resolved completely. However, nearly 5% of patients had nerve injury with residual deficit. Additionally, in several patients the complete device had been removed due to infectious complications. In at least one of these patients a device was later successfully re-implanted. Fortunately with the second generation device, the 30-day complication rate could be reduced to <10% and all of the reported complications were only mild to moderate and recovered [16].

The technique for implanting carotid sinus leads has been refined over the past 5 years. One question when chronic studies began was whether or not such a lead would impact patency of the carotid arteries. Thus, serial duplex ultrasound images were recorded for each carotid artery at baseline and after 3 and 12 months of the therapy. Images were evaluated by an independent core laboratory, which classified the patient’s status according to the degree of carotid stenosis: 3- and 12-month images were rated as unchanged, increased or decreased compared with the baseline. After 12 months of the therapy, stenosis was rated 82.5% unchanged, 7.5% increased and 10.0% decreased in the Debut-HT study. The low level of change in the group indicates that a chronic carotid sinus lead has no appreciable deleterious effect on carotid artery stenosis. No interventions to address carotid stenosis were required.

Another focus of the safety evaluation at the inception of chronic studies was to evaluate heart rate and BP adaptations to a change in posture. No orthostatic hypotension was observed. Moreover, physiological baroreflex regulation of the heart rate and MSNA appears to be preserved with electrical carotid sinus stimulation [12].

Effect on cardiac structure and function

In the Pivotal study a sub-group of patients had echocardiographic examination at baseline and after 12 months [18]. One year of baroreflex activation therapy reduced left atrial (LA) dimension by −1.2 ± 0.3 from 20.9 ± 0.5 mm/m² (P < 0.01), LV wall thicknesses by −1 (−2 to 0) from 14 (13–15) mm (P < 0.001), LV mass index by 24.6 ± 3.9 from 138.9 ± 6.0 g/m² (P < 0.001) and LV
stroke work by $31.3 \pm 10.5$ from $199.6 \pm 8.8$ (P < 0.01). Taken together, these results indicate that in addition to reducing arterial pressure, baroreflex activation therapy may improve LA and LV structure and function. However, the lack of a control group makes it difficult to interpret these findings.

Renal denervation and baroreflex activation therapy

In the last few years promising results regarding the effectiveness of renal denervation in patients with resistant hypertension have been published and have led to a widespread implementation of the technique in European countries, particularly in Germany [19]. More recently, the European Society of Hypertension published a position paper on the potential impact of renal denervation on the treatment of patients with resistant hypertension and discussed limitations and open questions as well as eligibility criteria for renal denervation [20]. For further information on the effect of renal denervation, we recommend a recently published review by Persu et al. [21], who critically analyse the published data.

The question arises how renal denervation and baroreflex activation therapy could be integrated in the management of patients with treatment resistant arterial hypertension. Is one methodology superior in terms of efficacy or safety? Can baroreflex activation therapy still be applied when renal denervation fails? Lohmeier et al. [22] analysed the effect of baroreflex activation therapy with the Rheos system in dogs for 7 days before and after surgical renal denervation. Denervation was achieved by removal of all visible nerves along the renal artery and vein and stripping of the adventitia. Baroreflex activation therapy still reduced BP, heart rate and plasma norepinephrine following surgical renal denervation. In a subsequent study, the same group demonstrated in dog that baroreflex activation therapy and bilateral surgical renal denervation have different effects on sympathetically mediated, obesity-induced hypertension [23]. Both treatments decreased BP and suppressed renin release to a similar degree. However, elevated plasma norepinephrine levels were normalized by baroreflex activation therapy but not affected by renal denervation, even though norepinephrine levels within the renal cortex were markedly reduced by renal denervation. Consistent with these changes might be the fact that tachycardia was only reduced during electrical stimulation. Additionally, the obesity-induced hyperfiltration was reduced and fractional sodium excretion increased. In contrast, renal denervation did lead to a further increase in the hyperfiltration. Consistent with the finding that renal denervation has only a limited effect on sympathetic activity are new data from our Centre. We studied muscle sympathetic nerve activity, HRV and BP variability in 12 patients with resistant hypertension before and 3–6 months after renal denervation [24]. Contrary to a previously published case report [25], we found no change in the three parameters indicating that renal denervation has no significant effect on central sympathetic activity.

Overall, both, catheter-based renal nerve ablation and baroreflex activation therapy are promising. Yet, both treatments have not been sufficiently tested in randomized and controlled clinical studies. Differences between the techniques are depicted in Table 1.

Interestingly, six patients enrolled in the study with the second generation device had prior renal denervation [16]. In these patients, BP decreased 22/11 mmHg below the baseline measurement at Month 6 suggesting that baroreflex activation therapy could be a therapeutic option in patients unresponsive to renal denervation.

