Chapter 8
Novel Baroreceptor Activation Therapy

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Introduction

Hypertension still is a leading cause of cardiovascular complications. Apart from stroke and coronary artery disease, impairment of renal function is a well-known sequel of the hypertensive process. Indeed, hypertension accounts for at least one quarter to one third of all patients coming to dialysis. Over the past 50 years, numerous trials have shown that antihypertensive treatment reduces the risk of complications although the magnitude of the effect differs somewhat for the various forms of organ damage. It seems as if lowering the pressure has a greater impact on the cerebrovascular system than on the kidney. However, it is possible that it takes a longer time to slow down renal deterioration than it takes to protect the brain and that the trials simply have not lasted long enough to show all benefits of treatment.

Whereas it is clear that antihypertensive drug treatment confers substantial benefit in the population at large, there are still many patients in whom blood pressure does not fall or is reduced insufficiently during such treatment. Leaving inadequate blood pressure measurements, white coat hypertension, and problems with adherence as "causes" of ineffective treatment (i.e., pseudo-resistance) aside, true treatment resistance is one of the challenges of contemporary hypertension research. As a matter of fact, true resistance is rare and difficult to define. Admittedly, there is a consensus statement defining the condition [1], but this leaves a lot of room for debate. Indeed, true resistance would imply that a patient does not respond to any antihypertensive drug, whether given alone or in combination with other agents. In reality, however, only a fraction of the available drugs is being tested in a particular patient, and defining resistance as a condition where there is an insufficient response to a combination of three drugs, optimally dosed and containing at least a diuretic, is too simple. Certainly, a better term would be "difficult-to-treat hypertension."

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Pathophysiological Aspects of Difficult-to-Treat Hypertension

Under normal circumstances, the capacity of the body to counteract a rise in pressure is substantial. Accordingly, hypertension must be regarded as a consequence of failing circulatory homeostasis. Two organs have traditionally been linked to the pathogenesis of hypertension: the kidney and the autonomic nervous system. According to Guytonian physiology, hypertension can only persist in the long run when the ability of the kidneys to excrete water and salt is impaired [2]. In other words, if the kidneys for whatever reason fail to appropriately excrete a certain salt load, blood pressure will go up; otherwise, pressure natriuresis in the kidney will get rid of the excess of total body sodium and restore pressure to its initial level. Although the concept has been criticized, a wealth of experimental and clinical data supports this theory.

The autonomic system also has a role in counteracting pressure rises and it does so primarily through the baroreceptor system. An increase in pressure from whatever cause will activate the baroreceptor system, which will then reduce sympathetic outflow and enhance parasympathetic tone. Consequently, blood pressure will return to its original level. For decades, one has believed that this neurogenic mechanism was intended to buffer only acute changes in blood pressure. Nevertheless, several investigators have argued repeatedly that the autonomic system plays an important role in the long-term regulation of blood pressure as well [3].

Clinical trials have shown that treatment with antihypertensive drugs can lower the pressure, although it is often necessary to switch from one drug to another or to combine several agents [4]. This is best explained by the fact that a variety of compensatory mechanisms may counteract or even offset the primary effect of any blood-pressure-lowering drug. As such, virtually all physiological systems with a role in cardiovascular regulation could be involved. Alternatively, structural changes in the cardiovascular system may prevent the drugs to be fully effective. Based on the pressure-natriuresis phenomenon mentioned above, it is also possible that the kidneys respond to a lower pressure by retaining sodium and water in an attempt to bring the pressure back to its level before treatment. This is a form of pseudo-resistance and the reason why one should always administer a diuretic before concluding that a patient is resistant to treatment.

Unless the antihypertensive drugs have a direct effect on the autonomic regulation of blood pressure, the fall in pressure may activate the baroreceptor reflex, which will result in enhanced sympathetic outflow and attenuation of the hypotensive response. Finally, it is conceivable that the set point, i.e., the operating pressure that the kidney and/or the autonomic system try to maintain, is shifted towards a higher value in hypertensive patients (resetting). If that would be the case, the renal and autonomic responses would have to be regarded as appropriate given the higher set point.

