Baroreflex stimulation for treating resistant hypertension: ready for the prime-time?

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The search of alternative methods for improving clinical management and outcomes of individuals affected by resistant hypertension has become a true health priority. In this review, we aimed at providing a timely overview and evidence synthesis on baroreflex activation therapy (BAT) and endovascular baroreflex amplification (EBA), two device-based therapies which rely on the principle of lowering blood pressure by stimulating the carotid baroreflex to decrease the sympathetic and enhance the parasympathetic activity. In resistant forms of arterial hypertension, accruing evidence has confirmed the capacity of these techniques to improve blood pressure control and to reduce the amount of anti-hypertensive therapy at cost of few side effects. Future results from ongoing randomized sham-controlled trials are eagerly awaited to best define the efficacy, safety and durability of effects in the long term before such an invasive approach may be considered as a suitable option in daily clinical practice.

Keywords
Resistant hypertension; baroreflex activation therapy; endovascular baroreflex amplification

1. Introduction

Hypertension remains a major public health problem worldwide. In the US, approximately one-third of adults are hypertensive with a total burden estimate of 78 million people (Go et al., 2014) and in 2007 hypertension has been responsible for 17.4% of total mortality in this country (Roger et al., 2012).

In 2000, the prevalence of this condition at the global level reached 26% and time forecasts anticipate that more than 1.5 billion individuals will be hypertensive by 2025 (Kearney et al., 2005). Mild hypertension, which fortunately represent the majority of cases, is easily manageable with available medications and targeted lifestyle approaches. Yet, the overall rate of actively treated individuals with unsatisfactory BP values is on the rise, particularly in western countries (Jones and Hall, 2004).

The American Heart Association (AHA) defines as "resistant hypertension" an office blood pressure ≥ 140/90 mmHg in individuals taking at least three different classes of antihypertensive agents (including a diuretic) at maximally tolerated doses or using ≥ 4 medications regardless of blood pressure (Calhoun et al.,

2008). Not infrequently, resistant hypertension goes along with heart failure, sleep apnea, as well as albuminuria or overt renal dysfunction (Sander and Giles, 2012). Despite individuals with resistant hypertension are usually older, diabetic, non-Hispanic black and more frequently obese or overweight (Sarafidis et al., 2013), ambulatory blood pressure monitoring (ABPM) remains the key-test for differentiating true resistant hypertension from secondary forms or other pseudo-conditions, such as white coat effect.

Targeted analyses of the National Health and Nutrition Examination Survey (NHANES) cohort indicated that resistant hypertension is not as infrequent as commonly believed, with roughly 6 million US adults (13%) receiving anti-hypertensive treatment who potentially met the AHA criteria to be diagnosed with this condition (Roberie and Elliott, 2012). Various approaches have been proposed to manage the refractory high blood pressure, spanning from dietary to sustained lifestyle modifications in addition to maximally tolerated pharmacological therapy. In the last decade, renal denervation by a minimally-invasive, catheter-based procedure has extensively been studied as a promising tool, based on the premises that sympathetic over-reactivity of the renal nervous autonomic plexus plays a key-role in the pathophysiology of arterial hypertension. Unfortunately, encouraging results from small pilot uncontrolled studies were not fully confirmed by larger randomized, sham-controlled trials, calling into question the effective usefulness and overall applicability of this technique.