To compare the efficacy of these two new nonpharmacological treatments Sleight [26] recently suggested that a study should be performed in which renal denervation, baroreflex activation therapy, both or neither should be compared. Such a study would be indeed very promising but unlikely that any device-manufacturer would fund it. Therefore, such a study needs to be funded by national institutes.

Future direction

An unresolved clinically relevant question is how baroreflex activation therapy and antihypertensive medications interact in terms of BP reduction. Baroreflex and certain

<table>
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<tr>
<th>BP reduction</th>
<th>Baroreflex activation therapy (BAT)</th>
<th>Renal denervation</th>
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<tbody>
<tr>
<td>Responder rate</td>
<td>30–40/15–25 mmHg</td>
<td>25–35/10–20 mmHg</td>
</tr>
<tr>
<td>Double-blind data</td>
<td>75–85%</td>
<td>80–90%</td>
</tr>
<tr>
<td>Renal denervation failed</td>
<td>Own experience: no benefit of renal denervation if BAT</td>
<td>No (in progress)</td>
</tr>
<tr>
<td>Complication rate</td>
<td>&lt;10% with second generation device</td>
<td>&lt;3%</td>
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Table 1. Comparison of baroreflex activation therapy with renal denervation [14, 15, 17, 19, 32, 33]
drugs could have a synergistic BP lowering effect. On the other hand, unsuitable combinations could obscure the benefit of baroreflex activation therapy. For example, baroreflex activation therapy could decrease the response to sympatholytic drugs, such as clonidine. Yet, physiological studies suggested that clonidine may sensitize the baroreflex to afferent stimulation, which could improve the response to baroreflex activation therapy. Because baroreflexes affect the renin-angiotensin aldosterone system (RAAS), baroreflex activation therapy could also interact with RAAS inhibitors. The long-term response to sympatholytic medications, such as guanethidine, is limited by sodium retention. Therefore, these medications are commonly combined with diuretics. Whether or not diuretics are required for a sustained hypotensive response to baroreflex activation therapy is unknown. Future clinical trials should address these issues.

Continuous baroreceptor stimulation throughout the cardiac cycle is unphysiologic and might desensitize baroreceptors or cardiovascular control centres in the brain. Alnima et al. [27] did not observe response adaptation or tachyphylaxis after 1 year of baroreflex activation therapy. Nevertheless, stimulation mode may have a bearing on treatment success as suggested by new data from the Pivotal trial [17]. In this trial, only continuous stimulation was allowed during the first 12 months. At the end of this period 73 patients had not fulfilled the responder criteria. By changing the stimulation parameters 49% of these patients were responders with an additional BP drop of 20±26 mmHg. In many of these patients this was achieved by using a duty-cycled mode, which is characterized by on and off phases that can be selected individually. Because the electrocardiogram is not sensed, these alternative stimulation modes are not synchronized with physiological cardiovascular control. Perhaps, the electrocardiogram or the carotid pulse contour could be sensed such that electric stimulation can be targeted to a more physiological time frame. The approach could improve the response or at least reduce the number of discharges required for a similar BP reduction. The battery life, which was far too short in the initially developed devices, could be lengthened.

Summary

Uncontrolled hypertension remains a significant public health challenge despite decades of work to improve awareness, treatment rates and efficacy of medical therapy. Chronic studies of baroreflex activation therapy in resistant hypertension suggest a sustained improvement in BP control.

Efficacy

- Improved HRV with a shift towards enhanced parasympathetic activity.
- Acute BP reduction >100 mmHg in individual patients.
- Long-term reduction of office cuff BP by 30–40/15–25 mmHg.
- 10–20/5–15 mmHg reduction with ambulatory BP monitoring.
- Patients unresponsive to renal denervation may still respond.
- Effective also in patients with renal impairment.
- LV mass is reduced.

Safety

- First generation device: 20–30% with mild-to-severe post-operative complications, <5% with residual injury.
- Second generation device: <10% with mild-to-severe post-operative complications, all recovered.
- No orthostatic hypotension, maintained baroreflex control.
- So far no evidence for induction or exacerbation of significant carotid stenosis.

The presented results from chronic studies indicate that baroreflex activation therapy could be considered as a treatment for patients at very high cardiovascular risk inadequately responsive to anti-hypertensive medications. Even though additional data from controlled clinical trials will be required before more widespread use can be recommended, this treatment option is now approved in Europe for the treatment of severe resistant hypertension. As the treatment is costly and needs experience, it should be only performed in centres in which the experienced vascular surgeons and hypertension specialists collaborate closely to select appropriate patients.

Conflict of interest statement. J.M. and H.H. have received honoraria from CVRx for presentations at scientific meetings.

References

Baroreflex activation therapy


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