In the past, many attempts have been made to modulate these compensatory mechanisms but with only partial success. Recently, however, a new technique has become available, which has made it possible to alter sympathetic outflow by direct

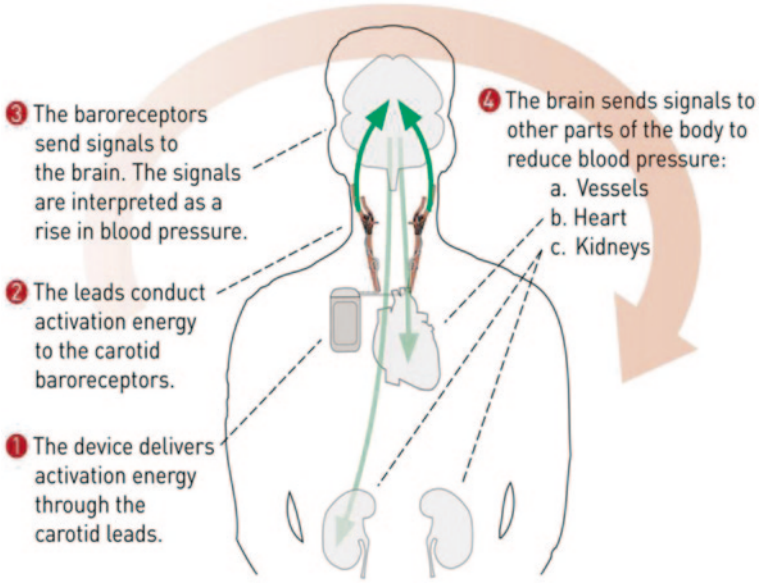

Fig. 8.1 Schematic representation of how baroreceptor activation therapy works. (Courtesy of CVRx Inc.)

stimulation of the baroreceptor area (Fig. 8.1). Currently, this technique is being tested in clinical trials to explore its potential to alleviate the hypertensive burden in patients with treatment resistance.

The Principle of Baroreceptor Activation Therapy

Baroreceptors are located in the aortic arch and at the carotid sinus level. In humans, the carotid and the aortic baroreceptor systems cannot be studied separately unless one of these would be eliminated. Hence, all we know about the functioning of the baroreceptor system in man is based upon the two acting in concert. Nevertheless, it is possible to modulate the input signal at the level of the carotid system only, for instance by applying a positive or negative pressure on the neck by means of a neck chamber. This experimental technique has been very useful to enhance our understanding of the baroreceptor system [5]. Contrary to what is often believed, baroreceptors do not respond to pressure changes but to changes in distension of the vascular wall. In other words, the input signal (a change in transmural pressure) essentially comes from within the vascular lumen. This is also what happens when one applies the neck chamber technique. Baroreceptor activation therapy (BAT), on the other hand, stimulates sensitive elements at the outside of the vascular wall. Indeed, stimulation electrodes are placed at or around the carotid artery at a spot where acute stimulation produces the greatest response. Whether in physiological

terms, the effect of external stimulation is comparable to that of stimulation from within the vessel is presently unknown.

Current devices for BAT stimulate the carotid baroreceptor area only. When one applies BAT, it is necessary to consider several stimulation characteristics during the programming such as start and stop times, ramp function, dose settings, burst settings, pulse amplitude, pulse width, and pulse frequency. In case of bilateral stimulation, this has to be decided on separately for the left and right lead. The most common approach is to set the voltage and the frequency depending on the prevailing level of blood pressure and heart rate and the patient's response to stimulation. Sometimes it is necessary to use different settings during daytime and nighttime. At any rate, it is a matter of trial and error to find the optimal settings in a particular patient.

Another important question is whether one should stimulate the baroreceptor area at both sides or unilaterally. Early data in animals suggested that unilateral stimulation with a bipolar electrode which was attached directly to the carotid sinus nerve was sufficient to reduce blood pressure [6]. In man, studies with BAT initially involved bilateral stimulation but the most recent device has been developed for unilateral stimulation only. Preliminary data indicate that stimulation at one side is indeed as effective as bilateral stimulation [7].

Baroreceptor Activation Therapy in Man

The idea behind BAT in hypertension is not novel as the technique was already applied some 50 years ago. However, at that time, technology was not yet ready for introduction on a wider scale into the clinic. Short-term observations in a limited number of patients confirmed that BAT could reduce blood pressure and heart rate but long-term data yielded equivocal results. No randomized controlled trials with the devices have been done at that time so that the true value of the technique remained enigmatic. Due to the introduction of a variety of antihypertensive drugs that were well tolerated, there was less and less need for invasive procedures and the further development of devices for BAT was considerably delayed for a long period of time.

