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DEVICE BASED STRATEGIES FOR THE MANAGEMENT OF RESISTANT HYPERTENSION: ROLE OF CAROTID BARORECEPTOR STIMULATION AND CONTINUOUS POSITIVE AIR PRESSURE VENTILATION

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Treatment-resistant hypertension (TRH) is defined as the presence of systolic/diastolic blood pressure (BP) levels persistently above normalcy thresholds despite the concurrent use of at least three antihypertensive medications at optimized doses from different classes, including a diuretic [1]. Overall, TRH affects about 10 to 30 % of subjects within the general hypertensive population [1], its prevalence being significantly higher (i.e. up to 50%) in conditions characterized by high sympathetic activity, such as chronic kidney disease and obstructive sleep apnea syndrome (OSAS). The high cardiovascular risk and global disease burden associated with persistent elevation in BP levels, has motivated the search of alternative, non-pharmacological strategies to achieve BP control in subjects with hypertension non responding to conventional drug treatment.
The present newsletter will review the impact of two of these non pharmacological approaches to management of TRH, namely Baroreflex Activation Therapy (BAT) and Continuous Positive Air Pressure (CPAP) ventilation. Although these techniques influence different pathophysiological targets, both of them are effective in reducing the sympathetic nervous system (SNS) overdrive, which is a major contributing mechanism for TRH. Another technique proposed in this context is catheter-based renal denervation (RDN), the application of which is addressed in a separate newsletter.

Baroreflex Activation Therapy in treatment resistant hypertension

Carotid baroreceptors play a key role in BP regulation. They sense the increase in carotid transmural pressure induced by an increase in BP levels, which results in an increase of efferent baroreceptor neural influences directed to the brainstem, inhibiting sympathetic and stimulating parasympathetic centers. The result of arterial (carotid) baroreceptor stimulation is thus a suppression of central sympathetic drive to the heart [reducing heart rate (HR), myocardial work and O2 consumption], to the peripheral circulation (reducing arterial stiffness in large arteries and reducing vascular tone in the arteriolar bed) and to the kidneys (reducing renin-angiotensin-aldosterone-system activity and increasing natriuresis and diuresis) [2]. The net result is a reflex reduction in BP and HR, aimed at counteracting the initial pressor stimulus on these receptors and thus at maintaining homeostasis. An impaired arterial baroreflex modulation of cardiovascular system and/or a resetting of arterial baroreceptors at persistently high BP levels, contributes to chronic sympathetic activation and sympatho-vagal imbalance, which in turn have been associated with the pathogenesis, progression and maintenance of arterial hypertension [3]. The cardiovascular impact of an impaired baroreflex function and the marked increase in central sympathetic drive characterizing arterial hypertension stimulated the first development of BAT devices in the twentieth century for the management of TRH, although with limited clinical applications. The recent significant improvements introduced in the technology of last generation BAT systems, as well as the progress in the device implantation procedures, have led to a renewed interest in the use of this interventional strategy for the treatment of TRH.

Features of BAT systems and procedural methodology

Overall, BAT systems consist of a programmable impulse generator which delivers an electrical stimulus to the carotid sinuses. This stimulus is interpreted by the central nervous system as if it were due to increased BP levels, leading to reflex inhibition of sympathetic drive, stimulation of parasympathetic activity and subsequent reflex reduction in BP levels. Following the initial demonstration that BAT was effective in inducing acute and marked reductions in BP levels in humans [4], subsequent studies in subjects with TRH also confirmed the ability of BAT to provide important and sustained reductions in BP levels over time [5]. However, ethical and technical concerns limited the extensive use of early BAT prototype devices, even in the context of research studies. Over the years, several improvements in the device technology have been introduced, and smaller and safer prototypes have been developed, allowing local and bilateral direct electrical stimulation of carotid nerves, thus preventing the pain associated with external and/or poorly selective baroreceptor nerve stimulation. These systems (produced by CVRx®, Minneapolis, Minnesota, USA), also allow external programming of the frequency and amplitude of discharge by means of a radiofrequency control system. This, along with the progress in surgical and anaesthesiological techniques for the implantation procedure, has significantly reduced the incidence and severity of adverse events related to this approach. Recently, a BAT device based on monolateral carotid nerve stimulation and a smaller stimulating system (Barostim neo™) has been successfully developed, simplifying the implantation procedure without weakening the effectiveness of this approach.

