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UPDATE ON DEVICE THERAPIES FOR RESISTANT HYPERTENSION

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A. RENAL SYMPATHETIC DENERVATION

Based on the solid pathophysiologic association of sympathetic nervous system activity to hypertension, renal sympathetic denervation (RDN) was also supported by preclinical studies as well as proof of principle, non-randomized or randomized trials that provided evidence for office, as well as ambulatory blood pressure (BP) reduction in patients with resistant hypertension [1]. After the single electrode radiofrequency ablation Symplicity catheter, radiofrequency multielectrode catheters of a spiral, basket or balloon-based design, as well as other methods including ultrasound and chemical denervation were introduced [2]. However, the initial enthusiasm was halted by the neutral results of the SYMPLICITY HTN-3 study [3]. The present newsletter is also an update of the one published in 2012, presenting the current status of the method.

Update on safety

Overall, safety of the procedure has been consistently documented in RDN trials, and recording of adverse events continues in trials and registries [2-4]. Preclinical and optical coherence tomography studies have shown that endothelial-intimal edema, thrombus formation and renal artery spasm or even small dissections are expected after RDN, but with no clinical sequelae. Clinical trial follow-up extending to 36 months post-RDN has documented sporadic cases of vascular access site complications, renal artery dissections and other rare events not marked as device-related [4].

With respect to renal function, the majority of available data show no significant deterioration, at least beyond what is expected in the high cardiovascular risk resistant hypertension patients and with the progression of age, either acutely or in the mid - to long-term [2-4]. It is thus considered reassuring that overall a relatively stable renal function during follow-up has been documented in uncontrolled studies and registries, as well as controlled studies. A series of case reports have documented the development of unilateral or bilateral significant renal artery stenosis in patients with a high atherosclerotic risk [5]. These events were documented as early as 2 months and as late as 2 years after RDN and usually associated with a relapse of high BP or deterioration of renal function. Based on the above, current contraindications for RDN include previous renal artery interventions and renal artery stenosis > 30 %, while energy delivery on atherosclerotic lesions should be avoided [2]. Autonomic function has been tested to be maintained with no orthostatic hypotension or heart rate and BP unfavorable changes after tilt-test [6].

Update on efficacy

Symplicity HTN-3 study was a prospective, randomized, sham controlled study, designed to validate the safety and efficacy of RDN observed in most earlier trials, in order to fulfill regulatory requirements [3]. The study succeeded in the primary safety endpoint but failed in the primary efficacy endpoint. Office systolic BP at 6 months decreased by −14.1mmHg in the RDN and −11.7mmHg in the sham procedure group (between group p = 0.26, with a superiority margin of 5 mmHg). Similarly, the change in ambulatory BP at 6 months was −6.7 mmHg in the RDN and −4.7 mmHg in the control arm (between group = 0.98, with a 2 mmHg superiority margin). These findings were again observed at the 12-month follow-up. Subsequent comprehensive sub-analysis of the results of the trial, along with interesting new preclinical data regarding the renal fibres, improved our insight on the potential confounding factors, including incomplete ablation and non-adherence to medical therapy, that may explain the unexpected BP responses in both RDN and sham ablation groups [7].

Other smaller studies were published that also concluded in non-superior efficacy results, when comparing RDN to intensified regimens that included spironolactone or impedance cardiography-driven drug therapy [8]. On the other hand, the French Renal Denervation for Hypertension (DENERHTN) trial, a prospective, open-label randomized controlled trial, showed that when applying standardized-stepped-care antihypertensive treatment, a higher decrease in daytime ambulatory blood pressure by 5.9mmHg was observed 6 months after RDN compared to standard management [9].

The current status of RDN

Our approach to RDN has altered from a relatively simple procedure to a complex treatment affected by diverse parameters. From a technical aspect, optimal settings regarding electrode-tissue contact pressure, time/amount of energy and ablation depth are under investigation [2,7]. The efficacy is influenced by fewer ablations or not successful ablations in all four quadrants of the renal artery, an issue managed with the newer multielectrode catheters that provide circumferential or helical ablation [7]. Peri-arterial nerve distribution varies and this may need to be especially considered in the context of chronic hypertension or atherosclerotic changes [10]. The highest average number of nerves is found in the proximal and middle segments of the renal artery and a longer distance from the lumen to the nerve is observed in the proximal, compared to distal segments. It is suggested to perform symmetric and more distal renal artery targeting to achieve effective ablation, while delivery of energy in the branches is under investigation.