Since the beginning of the twenty-first century, new devices with improved technology are available. So far, the most important of these and the ones that have been tested clinically are the Rheos™ Baroreflex Hypertension Therapy System and its successor, the Barostim *neo*™ device. These are open-loop systems with electrodes that are attached surgically to the carotid artery at close proximity to the bifurcation. While the Rheos device still worked through bilateral stimulation, the other one has been designed for unilateral implantation and stimulation. The devices further consist of an implantable pulse generator and an external programmer.

The Rheos device was initially tested intra-operatively in patients who needed elective carotid artery surgery [8]. Baseline blood pressure of these patients was 146 ± 30 mmHg systolic and 66 ± 17 mmHg diastolic. When blood pressure and

heart rate had stabilized, the investigators constructed some kind of dose–response curve by applying incrementally increasing electrical currents. Blood pressure and heart rate fell significantly in a voltage-dependent way by, on average, 23 mmHg systolic and 16 mmHg diastolic. These observations paved the way for application of the device in patients with difficult-to-treat hypertension.

The Device-Based Therapy in Hypertension (DEBuT-HT) Trial was the first multicentre, prospective, nonrandomized feasibility study to assess safety and efficacy of the Rheos system over a period of 3 months in treatment-resistant hypertensive patients [9]. Treatment resistance was defined as a blood pressure equal or above 160/90 mmHg despite treatment with at least three antihypertensive agents, including a diuretic. Secondary hypertension and nonadherence to treatment had to be excluded. Patients who qualified for the study had the baropacer implanted (bilaterally) but to allow undisturbed tissue healing, the device was not activated until 1 month after the surgical procedure. To avoid a confounding effect of medication, drug dosages had to remain constant during the 3 months of the study that the device was on. Altogether, 45 patients entered this trial. Their mean age was 54 years and their blood pressure 179 ± 29 mmHg systolic and 105 ± 22 mmHg diastolic. At the end of the 3-month period with the device on, blood pressure had fallen significantly by an average of 21/12 mmHg. Although a few side effects were noted, by and large the safety profile was favorable [9]. Thus, the study showed that it is possible to lower blood pressure in patients with drug-resistant hypertension by modulating baroreceptor function without major adverse events. It is also very likely that the effectiveness of the device relates to its potential to reduce sympathetic traffic in the body. Indeed, when intra-arterial blood pressure and muscle nerve sympathetic activity (MSNA) were recorded simultaneously in 12 patients who had the baropacing system implanted, electrical stimulation caused a sharp fall not only in pressure but also in MSNA [10]. In the responders, the decrement in pressure correlated with the fall in MSNA. Throughout the stimulation period, MSNA remained below baseline levels. Switching the device off was associated with reversal of these effects.

Several patients who had participated in DEBuT-HT could be followed for a longer period of time. Over the years, they maintained their blood pressure reduction and it was even possible to withdraw some of their medication [11]. However, since DEBuT-HT was an uncontrolled feasibility and proof-of-principle trial, it did not have the power to prove unequivocally that BAT is beneficial in resistant hypertension. Therefore, the Rheos Pivotal Trial was designed as a randomized, double-blind, parallel-design clinical trial comparing immediate and delayed BAT. It included 265 patients with resistant hypertension (average baseline blood pressure 178/103 mmHg) over a period of 6 months who were randomized in a 2:1 ratio to either immediate activation of the device (i.e., 1 month after the implant, group A) or delayed activation (7 months after the implant, group B). Thus, the second, smaller group could be considered as a sham-operated or placebo group in this respect. The trial had five primary outcome variables related to efficacy and safety at 6 months of stimulation [12]. After the 6-month assessment, the baropacer was switched on in patients from group B as well and 6 months later all measurements

were repeated. Although the drop in pressure was numerically greater with the device on, the difference in responder rates between both groups at 6 months was smaller than the prespecified primary efficacy end point of 20 %. Thus, in this randomized trial, baropacing was not more effective than sham operation during a period of 6 months. Possibly, the placebo effect and the effect of participating in a trial were greater than anticipated. Nevertheless, the proportion of patients who reached the goal pressure of 140 mmHg systolic or below (a secondary end point) was greater in group A (42 vs. 24 %; $p<0.005$). Moreover, at 12 months when all patients had the device on, the two groups showed a comparable drop in blood pressure as compared to baseline. No major safety concerns were encountered and only short-term procedure-related adverse events were seen, most of which disappeared after some time [12]. After the formal part of the trial, patients were followed for more than 2 years [13]. The vast majority of these patients continued to exhibit lower blood pressures and among the responders to BAT the number of prescribed medications could be reduced by 1–2 classes.