Short and long term BP lowering effects of BAT

Experimental studies in humans with TRH have confirmed the effectiveness of recent BAT devices in reducing BP and heart rate levels immediately after the interventional procedure [6], [7]. Remarkably, the direct correlation between the magnitude of acute BP reduction and decrease in markers of adrenergic activity such as muscle sympathetic nerve activity (MSNA), plasma norepinephrine (NE) concentrations and whole-body NE spillover, has supported the concept that BAT suppresses overall sympathetic outflow from the brain [8], [2]. BAT has also been shown to be effective in suppressing renal sympathetic nerve activity (RSNA), decreasing plasma renin concentrations, enhancing pressure natriuresis and promoting sodium excretion [8], [2]. The mechanisms responsible for acute effects of BAT also explain its long-term effects on BP regulation. However, after prolonged reductions in BP levels, baroreceptors reduce their ability to chronically modulate sympathetic activity as a result of the baroreflex resetting phenomenon. Although this phenomenon initially raised important concerns about the long-term efficacy of BAT, a series of studies have indicated that reductions in BP levels, heart rate and different markers of adrenergic activity with this approach are sustained over time [8], indicating that adaptation within the CNS does not seem to offset the long-term sympathoinhibitory and BP lowering effects of BAT. In addition, the sustained reductions in RSNA and RAAS activity (which in turn increase sodium excretion and pressure natriuresis) [9], with long-term use of BAT, are against the hypothesis that baroreflex induced BP reduction might be counteracted with time by a renal feedback mechanism.

Safety and efficacy of BAT for the treatment of TRH: evidence from interventional studies

Overall, BAT has been shown to be effective in producing marked reductions in BP levels and in improving achievement of BP control immediately after the implantation procedure and throughout the follow-up stimulation period [2], [10], [11].
In the **Rheos feasibility trial**, in subjects with multidrug-resistant hypertension [12], BAT was effective in reducing systolic/diastolic BP levels by 41/21 mmHg before discharge from hospital [12]. In the frame of the Device Based Therapy of Hypertension (**DEBuTHT**) trial, office BP levels were reduced by 21/12 mmHg after 3 months of BAT[13], and by 33/22 mm Hg after 2 years of follow-up [11]. In this study, BAT was also able to significantly reduce 24h ambulatory (A) Systolic (S)/diastolic(D) BP (-24/-13 mmHg, respectively) [11]. Evidence on the efficacy of BAT in improving achievement of BP control, was provided in the **Rheos Pivotal Trial** [10]. In this study compared to subjects receiving "delayed" BAT (i.e. with device activated at the 6th month after implantation), those receiving "early" BAT (i.e. with device activation within the first 6 months following implantation) achieved office systolic BP control (i.e. SBP ≤140 mmHg) more frequently (42% vs. 24% respectively) but the changes in office BP at 6 months did not significantly differ. However, after 12 months of follow-up, about 50% of subjects in both groups achieved SBP ≤140 mmHg [10]. Remarkably, these studies have shown a favorable safety profile for BAT without significant increases either in morbidity or in adverse events attributable to the electric stimulation, both in the short or in the long-term. When present, the side effects reported were more related to surgical or anesthetic procedures (local surgical complications, nerve injury, stimulation of adjacent organs, etc.) than to BAT itself [10]. Although in the past some concerns were raised on the potential adverse effects of BAT on renal function [11], a post-hoc analysis of the Rheos Pivotal Trial, showed that the mild decrease in glomerular filtration rate accompanying BP reductions within the first 6 months of BAT, did not further progress after 12 months of follow-up [14]. Of note, chronic BAT has been shown to confer beneficial effects on cardiac structure and function [15] without causing injury, remodelling, or stenosis of the carotid arteries [16]. Moreover, studies exploring the effects of BAT on TRH subjects with pacemakers, have indicated that it can be safely used without causing significant interactions with the cardiac pacemaker function [17]. Of note, it is not yet known whether the device is MRI compatible, which is an important information for patients with severe hyperteion who may suffer from stroke/TIA during their follow-up.

