Review

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Advances in Nonpharmacological Approaches, Such as Baroreceptor Stimulation, for the Treatment of Resistant Hypertension

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Advances in Nonpharmacological Approaches, such as Baroreceptor Stimulation, for the Treatment of Resistant Hypertension

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Abstract

Resistant hypertension (HTN) affects up to 20% of patients who fail to achieve blood pressure (BP) control despite standard triple-drug therapy. As pharmacological treatments remain inadequate for these patients, baroreflex activation therapy (BAT) has emerged as a promising nonpharmacological alternative. By electrically stimulating baroreceptors in the carotid sinus, BAT restores autonomic balance through increased parasympathetic and reduced sympathetic activity, resulting in substantial BP reductions. Modern implantable devices such as the Rheos® and BAROSTIM NEO® systems have demonstrated significant and sustained decreases in both systolic and diastolic BP in treatment-resistant HTN, as well as clinical benefits in heart failure and end-stage renal disease. Despite these advances, BAT remains limited by its surgical invasiveness, adverse effects, and narrow patient eligibility. Ongoing research aims to develop less invasive stimulation methods and refine patient selection criteria. Large-scale, randomized, double-blind trials are still needed to establish BAT's long-term safety, efficacy, and clinical applicability. Overall, BAT represents an innovative, device-based therapeutic strategy for managing resistant hypertension.

Keywords: resistant hypertension; hypertension; blood pressure; baroreceptor

Introduction:

Hypertension (HTN) is one of the leading preventable risk factors for many cardiovascular diseases and causes of death in the USA and around the world (Dorans, Mills, Liu, & He, 2018). Globally, more than one billion people are suffering from HTN (Mills, Stefanescu, & He, 2020).

A systolic blood pressure (BP) >130mm of Hg and diastolic BP >80mm of Hg is considered as HTN (according to American College of Cardiology and American Heart Association) (Dorans et al., 2018). Despite the advancement of pharmacological therapeutics where patients take regular standard antihypertensive medication (containing three different classes of drugs; thus called triple-drug therapy), around 15% of hypertensive patients struggle to control their BP in daily life (Noubiap et al., 2019). This type of HTN is resistant to standard antihypertensive drug therapy. Therefore, it is termed resistant HTN.

As pharmacological treatment is ineffective in resistant HTN, non-pharmacological options (such as baroreflex activation, endovascular baroreflex amplification, and renal denervation) are evolving as new therapeutic strategies for the treatment of resistant HTN. The subsequent section of this review will only focus on the baroreflex activation strategy as a potential therapeutic treatment (non-pharmacological) for resistant HTN.

Baroreceptor and baroreflex physiology: Baroreceptors are special types of mechanoreceptors located in the carotid body, carotid sinus, and aortic arch. They are an integral part of the autonomic nervous system that plays a significant role in the regulation of BP. Upon activation, baroreceptors exert baroreflex, which is a negative feedback homeostatic mechanism for maintaining optimum BP (Armstrong, Kerndt, & Moore, 2023). In normotensive (normal BP) conditions, baroreceptors predominantly remain inactive. However, when BP increases, the carotid body, carotid sinus, and

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aortic sinuses become distended, which activates the mechanosensitive baroreceptors. These baroreceptors send their axonal projection to the nucleus tractus solitarious (NTS) (Seller, 1991), rostral ventrolateral medulla (RVLM) (Barman & Gebber, 1985) and nodose ganglia (Donoghue, Garcia, Jordan, & Spyer, 1982). Upon baroreceptor activation, these neuronal circuit integrates the signal and modulate the autonomic nervous system by stimulating the parasympathetic (Vagus) and inhibiting the sympathetic nervous system. Parasympathetic activation and sympathetic inhibition concurrently reduce the BP by reducing heart rate and force of myocardial contraction.

The first documented report for baroreflex activation therapy (BAT) was published in 1958 (WARNER, 1958). In that study, they used a dog model to surgically place bipolar electrodes in the carotid sinus to stimulate baroreceptors. Later on, using a similar methodology, BAT was implemented in an experimentally induced hypertensive dog model, showing a significant reduction of BP in response to BAT (Bilgutay & Lillehei, 1965). Because of its consistency in BP reduction, BAT has been implemented in human studies too. First reported human study was published in 1966, where bipolar electrodes were surgically placed in the carotid sinus, to stimulate baroreflex (also known as BAT), showing a significant reduction of BP (Bilgutay & Lillehei, 1966). Despite the successful reduction of BP, BAT procedure had some inherent limitations. For example, the procedure was surgically invasive, associated with a certain degree of infections, and the longevity of the battery powering the electrode was short. Moreover, during that time multiple highly potent antihypertensive drugs started to appear in the market. Taken together, all those confounding factors made the BAT very unpopular for the next two decades.