The need of finding alternative methods for improving clinical management and outcomes of individuals with resistant hypertension has therefore progressively mutated into a true research priority with several (mostly) non-pharmacological approaches that are currently object of active investigation. In this review, we aimed at providing a complete and up-to-date evidence synthesis on baroreflex activation therapy (BAT) and endovascular baroreflex amplification (EBA), two device-based therapies that are currently object of intensive investigation as a new potential approach to resistant hypertension. We will start focusing on the pathophysiological basis of the baroreflex which underlies the first device concept. Clinical successes, challenges and future directions of research will be also outlined.
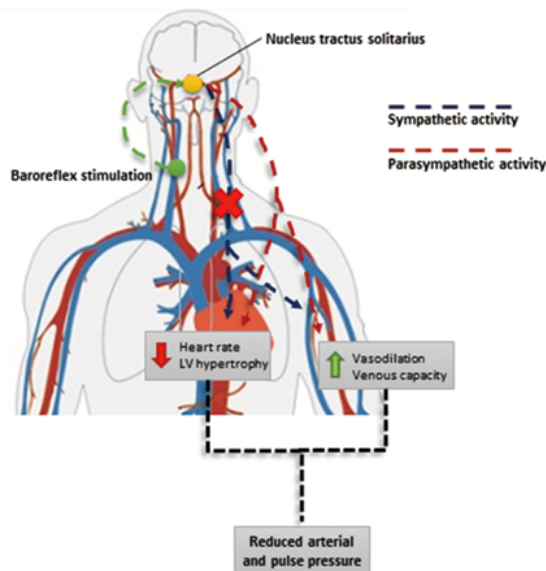
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Figure 1. Mechanisms of baroreflex stimulation to improve blood pressure control. Carotid baroreflex stimulation by BAT or EBA enhances central parasympathetic activity and inhibits sympathetic firing, thus decreasing blood pressure by directly acting on heart and vascular activity.

2. Baroreflex stimulation for resistant hypertension: from pathophysiology to clinical devices

The central involvement of the baroreflex in the physiology and pathology of blood pressure control is a well-acknowledged notion. Arterial baroreceptors are mechano-sensitive nerve fibers positioned close to the bifurcation of the carotid sinus, as well as in the aortic arch. Such fibers contain myriad ion channels that are responsive to mechanical distortion (Hajduczok et al., 1994). Increase in wall strain elicits sodium and calcium ions inflow through these channels, which generates action potentials traveling along the afferent sympathetic nerve into the nucleus tractus solitarius of the central nervous system (Chapleau et al., 2001). This negatively modulates the efferent sympathetic nervous system discharge and increases the parasympathetic outflow with a consequent reduction in heart rate, improved left ventricular geometry, vasodilatation and augmented venous capacitance. Although the rate of baroreceptors firing is influenced by the extent of vascular distortion, in hypertensive patients a compensatory mechanisms exists aiming at avoiding tachycardia and sustained vasoconstriction due to reflex saturation (Mancia and Grassi, 2014). Hence, in these individuals, carotid and aortic baroreceptors fire at higher pressures as compared to healthy individuals.

Baroreflex activation therapy (BAT) and endovascular baroreflex amplification (EBA) rely on the principle of lowering blood pressure by stimulating the baroreflex to decrease the sympathetic and enhance the parasympathetic activity. This, however, may be achieved through two main mechanisms. In fact, BAT increases the rate of firing by directly stimulating the baroreceptor nerve endings with electric pulses delivered on the outer wall of the carotid sinus. Conversely, EBA elicits mechanical changes of the geometric shape of the carotid sinus during cardiac systole that, in turn, increases pulsatile strain Fig. 1 and 2.

The Rheos Baroreflex Hypertension Therapy system (CVRx Inc., Minnesota, US) was the first implantable device tested for baroreflex activation therapy in the treatment of resistant hypertension Fig. 3a. This device consisted of a pulse generator placed inferior to the clavicle and two leads with electrical stimulators extending to the outer wall of the carotid sinus through finger-like projections. Given the big size of the generator and the need to expose bilateral carotid bulbs, correct placement of this device required a surgical procedure similar to that of a cardiac pacemaker. The substantial incidence of surgical complications and nerve injury, coupled with an evidence of better efficacy of unilateral (rather than bilateral) stimulation, prompted the stage for the development of a second-generation BAT device, the Barostim neo (CVRx Inc., Minnesota, US). This consists of a smaller pulse generator and a simplified lead/electrode apparatus which allows unilateral implantation, hence minimizing the entity of neck dissection with reduction in the rate of peri- and post-operative complications Fig. 3b.

