Surgical, Interventional, and Device Innovations in the Management of Hypertension

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Abstract

Keywords

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The prevalence of hypertension around the world has increased significantly with projections for an increasing major global burden of hypertension. Medication-resistant hypertension can be perplexing and frustrating. The existence of these difficult patients results in the need for additional approaches to treatment including surgery, percutaneous interventions, and device management. The sophistication of these techniques has progressed markedly and initial procedures such as classical sympathectomy and renal artery bypass are almost never performed. Newer techniques of angioplasty with stenting, renal artery denervation, and baroreflex activation therapy via electrical stimulation of the carotid baroreceptors are now in use with increasing evidence for significant benefit.

Pooled data of the prevalence of hypertension from different regions of the world from the year 2000 have yielded startling numbers and resulted in projections of a major global burden of hypertension by the year 2025.¹ In 2000, 26.4% (95% confidence interval [CI], 26.0–26.8%) of the adult population had hypertension, involving 26.6% of men (95% CI, 26.0–27.2%), and 26.1% of women (95% CI, 25.5–26.6%). The estimated total number of hypertensive adults in 2000 was 972 million, with 333 million in economically developed countries, and 639 million in developing countries. For the year 2025, it is estimated that there will be a 60% increase in the prevalence of hypertension with a total of 1.56 billion adult hypertensive patients (►Fig. 1). Such data from Kearney et al¹ emphasize the clinical and public health challenges of this major cardiovascular (CV) disease. Although some patients can improve their blood pressure (BP) by diet and exercise, medical treatment is the approach used in the majority of patients. However, there exists an extreme patient group that does not respond to a medical approach, and this is where surgical and device innovations play a major role in care.

Prevalence, Treatment, and Control of Hypertension

During the years 2005 to 2008, 31% of United States adults who were 18 years or older (~68 million individuals) had hypertension, with no improvement noted in the past decade.² Of these 68 million adults, 48 million (70%) were receiving some medical treatment, but only 31 million (or 46%) of those affected had achieved good control of their BP. One notable observation is that even though the prevalence of hypertension did not change from the period of 1999 to 2002 to the period of 2005 to 2008, there was some improvement in treatment and control. If optimum BP control were the norm, almost two-thirds of all strokes and one-half of all myocardial infarctions could be prevented, as estimated by the Canadian Hypertension Education Program, a country-wide attempt to improve the limited impact of traditional hypertension guidelines.³ However, even in such a publicly funded health care system with medication costs subsidized, only a minority of hypertensive individuals achieve target BPs. A recent goal in Canada is to decrease prevalence of

Fig. 1 Number of people with hypertension aged ≥ 20 years by gender and by world region in 2000 (upper panel) and projections for 2025 (lower panel). Adapted with permission from Kearney et al.¹

hypertension to 13% of adults and increase hypertension control to 78%.⁴

Control of BP around the world shows wide variability and never an overall ideal control. From Latin America and the Caribbean for the 10 years before 2012 as estimated in peer-reviewed literature, there is a prevalence of hypertension from 7 to 49%. Such studies were predominantly from urban centers and reflect an inadequate assessment.⁵ Other samples of hypertension prevalence include a 52.1 to 58.7% prevalence in Lithuanian men from 1983 to 2002,⁶ a prevalence range for hypertension in Ghana from 19 to 48% during 1996 to 2008,⁷ and a 50% prevalence for men older than 55 years of age in Iran during 1996 to 2004.⁸

Hypertension Guidelines and Screening

End-organ damage associated with hypertension can be detected early and accurately, which mirrors the CV risk of the hypertensive patient.⁹ Treatment of this end-organ damage focuses on reduction of the BP and blockade of the renin-angiotensin-aldosterone system and is essential to diminish early end-organ damage. When CV risk is markedly increased, as in the case of hypertensive patients with diabetes mellitus (DM) and coronary heart disease, tight control of systolic BP is associated with improved CV outcomes, as compared with usual control.¹⁰ With this type of evidence, guidelines have been established such as the Seventh Joint National Committee on Prevention, Detection, Evaluation,

and Treatment of High Blood Pressure (JNC-7).¹¹ Ideal BP is considered to be less than 120/80 mm Hg (and beginning at 115/75 mm Hg); CV risk then doubles with every BP increment of 20/10 mm Hg.