BAT vs. Renal denervation and intensified antihypertensive treatment

Although the evidence seems to support the efficacy of BAT for the management of TRH, the safety and tolerability profiles of this technique are affected by the surgical nature of the implantation procedure, which is frequently performed under general anesthesia. Although newly monolateral devices have limited the implantation procedure to one side only, the potential beneficial effects of BAT should be balanced against the invasive nature of the procedure, and against the need for periodical control and replacement of the generator battery or reintrervention in case of device failure. In consideration of these difficulties, other minimally invasive strategies were proposed, such as renal denervation (RDN), which in uncontrolled studies was reported to achieve similar BP reductions and rates of BP control than BAT. However, the results of the recently published SIMPLICITY HTN-3, a blinded, sham-controlled trial overwhelmingly showed that RDN had no significantly greater effect on office or 24-h ambulatory systolic BP, than a sham surgical procedure, failing to meet a prespecified between-group difference in 24-hour ambulatory systolic BP of only 2 mmHg [18]. Besides, the results of a recent small study investigating the BP-lowering effect of RDN vs. clinically adjusted drug treatment in true treatment-resistant hypertension (TRH), suggested inferiority of RDN, as compared with optimized drug treatment [19]. One the background of these results, also the real impact of BAT should in the near future be further addressed through properly designed, sham controlled studies, also addressing the relative effects of BAT vs. optimized antihypertensive treatment. A final consideration, when considering the possibility of BAT, is related to the need of confirming

whether TRH is true or corresponds to false resistant hypertension. This requires the routine combined use of office and out-of-office BP monitoring measurement techniques (the latter through ABP or home BP monitoring) [20]. Moreover, before proceeding with BAT, several possible interfering factors responsible for a BP elevation should also be excluded, such as secondary causes of hypertension, inappropriate drug choices or doses, concurrent use of drugs that may interfere with prescribed antihypertensive agents, or failure of the patient to adhere to the prescribed treatment regimen. Based on the ongoing discussion in relation to the real effects of RDN and to the discrepant assessment of treatment efficacy provided by office and by out-of-office BP monitoring [21], a general requirement for all future studies aimed at evaluating the effects of BAT is the need of combining BP measurements obtained in the office and in daily life (in particular through 24h ABPM) both at baseline and during follow-up.

CPAP ventilation in obstructive sleep apnea with treatment resistant hypertension

Obstructive sleep apnoea syndrome (OSAS), combining intermittent obstruction of upper airways during sleep with daytime somnolence, is a suggested cause of secondary hypertension [1] and has been associated with a high prevalence of severe and resistant hypertension [22], [23]. Indeed, current guidelines for the management of arterial hypertension have included OSAS among the modifiable causes to be discarded during the diagnostic approach to resistant hypertension [24], [1]. However, whether specific treatment strategies for OSAS (i.e. implementation of continuous positive airway pressure) are effective in achieving BP control on top of antihypertensive treatment, this has not been consistently clarified yet.

Obstructive sleep apnea syndrome and blood pressure levels

Alterations in breathing patterns in OSAS may importantly influence many regulatory mechanisms involved in BP regulation. OSA events occurring during night (i.e. alternating obstructive apnea and hyperventilation episodes during sleep) have been shown to be accompanied by acute changes in autonomic and hemodynamic parameters, which in turn induce marked increases in BP levels during night-time [25] [26].