The MobiusHD (Vascular Dynamics, California, US) is the only device available so far for endovascular baroreflex amplification. This is represented by a self-expanding nitinol implant Fig. 3c, very similar to any modern vascular stent, that increases pulsatile wall stretch of the carotid sinus by producing a geometric shape change with passive activation of the baroreceptor. The mechanism of action is rather complex and relies on a dynamic contrast between the passive outer radial forces of the nitinol structure and the carotid bulb across the range of systolic and diastolic phases of the cardiac cycle. The device is available in rest dimension sizes ranging from 5.00 to 8.00 mm and its placement is made into the internal carotid artery in a less invasive way by a dedicated catheter that is introduced via a femoral access.
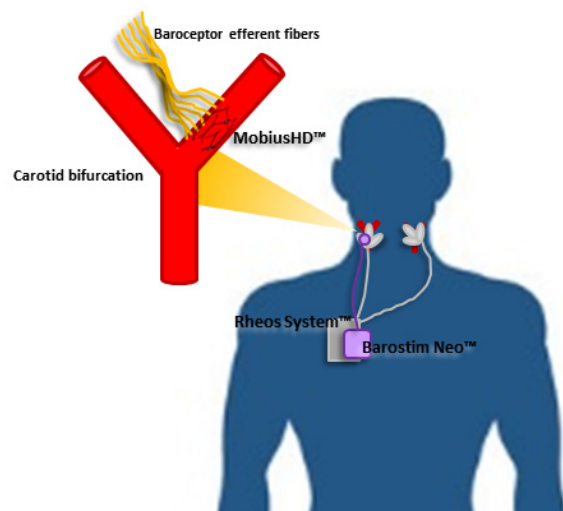

Figure 2. Baroreflex activation therapy by the Rheos system™ and the Barostim Neo™ and Endovascular baroreflex activation by the MobiusHD™ implant. See main text (Section 2) for further details.

Table 1. Main studies on BAT and EBA for treating uncontrolled hypertension.

Study Year	Design	Population characteristics	Study group(s)	Endpoints	Results
DEBuT-HT 2007	Multicenter, uncontrolled	45 patients with resistant hypertension	BAT by the Rheos system	Blood pressure change from baseline	Mean systolic/diastolic blood pressure decrease of 21/12 mmHg at 3 months and 33/22 mmHg at 2 years.
Rheos Pivotal Trial 2011	Multicenter, quadruple-blind, (2: 1 fashion) randomized, placebo-controlled	265 patients with resistant hypertension	BAT by the Rheos system with: -Early (1 month post-implantation) vs. -Delayed (6 months post-implantation) device activation	Primary efficacy end point: comparison of number of patients experiencing a ≥ 10 mmHg drop in systolic BP after 6-month follow-up between the two study arms. -Secondary endpoints: percentage of subjects in group "Early" achieving and maintaining the primary efficacy endpoint at 12 months; Serious Procedure- or System-related Adverse Event-free rate, therapy-related and hypertension-related adverse event free rate in both groups at various time-points.	-No differences between groups in the primary efficacy end point. -42% of participants in the early group vs 24% of the delayed group achieved systolic BP < 140 mmHg. -In responders, mean systolic blood pressure reduction of > 30 mm Hg and diastolic blood pressure reduction of > 16 mmHg maintained over at least 5 years of follow up. -4.4% and 4.8% of patients developed transient or permanent facial nerve injury.
Barostim neo Trial 2012	Multicenter, uncontrolled	30 patients with resistant hypertension and stable anti-hypertensive therapy for at least ≥ 4 weeks before baseline assessment	BAT by the Barostim Neo device	-Blood pressure reduction at 3 and 6 months	- Mean systolic reduction of 26.1 ± 3.3 mmHg ($P < 0.001$) achieved after 3 months and persisting until the 6-month follow-up -43% of participants reached target pressure values of < 140 at the established 6-month -Significant and stable decrease in 24-h ambulatory systolic (from 148 ± 17 to 140 ± 23 mmHg, $P < 0.01$), diastolic (from 82 ± 13 to 77 ± 15 mmHg, $P < 0.01$), day- and night-time systolic and diastolic blood pressure (all $P ≤ 0.01$), as well as reduction in the number of prescribed anti-hypertensive classes.
Barostim neo Hypertension Pivotal Trial 2018	Multicenter, randomized, open label	310 patients with resistant hypertension and stable anti-hypertensive therapy for at least ≥ 4 weeks before screening	-BAT by the Barostim Neo device plus medical therapy. -Standard medical therapy	-Primary endpoints: safety 30 days post-implant, efficacy in reducing SBP from baseline to 6 months post-activation. -Secondary endpoints: efficacy from baseline to 12 months post-activation, safety 6 months after implantation.	Ongoing (currently suspended due to financial restrictions)
CALMFIM 2017-2019 (Expected)	Multicenter, uncontrolled	30 patients with stage 2 resistant hypertension, treated with a minimum of 3 antihypertensive drugs	-EBA by the MobiusHD implant.	Primary endpoint: incidence of serious adverse events and unanticipated adverse device effects reported from implantation through 6 months of follow-up. -Secondary endpoint: Decrease in office cuff blood pressure	Results available only for the European sub-study (CALMFIM _EUR) -No occurrence of unanticipated adverse device effects. - 2 patients treated because of severe hypotension, 2 because of worsening of hypertension and 1 because of dislodgement of the femoral closure device. -Minor adverse events included dizziness, musculoskeletal pain, hypotension and groin hematoma. -Mean office blood pressure decreased by 24/11 mmHg at 3 months and 24/12 mmHg at 6 months. -Reduction in the number of antihypertensive medication by 0.5.