Recently, the very first results obtained with the newer Barostim *neo* device were published [7]. The trial was a single-arm, open-label study in 30 drug-resistant patients. Interestingly, six patients had previously undergone renal nerve ablation without success. In most patients, the implant was done on the right side. After 6 months, blood pressure had fallen by an average of 26/12 mmHg (baseline blood pressure amounted to 172/100 mmHg). Similar results were obtained in patients with or without prior renal nerve ablation. Although this was again an observational study, the data suggest that with the unilateral device comparable results can be obtained as with the bilateral device. It is also reassuring that intact renal nerves are not a requisite for BAT to exert its effect.

Baroreceptor Activation Therapy and Target Organ Damage

A post hoc analysis of a subgroup of patients, who participated in the DEBuT and US Trials of the Rheos System, showed that left ventricular mass index fell significantly from 139 ± 35 to 108 ± 34 g/m^2 ($p<0.01$) after 1 year of BAT as compared to baseline [14]. Midwall fractional shortening was significantly increased ($p<0.01$) as did left ventricular outflow tract diameter and arterial compliance. Unpublished data also suggest that BAT improves myocardial energy kinetics and diastolic flow velocities. Since no significant correlation was observed between the changes in systolic blood pressure and those in left ventricular mass index, it is possible that BAT not only reduces blood pressure but also induces reverse cardiac remodeling due to interruption of sympathetic traffic to the heart.

As far as kidney function is concerned, long-term data are now available from the pivotal trial [15]. During the initial 6 months of BAT serum creatinine increased significantly in both groups by about 6 %. At 12 months, when the two groups had received BAT for 12 and 6 months, respectively, serum creatinine did not change any

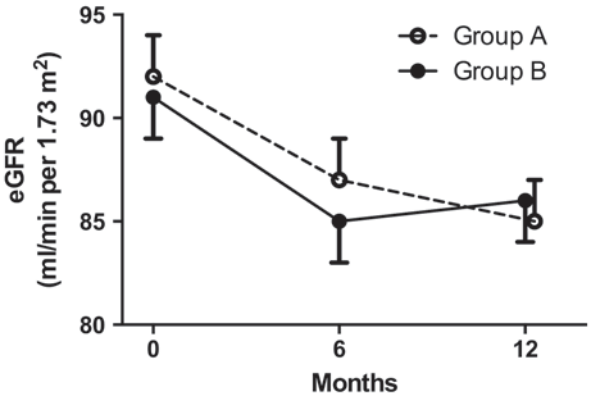

Fig. 8.2 Changes in estimated glomerular filtration rate (*eGFR*) in the pivotal trial. *Group A*, immediate stimulation. *B*, start stimulation 6 months after implant. (Based on data derived from [15])

further but remained significantly increased compared to screening values in both groups. Similar results were found when not serum creatinine but estimated glomerular filtration rate was taken as the dependent variable (Fig. 8.2). The reduction in systolic pressure appeared to be the most significant determinant of the changes in serum creatinine. This suggests a pressure-related hemodynamic phenomenon rather than an intrinsic BAT-related influence on renal function. No significant effects were seen with respect to urinary albumin excretion. Data, which have not yet been published, show that, on average, plasma renin levels do not change during BAT. This may seem odd, as one would expect a decline in renin when sympathetic outflow is reduced. On the other hand, the fall in pressure probably counteracts any fall in renin. Moreover, patients continue to take medication with a possible effect on renin.

At the present time, there is not enough information regarding cerebrovascular changes during BAT.

Conclusions

The available data clearly indicate that BAT is a promising new technique to treat hypertensive patients who are unresponsive to medical treatment. Insofar as the evidence is available, target organ damage is also favorably influenced by BAT. However, in itself, this is insufficient to recommend BAT as a regular form of treatment as it is also necessary that this treatment improves prognosis. Such data do not yet exist.

An area of research that is extremely relevant for the future treatment of drug-resistant hypertension will be a head-to-head comparison of BAT with its competitor: renal denervation [11]. In the few patients in whom renal denervation failed to adequately lower blood pressure, the Barostim *neo*™ still was able to reduce pressure to the same extent as in those without prior renal denervation. Future research must also be directed towards finding the optimal spot to stimulate and to explore whether external stimulation is possible, i.e., without the need to operate.

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