However, as more and more reports were demonstrating that at least 18-20% of hypertensive patients were resistant to standard triple therapy of antihypertensive drugs (Carey, Sakhuja, Calhoun, Whelton, & Muntner, 2019), the possibility of alternative non-pharmacological treatment such as BAT resurfaced again as a feasible option for treatment-resistant (TR) HTN (Blazek & Bakris, 2023). During the late 1990s and early 2000s, battery technology improved significantly, together with the advancement of the electrodes and associated electronics. Therefore, the size of the electrode reduced significantly, making the implantation process less invasive (easier to place it in the carotid sinus) and more durable (battery life ~3years).

Rheos® system developed by CVRx® (CVRx®, Inc., Minneapolis, MN, USA) as the very first implantable carotid sinus stimulator. It is composed of two (bilateral) electrodes, implanted in the perivascular space around each carotid sinus to stimulate the baroreceptors in the carotid sinus (Lohmeier & Iliescu, 2013). By using this system, Illig *et al.* reported 41mm of Hg reduction of systolic BP (Illig et al., 2006). Scheffers et al. published a non-randomized multicenter study (also called 'Device Based Therapy in Hypertension Trial') in 2010 using the Rheos® system, reporting that 3 months of BAT reduces both systolic and diastolic BP by 21/12 mm of Hg (Scheffers et al., 2010). The same study highlighted that, with a longer duration of the BAT, the reduction of BP is more pronounced. For example, 12 months and 24 months of BAT significantly reduce the systolic and diastolic BP by 30/20 mm of Hg and 33/22 mm of Hg respectively (Scheffers et al., 2010). In both Illig *et al.* and Scheffers et al. study, the population sample size was small (around 50 in each study). As both studies demonstrated a significant reduction of BP using the Rheos® system, in 2017, de Leeuw et al. conducted a large-scale study (also called 'Rheos Pivotal Trial') with 383 patients suffering from TR HTN. This study demonstrated that BAT significantly reduces systolic BP from 179 ± 24 to 144 ± 28 mm of Hg and diastolic BP from 103 ± 16 to 85 ± 18 mm of Hg (de Leeuw et al., 2017). Out of the 383 patients, those who had preexisting heart failure showed the highest reduction of both systolic and diastolic BP (46 and 24 mm of Hg reduction respectively) (de Leeuw et al., 2017).

Despite the small electrode size, Rheos® system had two electrodes that needed to be implanted bilaterally, which made the implantation procedure lengthy and time-consuming. Moreover, patient compliance for this dual electrode was poor. In addition, de Leeuw et al. conducted a study where they studied Lt and Rt-sided electrode stimulation. Results demonstrated that Rt-sided electrode stimulation produced a robust reduction of BP compared to the Lt-sided stimulation (de Leeuw et al., 2015). Moreover, BP reduction from Rt-sided electrode stimulation is comparable to bilateral

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stimulation (de Leeuw et al., 2015). Taken together, this observation paved the idea for the development of a BAT device with single electrode. With this view in mind, a new device called 'BAROSTIM NEO®' was first developed by CVRx Inc in 2012. BAROSTIM NEO® system is equipped with only one electrode and hence, the implantation procedure is only minimally invasive. Subsequently, CVRx Inc has developed a second generation of BAROSTIM NEO® system which was approved by the FDA in 2019 (https://www.cvrx.com/fda-approval/#:~:text=About%20CVRx%2C%20Inc.,Area%2C%20Colombia%20and%20New%20Zealand.).

A non-randomized trial of BAT using BAROSTIM NEO® system demonstrated a robust reduction of BP from 171 ± 24 mm of Hg/91 ± 18 mm of Hg (systolic BP/Diastolic BP) to 151 ± 26 mm of Hg/82 ± 17 mm of Hg (systolic BP/Diastolic BP) (Wallbach et al., 2016).

Apart from stimulation of baroceptors/ BAT, low-intensity stimulation of the baroreceptors afferent fibers in a spontaneously hypertensive model (rat) significantly reduces the mean arterial pressure (MAP) by 20-30mm of Hg (Salman et al., 2022).