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Table 1. Continued

| Study Year	Design	Population characteristics	Study group(s)	Endpoints	Results
Nordic BAT Study 2020 (Expected)	Multicenter, randomized, double-blind	100 patients with resistant hypertension and stable anti-hypertensive therapy for at least ≥4 weeks before enrolment	-BAT by the Barostim Neo device (switched on). -Placebo (device switched off)	-Primary endpoint: entity of reduction in 24-h systolic ambulatory blood pressure at 8 months of follow-up. -Secondary end points: effect duration over follow-up and possible effects of BAT on baroreflex sensitivity and heart rate variability.	Ongoing
CALMDIEM 2020 (Expected)	Multicenter, uncontrolled	200 patients with primary resistant hypertension	-EBA by the MobiusHD implant	-Primary endpoint: Change in the mean 24-h systolic Ambulatory Blood Pressure Measurement (ABPM) from baseline to 90 days post treatment. -Incidence of serious adverse events and unanticipated adverse device effects reported from implantation through 3 years of follow-up.	Ongoing
CALM-2 2020 (Expected)	Multicenter, randomized, triple-blind, sham-controlled	300 patients with resistant hypertension	-EBA by the MobiusHD implant -Sham intervention	-Primary endpoint: change in mean 24-hour ambulatory systolic blood pressure from baseline to the 180-day visit. -Secondary endpoints: Composite measure of death, MI, stroke, device embolization, carotid occlusion, new ipsilateral carotid stenosis requiring surgical or percutaneous intervention and bleeding events from randomization through the 90-day visit. All other adverse events.	Ongoing
CALM-START 2021 (Expected)	Multicenter, randomized, double-blind, sham-controlled	111 patients with resistant hypertension, following at least 30 days on a stable antihypertensive medication regimen. -A mean systolic 24-hour ABPM of 135-170 mmHg after washout of all antihypertensive medications.	-EBA by the MobiusHD implant -Sham intervention	-Primary endpoint: difference in the change in mean systolic 24-hour ABP from baseline to 90 days post-randomization, between the treatment arm and the sham arm. -Secondary endpoint: difference in the number of major adverse clinical events, including death, stroke, carotid interventions, and myocardial infarction, from baseline to 30 days post-randomization, between the treatment arm and the sham arm.	Ongoing
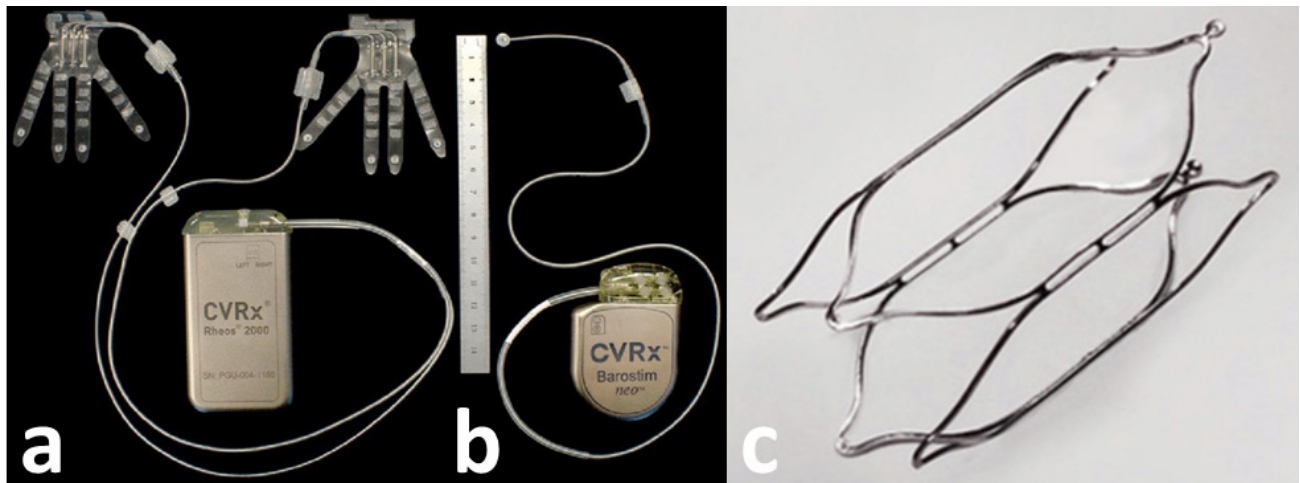
Figure 3. Illustration of the available devices for baroreflex stimulation. The Rheos system™ (a), the Barostim Neo™ (b) and the MobiusHD™ implant (c).

