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MINIREVIEWS

Place of baroreceptor activation therapy in the treatment of resistant hypertension

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Abstract

This mini review describes the development of the therapeutic concept of baroreceptor stimulation over the last fifty years alongside the more recent introduction of it for the treatment of drug - resistant hypertension. The pros and cons of this strategy of treatment over renal sympathetic denervation are also discussed in the light of the results of the studies done in the last decade.

Key words: Resistant hypertension; Treatment; Baroreceptor stimulation; Renal denervation

Core tip: We herein describe the development of the therapeutic concept of baroreceptor stimulation for the treatment of drug-resistant hypertension. The ups and downs of this treatment strategy are discussed in the light of the results of the studies done in the last decade.

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INTRODUCTION

Baroreceptor activation blunts sympathetic activity and enhances vagal tone, thus rebalancing the neural output to the heart, the vessels, and the kidney in favour of the latter. This treatment strategy, currently defined as baroreceptor activation therapy (BAT), was originally conceived 50 years ago with the ultimate aim of lowering blood pressure (BP): Proof-of-concept studies were first published by Bilgutay *et al*[1] and then by Torresani *et al*[2]. They could nicely document the achievement of a marked reduction in BP in patients who were resistant to the (few) drugs available at

Table 1 Therapeutic strategies in patients with resistant hypertension

Recommendations	Class of recommendation[1]	Level of evidence[2]
In resistant hypertensive patients it is recommended that physicians check whether the drugs included in the existing multiple drug regimen have any BP lowering effect, and withdraw them if their effect is absent or minimal	I	C
Mineralocorticoid receptor antagonists, amiloride, and the alpha-1-blocker doxazosin should be considered, if no contraindications exist	IIa	B
In case of ineffectiveness of drug treatment invasive procedures such as renal denervation and baroreceptor stimulation may be considered	IIb	C
Until more evidence is available on the long-term efficacy and safety of renal denervation and baroreceptor stimulation, it is recommended that these procedures remain in the hands of experienced operators and diagnosis and follow-up restricted to hypertension centers	I	C
It is recommended that the invasive approaches are considered only for truly resistant hypertensive patients, with clinic values ⩾ 160 mmHg SBP or ⩾ 110 mmHg DBP and with BP elevation confirmed by ABPM	I	C

Class of recommendation[1]: Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure; Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy; Class IIb: Usefulness/efficacy is less well established by evidence/opinion. Level of evidence[2]: Level of evidence B: Data derived from a single randomized clinical trial or large non-randomized studies; Level of evidence C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries. ABPM: Ambulatory blood pressure monitoring; BP: Blood pressure; DBP: Diastolic blood pressure; SBP: Systolic blood pressure.

that time. Unfortunately the delivering of this therapy involved an invasive process and, moreover, stimulation was achieved by means of an external device. Accordingly, it turned out to be unpractical out of the hospital. For these reasons, alongside the development of multiple effective BP-lowering medications, BAT was rapidly abandoned.

It took more than forty years for this simple physiological principle to find again its way to clinical application, thanks to the development of implantable devices. The latter were shown to unequivocally lower BP in the DEBUT study[3]. Furthermore, in the Heart Rate Variability sub-study, they were also reported to improve the sympatho-vagal balance[3]. At that time it became readily evident that the BAT not only lowered BP and sympathetic nerve activity to the muscles[4], but was also effective in regressing left ventricular (LV) hypertrophy, in improving LV geometry, and in decreasing BP all around the clock[3].

In June 2010, when the first international meeting on Resistant Hypertension was held in Padua, Italy[5], it seemed, therefore, that BAT was emerging as the "front runner" in the therapeutic armamentarium for the then resurfacing problem of resistant hypertension.

Strong competition in the therapeutic armamentarium

At about the same time the publication of the first study on renal denervation[6] and, immediately after, of the Simplicity HTN-1[7] introduced another strong competitor for BAT in the race for the best treatment of drug-resistant hypertension: Percutaneous renal denervation. This treatment modality, which is undoubtedly less invasive than BAT, was shown to be effective in decreasing BP in carefully selected cases.