Several studies have identified OSAS as an important risk factor for hypertension also showing a dose-response relationship between OSAS severity and the degree of BP elevation. It has also been shown that hypertension occurring in individuals with OSAS is more likely to be severe, resistant to treatment and associated with alterations in day-to-night BP changes (i.e. nocturnal hypertension and non-dipping profile of BP on 24h ABPM) [27], [22], [23]. Conversely, an extremely high prevalence of OSA of about 80% has been reported among adult patients with drug-resistant hypertension [28]. It has also been shown that rates of BP control decrease as the severity of sleep-related breathing disorder increases [29]. Although all the above evidence supports a potential role of OSAS in the pathogenesis of hypertension and drug-resistant hypertension, the mechanisms by which OSAS promotes arterial hypertension are not completely understood. Evidence provided by experimental and clinical studies has indicated that the pathogenesis of OSAS-related hypertension is likely to be multifactorial, involving alterations in several regulatory systems: activation of the sympathetic nervous system [30], alterations in autonomic cardiovascular modulation [31], [32], activation of renin–angiotensin–aldosterone system [33], [34] [35], endothelial dysfunction [36], systemic and vascular inflammation, oxidative stress, [37], [36], [38] , arterial stiffness [39], and metabolic abnormalities [40].

Effects of CPAP treatment on OSAS-related hypertension

Nasal continuous positive airway pressure (CPAP) is currently considered the optimal treatment for OSA of moderate to severe degree. When properly implemented, CPAP not only provides relief of clinical symptoms and reduction in the severity of OSA but also improves many of the acute and chronic pathophysiological alterations induced by OSAS. Of note, CPAP use has been shown to induce marked and acute reductions in MSNA not only during night-time sleep, but also during daytime wakefulness if maintained in the long-term [30]. Several studies have also shown the effectiveness of CPAP in improving baroreflex impairment [41], systemic inflammation [38], [36], endothelial dysfunction, [36], RAAS activation [42], arterial stiffness [41], and metabolic alterations [43].

Although improvements in these pathophysiological alterations should theoretically translate into substantial BP reductions, most interventional trials in OSAS and subsequent meta-analyses have indicated that, although CPAP has a significant effect on BP levels, the overall effect on 24-h, daytime and night-time systolic and diastolic ambulatory BP levels is rather small (on average in the order of 1-2 mm Hg only) [22], [23]. However, the effects of CPAP on BP levels have been shown to be variable in different studies, and in some subgroups of patients, particularly in those with more severe OSAS [44] or with resistant hypertension [45], more substantial effects of CPAP on BP levels have been reported. Indeed, effective CPAP treatment in patients with moderate to severe OSAS has been shown to induce important reductions both in day- and night-time BP levels [44]. This has also been the case of subjects with resistant hypertension in whom regular CPAP implementation has resulted in marked reductions in ambulatory BP levels not only during night-time but also during daytime wakefulness [45]. In a recent study addressing the effects of 1 year treatment with CPAP, whereas no effects on BP levels were observed in patients with BP controlled at baseline, marked and significant reductions in BP levels were observed in subjects with resistant hypertension [46].

There are two critical aspects, when assessing the clinical effects of CPAP, that were not properly considered in some of the available studies. These are the adequate titration of the air pressure for ventilation and the patients' adherence to therapy. Given the mechanical nature of CPAP (i.e. facial interface mask and the pressure required to prevent airway collapse) this treatment is not always well accepted by patients, in particular by those free of OSA related symptoms. On the other hand, several studies have indicated that in order to observe an effect of CPAP on BP, CPAP treatment should be implemented for enough time and for a sufficient number of hours per night, and that its effects on BP levels should ideally be assessed by means of ABPM. Prove of this has been provided by studies showing significant ambulatory BP reduction with CPAP both in OSAS patients with confirmed resistant hypertension, when CPAP was implemented for at least 3 months and for more than 5.8 hours per night [47], as well as in non-sleepy hypertensive patients with OSA, when using CPAP for more than 5.6 hours per night [48]. The discordant results obtained so far on the actual ability of CPAP treatment to control TRH, thus emphasize the need of further studies to be performed according to a proper methodology, i.e. based on use of 24h ABPM, adequate CPAP titration and sufficient patients' compliance with the night-time use of this device.

CONCLUSIONS: Based on available data, both BAT and CPAP ventilation of OSAS patients may represent interesting approaches for a better control of BP and for a reduction in the number of antihypertensive drugs while managing treatment resistant hypertension. Their actual effectiveness in this condition, however, needs to be further explored in the frame of randomized, placebo controlled longitudinal studies, including outcome assessment and implementing state of the art methodology for the evaluation of real life BP control.

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