Treatment-resistant hypertension (TRH) is defined as the presence of systolic/diastolic blood pressure (BP) levels persistently above normality 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 pregnancy-associated hypertension, with common initial upregulation of arterial baroreceptors. The 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. These approaches include both non-selective (e.g. surgery) and variable selectivity baroreceptor nerve stimulation, both in the short or in the long-term. When present, the side effects reported 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 hypertension who may suffer from stroke/TIA during their follow-up.

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

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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 Hypertension Therapy (DEBuTHT) trial, after 12 months of follow-up, about 50% of subjects in both groups achieved SBP ≤140 mmHg [13]. Remarkably, these results 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 occurring in patients treated with the implantation procedure to one group 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 reintervention in case of device failure. In consideration of these premises, other minimally invasive techniques or implantable devices targeting the renomedullary juxtaglomerular apparatus as renomedullary 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 SIMPLECITY HITN-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 and diastolic BP levels [18]. Besides, the recent results of a 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 clarified, building on the prospect of future strategies that emphasize targeting of arterial baroreceptors and aortic baroreceptors stimulation, both in the short or in the long-term. When present, the side effects reported 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 hypertension who may suffer from stroke/TIA during their follow-up.

**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 effector baroreceptor neural influences directed to the brainstem, inhibiting sympathetic and stimulating parasympathetic centers. The result of arterial (carotid) baroreceptor stimulation is decrease in markers of adrenergic activity such as muscle sympathetic nerve activity and stimulating parasympathetic centers. The result of arterial (carotid) baroreceptor stimulation on BP is decreased at the central level (that is, heart rate reduction) and peripheral (reducing peripheral vascular resistance), which results in an increase of carotid sinus barometric receptors, which are in turn increased by an increase in carotid sinus pressure. Overall, recent studies have shown that the use of BAT has been effective in producing marked reductions in BP levels in patients with 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 observation 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 BAT in the early stages of the 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 sinus nerve branches that were 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 procedures that were not necessary in the early stages of the implantation procedures 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 SIMPLECITY HITN-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 and diastolic BP levels [18]. Besides, the recent results of a 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 clarified, building on the prospect of future strategies that emphasize targeting of arterial baroreceptors and aortic baroreceptors stimulation, both in the short or in the long-term. When present, the side effects reported 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 hypertension who may suffer from stroke/TIA during their follow-up.

**B高血压 vs. Renal denervation and intensified antihypertensive treatment**

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%). However, 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 [13]. 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. Of note, chronic 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. Of note, chronic 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.
whether TRH is true or corresponds to false resistant hypertension. This requires the need of further studies to be performed according to a proper methodology, i.e. based on night-time use of this device.

3. At least 5.8 hours per night

4. In patients with confirmed resistant hypertension, when CPAP was implemented for at least 3 months 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 reported to improve BP control and reduce RAAS activation [42], arterial stiffness [41], and metabolic alterations [43].

5. Treatment for OSA of moderate to severe degree. When properly implemented, CPAP not only reduces snoring and daytime somnolence but also improves quality of life in patients with resistant hypertension [42]. Moreover, CPAP has been shown to reduce cardiovascular risk factors and to improve vascular function in patients with resistant hypertension [42].

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 improves sleep architecture and reduces sleep fragmentation but also improves BP control and reduces cardiovascular risk factors in patients with resistant hypertension [42]. Moreover, CPAP has been shown to improve vascular function in patients with resistant hypertension [42]. The effects of CPAP on BP levels are more pronounced in patients with hypertension [42]. However, some studies have shown that CPAP may have a beneficial effect on BP levels in patients with resistant hypertension [42].

The use of CPAP in patients with resistant hypertension has been associated with a reduction in BP levels [42]. However, the magnitude of this effect may vary depending on the severity of OSA and the degree of BP control [42]. Moreover, the long-term effects of CPAP on BP control in patients with resistant hypertension are still uncertain [42].

In conclusion, the use of CPAP in patients with resistant hypertension appears to be a promising strategy for BP control, particularly in patients with moderate to severe OSA and resistant hypertension. Further studies are needed to assess the long-term effects of CPAP on BP control and to determine the optimal CPAP settings for achieving this goal.