Apart from consistent predictive value of high baseline BP, baseline heart rate, age, aortic stiffness, as well as other markers such as acute changes in renal hemodynamics, noradrenaline spillover, per procedural veno-arterial noradrenaline gradient and changes in BP after high frequency stimulation in the renal artery have been proposed for efficacy markers but further data are needed.

Optimization of study design in the field of RDN has been the topic of expert consensus reports [11]. Assessment of ambulatory blood pressure as the primary endpoint, a run-in phase to minimize the regression to the mean bias, standardization of concomitant antihypertensive treatment and monitoring drug adherence, with methods such as mass spectrometry urinalyses, are strongly advised. A sham-control group that only undergoes renal angiography is needed, and a blinding index should be used. Study populations with earlier and milder forms of hypertension could provide clearer efficacy data compared to the resistant hypertensive patients that may have already irreversible vascular changes. In this context, two ongoing trials focus on the effect of RDN in hypertensive patients in the absence (SPYRAL HTN OFF-MED; NCT02439749) and presence (SPYRAL HTN ON-MED; NCT02439775) of antihypertensive medications. The SPYRAL HTN ON-MED study requires patients to be treated with a consistent mono or double or triple-therapy antihypertensive regimen, whereas the SPYRAL HTN OFF-MED study includes drug 'naïve' patients or patients after a 3-4-week drug washout period. The studies randomize patients with combined systolic-diastolic hypertension (with special attention to exclude isolated hypertension phenotype) to RDN or sham procedure [12]. Of similar design is the RE-INFORCE study (using the Vessix RDN system; (NCT02392351)) with the primary end point of ambulatory BP changes at 8 weeks post intervention and the RADIANCE-HTN (NCT02649426) which compares the ReCor Medical Paradise ultrasound system to a sham procedure with the primary endpoint change in average daytime ambulatory SBP from baseline to 2 months post-procedure in two separate on- (TRIO) and off-medication (SOLO) cohorts of patients with uncontrolled hypertension. In the TRIO cohort, participants with resistant hypertension will discontinue their current antihypertensive drugs and switch to standardized single-pill triple therapy. The results of these studies, since they address the major misconceptions regarding RDN (BP estimation by office and ambulatory measurements, stable medication, testing adherence to therapy and inclusion of sham-ablation arm) are empowered to provide the useful clinical information needed to resolve uncertainties for this neuromodulation therapy.

Conclusions

Since no safety issues regarding RDN are raised in any of the trials and registries and irrespectively of the neutral results of the HTN-3 trial, further research on RDN is a scientific need in order to address the clinical problem of uncontrolled hypertension. The effectiveness of this therapeutic approach should be tested in diverse settings of hypertension. The variable clinical results ranging from no response to excessive BP decreases reflect the multifactorial basis of hypertension and the resultant heterogeneity of patient response already observed with conventional drug treatment. Carefully designed ongoing studies will provide the evidence whether RDN is not only a safe, but also an efficacious treatment modality in hypertension. Their cost-effectiveness will have to be evaluated on the mid and long-term.

B. BAROREC EPTOR ACTIVATION THERAPY (BAT)

Introduction

One of the interventional therapies that can be applied in patients with treatment-resistant hypertension is baroreceptor activation therapy (BAT), sometimes called baropacing. When baroreceptors sense an increase in carotid transmural pressure, they respond by inhibiting sympathetic and stimulating parasympathetic centres in the brainstem. As a result, any increase in BP will be buffered effectively and BP will return to its initial level. With BAT, one stimulates the area in which the baroreceptors are located electrically to mimic as if they were activated by an endogenous signal. The system that has been used most extensively over the past ten years (Rheos™) consisted of a programmable impulse generator which was implanted subcutaneously in the thoracic area and which delivered an electrical impulse to the carotid sinuses. The leads that transmitted the current were attached to the carotid artery at a spot where stimulation produced the greatest BP response. Initially, electrodes were rather large and they had to be implanted at both sides. However, in the meantime a new device has been developed, the Barostim neo™ which is much smaller than its predecessor and which allows for unilateral implantation and stimulation.

Even more recently, a completely different device has been manufactured, the barostent MobiusHD, which is an endovascular implant that reshapes the carotid sinus and amplifies the BP signals which are perceived by the baroreceptors. Unlike the Barostim neo, this is not an electrical but rather a mechanical device. It is put in place by standard percutaneous catheterization.