3. Clinical evidence of baroreflex stimulation to treat resistant hypertension

3.1 BAT system

The first permanent placement of the Rheos system in humans was performed in 2006 in the DEBuT-HT trial, a multicenter, feasibility, uncontrolled study of 45 patients with resistant hypertension (office BP ≥ 160 mmHg systolic or ≥ 90 mmHg diastolic despite treatment with at least three antihypertensive medications, including a diuretic) (Tordoir et al., 2007). Implantation of this device produced a significant decrease in mean blood pressure of 21/12 mmHg at 3 months and 33/22 mmHg at 2 years (Scheffers et al., 2010). In a similar manner, the Rheos system reduced office blood pressure by 31/14 mmHg and heart rate by 5 beats/min in another uncontrolled study of 21 patients (Wustmann et al., 2009). Based on these preliminary positive findings, in 2007 the Rheos Pivotal Trial (Bisognano et al., 2011) randomized 265 patients with resistant hypertension to early (1 month post-implantation) or delayed (6 months post-implantation) device activation. Overall, no significant difference was reported in the primary efficacy end point of ≥ 10 mmHg drop in systolic BP after 6-month follow-up but 42% of participants in the early group vs 24% of the delayed group achieved systolic BP < 140 mmHg. Importantly, 4.4% and 4.8% of patients in the two groups developed transient or permanent facial nerve injury, respectively, while another targeted subgroup analysis showed that unilateral was more effective than bilateral stimulation, particularly if right-sided (de Leeuw et al., 2015). A first follow up extension was planned in individuals who achieved stable target systolic blood pressure (≤ 140 mm Hg or ≤ 130 mm Hg in patients with renal disease or diabetes) or a sustained reduction of ≥ 20 mm Hg from baseline values after 12 months (Bakris et al., 2012). Those patients maintained the observed decrease in systolic blood pressure and were able to reduce the number of antihypertensive medications over an average follow-up of 28 months. A further 5-year study extension confirmed a mean systolic blood pressure reduction of > 30 mmHg and average diastolic blood pressure reduction of > 16 mmHg from baseline measurements (Bakris et al., 2014).