In June 2013, based on the evidence provided in the Simplicity HTN-2 trial that was published thereafter[8], the ESC/ESH Guidelines released statements concerning the use of BAT or renal denervation (Table 1)[9]. With a class IIb level of recommendation C these guidelines affirmed that invasive procedures, such as denervation and baroreceptor stimulation, "may be considered" in case of ineffectiveness of drug treatment[9]. In other words, it was explicitly acknowledged that the evidence supporting usefulness/efficacy of these therapies was not well established by evidence/opinion (Class IIb), and that the level of evidence depended on consensus of experts, and/or small studies, retrospective studies and/or registries (Level of evidence C).

Of further importance, with a class I level C the ESC/ESH guidelines recommended that "these procedures remain in the hands of experienced operators and diagnosis and follow-up restricted to hypertension centers". It was further emphasized that these invasive approaches were to be "considered only for truly resistant hypertension".

In March 2014, the scenario changed again with the publication of the first randomized single-blinded, sham-controlled study on renal denervation, the Simplicity HTN-3. While conclusively proving the safety of renal denervation in experienced hands, this study failed on one of its primary endpoints, *e.g.,* the demonstration that renal denervation was more effective than a "sham" procedure in effectively lowering BP[10]. After the publication of this study, the results of a smaller multicenter French study, the DENERHTN[11], added further fuel to the debate. According to this study, when given on top of a carefully planned stepped pharmacologic treatment, renal denervation provided almost identical BP values as placebo at 6 mo follow-up, although the fall of BP, both systolic and diastolic, was greater in the renal denervation arm. However, this was apparently only because the patients in this group had slightly higher baseline values, suggesting the possibility of a "regression toward the mean" effect[11], and raising

questions about the effectiveness of renal denervation in lowering BP. According to the plot depicting the individual BP changes, some patients did show a marked BP reduction and others showed no BP fall whatsoever.

At about the same time, the Prague study[12] also found no evidence for superiority of renal denervation over medical therapy. In this study the patients were randomized to either a multidrug treatment comprising the mineralocorticoid antagonist spironolactone, or to renal denervation. The BP values at 6 mo follow-up were similar in the renal denervation and medical treatment arm. While the long-term results of this study are still awaited, it seems fair to say that it remains to be conclusively proven that renal denervation entails an all-round treatment for all patients with truly resistant hypertension. A head-to-head comparison of BAT and renal denervation is shown in Table 2.

Table 2 Similarities and differences between renal denervation and baroreceptor activation therapy

Features	Renal denervation	BAT
SNS	↓	↓
Invasive	Yes	Yes
Safe	Yes[1]	Yes[1]
BP short-term	↓	↓
BP long-term	?	?
Side	Bilateral	Monolateral
Evidence of success	Delay	Immediate
Reversible	No	Yes
Heart rate effect	↓	↓↓
Metabolic effect	Yes	?
Need for follow-up	Yes	Yes
Logistics[2]	+	+++
Costs	+	+++

SNS: Sympathetic nervous system; BP: Blood pressure; BAT: Baroreceptor activation therapy; [1]Complications rate < 3%; [2]Interventional Radiology *vs* Vascular surgery.

The challenges of proving effectiveness of treatments for resistant hypertension

There is no question that the diagnosis of true drug-resistant hypertension is a difficult one, particularly out of tertiary referral centers, *e.g.,* centers where all diagnostic tools cannot be available[12]. Of note, in the patients initially selected at the French specialized centers that participated in the DENEHRT study, about 50% were excluded because of secondary HT, a rate that is remarkably higher than commonly perceived. This observation suggests that out of the hypertension referral centers under detection of secondary forms of hypertension is a diffuse phenomenon, which recognizes several causes. Nevertheless, the high exclusion rate due to secondary hypertension in the French Study indicates that, in keeping with the guidelines, any invasive procedures for the treatment of HT should be restricted to the centers that are competent in reliably rule out secondary forms of HT. This is not an easy task in patients who are resistant to drug treatment for a very simple reason: these patients are, by definition, on multiple drugs; moreover, they can carry multiple conditions that affect renin-angiotensin-aldosterone system. Thereby, the measurements of renin and aldosterone, the two key biomarkers for the identification of the most common forms of secondary HT, *e.g.,* primary aldosteronism and renovascular hypertension, can be markedly biased. In most cases this problem can hamper the diagnosis.