In Addition to TR Hypertension, BAT Can Be Used for End-Stage Renal Failure and Heart Failure:

HTN is adversely affiliated with renal function. A study was conducted in end-stage renal failure patients, where patients were assigned to the BAT using BAROSTIM NEO® system. Results from that study showed that BAT significantly reduced systolic BP from 194 ±28 to 137 ± 16 mm of Hg, while diastolic BP reduced from 97 ±19 to 73 ± 17 mm of Hg and thereby reducing the morbidity and prolonging life expectancy (Beige et al., 2015). Indicating that, in addition to BP reduction, BAT also exerts a nephroprotective effect (Wallbach et al., 2018).

In addition to TR HTN, BAT has been demonstrated to reduce BP in chronic heart failure (CHF) (Ruddy, Kroman, Baicu, & Zile, 2024) and pulmonary artery hypertension (J. Wang et al., 2024). Multiple studies in patients suffering from heart failure with reduced ejection fraction (<35%) demonstrated that BAT alone can reduce symptomatic relief, blood pressure, heart failure morbidity, and cardiovascular mortality and improve left ventricular function (D. Wang et al., 2024; Zile et al., 2024).

International Council Evaluating BAT as a Treatment for TR HTN:

Due to the effectiveness of BAT, national and international medical societies are now positively evaluating whether BAT can be recommended as a regular treatment for the TR HTN. European Society of Hypertension and German BAT Consensus Group reported that the BAROSTIM NEO® system has promising potential. However, multiple randomized control trial needs to be done before it can be finally approved (Kuczera, 2023; Mancia et al., 2023). According to the American Heart Association (AHA) guidelines, BAT is considered a potential treatment option for patients with advanced heart failure, particularly those with treatment-resistant symptoms and TR HTN. However, more clinical trials should be made, and results from the ongoing clinical research should be evaluated with great care to make a decision for its regular use (Carey et al., 2018).

Limitation of BAT and Future Direction:

Despite the promising potential, BAT has some inherent limitations. Implanting electrodes to stimulate the carotid sinus requires surgical intervention. There is an unwillingness among some patients towards the surgical procedure. Therefore, it warrants further research to develop a non-invasive electrode/BAT device that can be introduced without any invasive surgical interventions.

Moreover, a patient's physical fitness is a prerequisite for any surgical procedure including BAT device implantation. In some preexisting conditions, such as uncontrolled diabetes, surgical intervention may not be possible due to the high risk of post-operative infection and delayed wound healing (Martin et al., 2016). Moreover, BAT has been reported with some adverse effects, including

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post-surgical complications (such as the formation of hematoma), hypertensive crisis, and hypotension with acute kidney injury (de Leeuw et al., 2017). Therefore, in order to avoid these adverse consequences, a careful patient evaluation is necessary before recommending the BAT. In a recent clinical study, it was reported that after cautious patient evaluation, only 7.8% of the patients were eligible for the BAT (Schäfer et al., 2021). Indicating that only a small proportion of hypertensive patients will likely benefit from BAT. In order to broaden the implication probability of BAT, further research is necessary to reduce all the adverse consequences associated with BAT.

A recent study conducted in spontaneously hypertensive rats demonstrated that stimulation of the baroreceptor afferent fibers located in the aortic depressor nerve can efficiently reduce BP (Salman et al., 2022). Moreover, it does not require any high-frequency or continuous electric stimulation. Indicating that aortic baroreceptor afferent fiber stimulation can be a suitable alternative to conventional device (BAROSTIM NEO) induced BAT. Anatomically, baroreceptors located in the aortic sinus are superficial compared to the aortic baroreceptor afferent fibers located in the aortic depressor nerve. Therefore, more research will be necessary in the future to design an electrode device and how to implant that device in the aortic depressor nerve to efficiently stimulate baroreceptor afferent fibers in humans.

Conclusions:

BAT was first invented in the 1960s. And over the years, the devices that were used for the implication of BAT, have improved significantly. All the studies and trials published so far showed a significant reduction of BP in TR hypertensive patients in response to BAT. Which indicates BAT has a promising therapeutic potential. However, as described before, only a small proportion of patients are eligible for the BAT (Schäfer et al., 2021). All the reported pre-clinical and clinical trials consisted of a small to moderate number of patients. One of the two largest reported trials conducted by de Leeuw et al. in 2017 (also called the 'Rheos Pivotal Trial') consisted of 383 hypertensive patients (de Leeuw et al., 2017). Another study consisted of 408 patients (with heart failure) (Zile et al., 2020). Clearly indicating the lack of sample size from the perspective of a clinical trial. In the future, the sample size needs to be increased (large scale) to elevate the strength of the trial. Moreover, previous studies were not always conducted as randomized-double-blind control trials. In order to reduce the methodological bias and improve the strength of the trial, robust randomized-double-blind control trials are required to validate their safety profile and patient compliance before BAT can be prescribed for routine use in daily life.

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