Clinical efficacy

As far as the barostent device is concerned, there are no clinical data yet. For this reason, we will not discuss this any further. On the other hand, there are limited data regarding the Barostim neo and there is considerable experience with the Rheos device. The DEBuT-HT study demonstrated that with the Rheos system, a substantial and sustained reduction in BP could be achieved over a period of three months in treatment-resistant hypertensive patients [13]. Subsequently, the Rheos Pivotal Trial evaluated the effect of BAT in a double-blind, randomized, prospective, sham-controlled trial in which patients were randomized to receive BAT either immediately or six months after implantation of the Rheos device. Overall, this study showed a significant advantage of BAT with respect to the endpoints of long-term efficacy and safety. Acute responses and side-effects were, however, not modified by BAT [14].

Recently, the 6-year follow-up data of these trials have been reported (paper in press). Overall, 383 patients were available for analysis; their office systolic BP fell from 179+24 mmHg to 144+28 mmHg (p<0.0001), while office diastolic pressure dropped from 103+16 mmHg to 85+18 mmHg (p<0.0001). Heart rate fell from 74+15 beats per minute to 71+13 beats per minute (p<0.02). The effect of BAT turns out to be somewhat greater than average in patients with signs of heart failure, and less than average in patients with isolated systolic hypertension. In about 25% of patients it was even possible to reduce the number of medications from a median of six to a median of three. Although side effects related to either the surgical procedure or to cardiovascular instability did occur, these did not require specific measures and resolved over time. Interestingly, the Pivotal Trial also showed that unilateral stimulation is as effective, if not more, than bilateral stimulation. With the Barostim neo one must choose at which side to implant the electrodes; if there are no contraindications, the right side is to be preferred.

There are no trials which compared head-to-head the older device with the new one. However, using a propensity-matched cohort analysis of the first- and second-generation systems, Wachter et al. could show that the latter showed similar therapeutic benefit and superior BP reduction, as well as improved safety [15].

Unfortunately, most studies on BAT took only office BP as criterion for efficacy and did not include 24-hour BP monitoring. There is one study in which the effect of the Barostim neo on 24-hour BP was assessed in 51 patients. After 6 months of therapy, 24-hour had fallen by 8/5 mmHg which was statistically significant [16]. The French Economic Evaluation of Baroreceptor STIMulation for the Treatment of Resistant HyperTensioN (ESTIM-rHTN) trial is ongoing and aims to study baroreceptor activation in patients with resistant hypertension and eGFR 30 mL/min per 1.73 m2 or higher with the primary endpoint change in average daytime ambulatory SBP from baseline to 2 months post-procedure (NCT02364310).

Other considerations

Despite the considerable fall in pressure, BAT does not adversely affect renal function. On the other hand, it does reduce left ventricular hypertrophy and arterial stiffness [17]. Presently, BAT is under investigation for other indications such as heart failure. The initial results with heart failure patients are positive as well. Finally, in a Markov model BAT seemed to be cost-effective in comparison to medical treatment.

C. CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)

Nasal continuous positive airway pressure (CPAP) ventilation is currently considered the optimal treatment for obstructive sleep apnea (OSA) of moderate to severe degree. When properly implemented, CPAP not only provides relief of clinical symptoms and reduction in the severity of OSAS, but also improves many of the acute and chronic pathophysiological alterations induced by OSA. Several studies have also shown the effectiveness of CPAP in improving baroreflex impairment, sympathetic overdrive, systemic inflammation, endothelial dysfunction, renin-angiotensin-aldosterone activation, arterial stiffness and metabolic alterations [18].

Current status of CPAP therapy in hypertension

Although improvements in these pathophysiological alterations should theoretically translate into substantial BP reductions, most interventional trials in OSA and subsequent meta-analyses have indicated that, although CPAP has a significant effect on BP levels, the overall effect on 24h, daytime and night-time systolic and diastolic ambulatory BP levels is rather small (on average in the order of 1-2 mm Hg only) [18,19]. However, the effects of CPAP on BP levels have been shown to be variable in different studies, and in some subgroups of patients, particularly those with more severe OSA or with resistant hypertension, more substantial effects of CPAP on BP levels have been reported [20].

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. In a 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 patients with resistant hypertension [21].

There are two critical aspects when assessing the clinical effects of CPAP: the adequate titration of the air pressure for ventilation and the patients' adherence to therapy. Proof of this has been provided by studies showing significant ambulatory BP reduction with CPAP both in OSA patients with confirmed resistant hypertension, when CPAP was implemented for at least 3 months and for more than 5.8 hours per night, as well as in non-sleepy hypertensive patients with OSA, when using CPAP for more than 5.6 hours per night [22, 23]. The discordant results obtained so far on the actual efficacy of CPAP treatment to control BP, thus emphasize the need for 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. A new interesting research topic is focused on the suggestion that BP responder status among OSAS patients with resistant hypertension could be predicted by measuring the plasma levels of 3 specific micro ribonucleic acids (microRNAs) [24].

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