The current place of BAT

Nowadays BAT devices allow switching on and off the implanted device; therefore, it provides the ideal within-patient design for assessment of the effect on BP. By such strategy the BP-lowering efficacy of BAT has been proven beyond any doubts[13]. Moreover, these features also allowed the demonstration that the effects of BAT are reversible and reproducible over time. Of much importance for the patients with resistant hypertension, who had a BP that was not controlled after renal denervation[14], BAT was shown to work well, albeit only in small subsets of patients.

Finally, BAT can be used in patients who have contra-indications to renal denervation because of unsuitable renal anatomy, previous renal endovascular treatment and/or impaired glomerular filtration rate. These advantages have to be weighed against its invasiveness, which however, has been diminished by the development of the smaller 2nd generation devices, and, more importantly, by the demonstration that unilateral BAT is not inferior to bilateral BAT at least for lowering BP[13]. Decreased invasiveness of the implantation, alongside improved experience of the surgeon and the medical team, will likely result into fewer complications and shorter hospital stay, thus decreasing the costs and increasing the acceptance of the BAT.

Technical aspects: Implantation technique

The system for delivering BAT consists of a carotid sinus lead and a pulse generator. Implantation of the pulse generator is generally performed by a vascular surgeon experienced in a subcutaneous infra-clavicular chest wall pocket, in the fashion of a pacemaker. Electrode implantation is also performed at the same time by a vascular surgeon experienced in carotid artery revascularization by surgical exposure of the carotid sinus through a transverse cervicotomy over the carotid bifurcation. The sinus region is then mapped by temporarily placing the electrode in various locations and applying electrical stimulation to determine the location with the greatest sensitivity to BAT. Sensitivity is measured by observing the hemodynamic changes, *e.g.,* reduction of heart rate and/or BP, associated with increased parasympathetic and/or decreased sympathetic nerve traffic. The electrode is then affixed to the sinus, while the opposite end of the lead is brought to the pulse generator pocket by means of a subcutaneous tunnel[15].

BAT dose is up-titrated over a series of follow-up

visits, much like medications are up-titrated; therapy is initiated at a moderate level in the absence of side effects, then therapy levels are uptitrated as long as the patient can tolerate it, with the objective of achieving full BP lowering at around 3 mo. Because the electrode-baroreceptor interface is unique to each patient, there is no standard dose of the therapy; the focus is therefore to tailor BAT to each individual patient to achieving a therapeutic dose in the absence of side effects[15].

Disadvantages and limitations of BAT

From what presented thus far, it might seem that BAT is the ideal treatment for all patients, but this is likely not the case, in that, as for all new techniques the initial studies aimed at proving the concept, should be followed by larger prospective multicentre studies in order to prove the effectiveness in the long-term control of arterial hypertension and, moreover, in the prevention of cardiovascular events and the improvement of survival. Overall, the main limitations of BAT entails its logistics requirements: The invasive nature of the procedure, the need for a vascular surgery unit, for general anesthesia, and of an outpatient clinic for periodical follow-up visits in order to check and replace generator battery, and/or timely determine if a possible device failure occurred. Finally, the costs, definitely higher than those of renal denervation, render BAT a therapeutic option to be reserved only for few very well selected patients.

CONCLUSION

Available accumulating data indicate that BAT is effective and safe. However, patients are required to follow the precautions that are mandatory for all those with implantable devices, and to stay in contact with the hypertension center for regular check-up and monitoring of the battery status. While these disadvantages can be easily overcome with proper logistic arrangements, whether BAT can reduce CV events in the long run is the key question that could only be answered with a large international multicenter study. What control group would be suitable and ethically acceptable to this end is a critical issue that also needs to be addressed.

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