The less invasive Barostim neo system has been firstly evaluated in 2010 in the Barostim neo trial (Hoppe et al., 2012), a small uncontrolled study of 30 individuals with resistant hypertension under stable anti-hypertensive therapy. Device implantation reduced mean systolic blood pressure by 26.1 ± 3.3 mmHg after 3 months, an effect which persisted over the entire 6-month follow-up. Overall, 43% of patients reached target pressure values of < 140 at the established 6-month visit. Following analyses also demonstrated a significant and stable decrease in 24-h ambulatory-systolic (from 148 ± 17 to 140 ± 23 mmHg, $P < 0.01$) and diastolic blood pressure (from 82 ± 13 to 77 ± 15 mmHg, $P < 0.01$), as well as in the number of antihypertensive drugs employed (from 6.5 ± 1.5 to 6.0 ± 1.8 $P = 0.03$) (Wallbach et al., 2016). Of note, all these benefits resulted comparable to those obtained with first-generation devices although with considerably fewer system- or procedure-related events. A following larger proof-of-principle, multicenter trial, would have randomized 310 resistant hypertensive patients to medical therapy vs. Barostim neo implantation to test efficacy and safety of this device over a 3-year follow-up period. Unfortunately, this trial has recently been suspended due to financial restrictions in company resources.

3.2 EBA system

Clinical utility of endovascular baroreflex amplification for managing resistant hypertension was initially tested by two multicenter, parallel, open-label trials which started in 2013, the CALMFIM_US and CALMFIM_EUR (Controlling and Lowering Blood Pressure with the MobiusHD™). The incidence of serious adverse events (SAEs) and unanticipated device effects (UADEs) at 6 months represented the primary endpoint of these studies. While the CALMFIM_US is still ongoing, no occurrence of UADEs has been registered in the CALMFIM_EUR cohort, which preliminary results are already available (Spiering et al., 2017). Conversely, with respect to SAEs, one patient needed treatment due to dislodgement of the femoral closure device, two because of worsening of hypertension and two for hypotensive crises. Minor adverse events recorded included groin hematoma, dizziness, hypotension and musculoskeletal pain. With respect to ef-

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ficacy, the MobiusHD implant significantly reduced mean office blood pressure and mean 24-h ambulatory BP by 24/11 mmHg at 3 months and 24/12 mmHg at 6 months, as well as the number of antihypertensive medications which decreased by 0.5 ($P < 0.05$ for all effects).

3.3 Ongoing trials on BAT and EBA

Other relevant larger studies are on the pipeline and will presumably throw more light on the true clinical applicability of BAT and EBA for treating resistant hypertension.

The Nordic BAT Study is a multi-center, randomized, double-blind, parallel clinical trial aiming at evaluating the effect of baroreflex activation therapy by the Barostim Neo device (switched on) vs. placebo (Barostim Neo switched off) on blood pressure and arterial and cardiac function/structure. The study has planned to enroll 100 individuals with resistant hypertension, as defined by daytime systolic ambulatory blood pressure ≥ 145 mmHg and/or a daytime diastolic ambulatory blood pressure ≥ 95 mmHg after antihypertensive treatment (including at least 3 antihypertensive drugs preferably including a diuretic), with an unchanged medication schedule for at least 4 weeks prior to enrolment. The extent of reduction in 24-h systolic ambulatory blood pressure at 8 months will be the primary efficacy endpoint. Other endpoints of interest will encompass effect duration over follow-up and the possible impact of this treatment on heart rate variability and baroreflex sensitivity. Study completion is expected by 2020.

The CALMDIEM trial is an uncontrolled, prospective, multicenter study aiming at performing post-market surveillance of the MobiusHD system up to 2020 in 200 individuals with resistant hypertension who underwent placement of this device. The CALM-2, a multi-center, randomized, crossover, triple-blind trial, will compare safety and clinical efficacy of the MobiusHD implant to sham control. The primary endpoint will be the change in mean 24-h ABPM from baseline to the 180-day visit. The secondary endpoint will be a composite of death, myocardial infarction, stroke, carotid occlusion and a series of relevant adverse event including but not limited to ipsilateral carotid stenosis, device embolization or bleeding, from randomization through the 90-day visit. First results are planned to be released in 2020. Finally, in the CALM-START study, 111 individuals with mean 24-h ambulatory systolic BP of 135–170 mmHg (despite a stable antihypertensive regimen of three to four drugs) will be randomized to implantation of the MobiusHD device or a sham procedure. Primary endpoint will be change in mean systolic 24-h ABPM from baseline to 90 days after proper antihypertensive drug washout. Secondary endpoints will focus on major adverse clinical events including death, myocardial infarction and stroke from baseline to 30 days post-randomization.

Table 1 provides a summary of main characteristics of the most relevant clinical studies testing BAT or EBA for resistant hypertension.

4. Possible future applications of baroreflex stimulation beyond resistant hypertension

In last years, evidence is accruing suggesting a possible role of baroreflex-mediated sympathetic activity on glucose metabolism, cardiac and renal function. Consequently, many studies are flourishing based on the hypothesis that baroreflex stimulation may also improve other organ outcomes beyond blood pressure control.

High sympathetic discharge has acknowledged harmful effects to the kidneys, spanning from deranged renin release, vasoconstriction and sodium reabsorption to smooth muscle cell proliferation and frank glomerulosclerosis (Joles and Koomans, 2004). In a small pilot, non-randomized study of 23 individuals with stage 3 chronic kidney disease (Wallbach et al., 2014), baroreflex activation by the Barostim neo significantly reduced proteinuria as compared to controls, despite it had no impact on estimated renal function.

In individuals with heart failure, sympathetic hyperactivity worsens left ventricular dysfunction and elicits arrhythmias, independently of blood pressure (Brunner-La Rocca et al., 2001). In this respect, uncontrolled evidence exists demonstrating that in chronic NYHA class III heart failure patients, baroreflex stimulation may improve quality of life, left ventricular ejection fraction and BNP (Gronda et al., 2014). Finally, but no less important, sympathetic (hyper)activation decreases skeletal muscle blood flow and glucose distribution to skeletal muscles due to vasoconstriction (Lembo et al., 1994), particularly when hyperinsulinemia is present (Masuo et al., 1997). Notwithstanding this, one randomized trial in blood pressure responders to BAT device implantation did not demonstrate significant changes in muscular glucose delivery and insulin sensitivity as compared to control (May et al., 2014).

5. Conclusions

There is an urgent demand for new, effective therapeutic strategies to improve patients' outcomes in individuals affected by resistant hypertension. The improved understanding in the role of the carotid baroreflex sympathetic nervous system, together with the progresses made in minimally-invasive devices technology, have opened new horizons of research, holding the hope to simplifying the complex clinical management of this dangerous disease condition.

Clinical studies have underlined the potential of BAT and EBA devices to improve blood pressure control and reduce the need of anti-hypertensive therapy at cost of few side effects despite the invasiveness of the procedure. Nevertheless, concrete proofs of efficacy, safety and durability overtime are lacking as the evidence accrued so far mostly relies on small uncontrolled trials on highly selected study populations, not adequately powered to catch differences on hard patient outcomes (e.g. mortality or CV events) and directly funded by devices industries.

Hence, results from larger multicentric, independent, randomized, sham-controlled trials are eagerly awaited before imaging a concrete implementation of baroreflex stimulation in daily clinical practice. Future research is warranted over the upcoming years, particularly to identify the optimal clinical profile of individuals who may benefit the most, as well as to test possible alternative applications and organ targets beyond blood pressure control.

Conflict of Interest

The authors declare no competing interests.

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