Screening for hypertension is an essential part of making guidelines practical. In general, screening for all adults is recommended and when low-cost therapy is used, there is a very favorable cost-effectiveness resulting from BP screening.¹² On the contrary, there is no direct evidence that screening for hypertension in children and adolescents improves adverse CV outcomes. Further study is essential to improve diagnosis and risk stratification of children with hypertension and to assess the risk and benefit of such treatment.¹³

The Medical Management of Hypertension

The medical management of hypertension can start with a diet such as the Dietary Approach to Stop Hypertension (DASH) diet which emphasizes vegetables, fruits, and low-fat dairy products and has been shown to be effective in lowering BP in the presence of high, intermediate, and low sodium intake.¹⁴ Various lifestyle interventions have also been shown to yield modest benefit for reducing BP.¹⁵ Medications not used to manage CV disease can occasionally be a cause of hypertension but are usually not much of a consideration. However, a comment about bevacizumab used in the treatment of cancer is worthy of mention. Bevacizumab is an

angiogenesis inhibitor with a fairly wide use in cancer therapy. From a review and meta-analysis of published, randomized-controlled trials, Ranpura et al found that the increased risk for high-grade hypertension with bevacizumab at a dose of 2.5 mg/kg/week showed a relative risk (RR) of 4.78 (95% CI, 3.59–6.36) and a 5 mg/kg/week dose demonstrated RR = 5.39 (95% CI, 3.68–7.90). The severity of hypertension associated with bevacizumab was increased with certain tumor types with mesothelioma especially significant. Monitoring of such patients is an essential part of the medical management of BP¹⁶ and this medication should be adjusted and/or changed should significant hypertension occur with its use.

In a review of first-line antihypertensive drug classes, including thiazides, β blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, α blockers, and angiotensin II receptor blockers, Wright and Musini analyzed outcomes and found that first-line, low-dose thiazides decreased all morbidity and mortality outcomes.¹⁷ First-line ACE inhibitors and calcium channel blockers appeared to be similarly effective but with less robust evidence. First-line high-dose thiazides and first-line β blockers were inferior to first-line low-dose thiazides.¹⁷ A relatively new medication, aliskiren, which is an oral renin inhibitor, has been shown to provide additional significant antihypertensive efficacy and have no rebound effects on BP in the case of withdrawal of the medication.¹⁸ Not all new medicines make such a contribution to care.

Medication-resistant hypertension can be perplexing and frustrating; its presence is a major factor in the need for additional approaches to treatment including surgery, percutaneous interventions, and devices. There is an increased occurrence of hyperaldosteronism in patients with resistant hypertension, which may be a factor¹⁹; hyperaldosteronism may also lead to associated obstructive sleep apnea.

Early History of Invasive Approaches to Hypertension

Total surgical sympathectomy and its effect on BP in dogs has been described as early as the 1930s.²⁰ Radical lumbo-dorsal sympathectomy was developed by Reginald Smithwick in the 1940s.²¹ He subsequently published a report on a large series of hypertensive patients undergoing sympathectomy, which demonstrated a significant improvement in BP control and in 5-year survival compared with those

treated medically.²² However, surgical sympathectomy was associated with significant operative morbidity and mortality. Another now almost-abandoned surgical procedure is renal artery bypass,²³ which has given way to percutaneous techniques.

Invasive Treatment of Hypertension

Current Surgical Approaches

The more radical open surgical procedures of the past that were involved in the management of hypertension have generally been replaced with minimally invasive techniques (►Table 1). An example is the evolution in the invasive surgical management of the hypertension associated with coarctation of the aorta. Basic coarctation of the aorta represents 5 to 7% of congenital heart disease.²⁴ Until the development of balloon angioplasty in the 1980s as an alternate management strategy for coarctation, open surgical treatment was all that was available. Balloon angioplasty does not yield better results over the long term and may increase the incidence of aneurysm formation. Stewart et al studied a group of 149 surgical repairs of coarctation, 42 of whom ultimately came in for followup examination.²⁵ Of the 42 postsurgical patients, 29 (69%) had developed a CV complication. There was no previously unrecognized major recoarctation, but 19 (46%) had hypertension and 7 (16%) had enlargement of the aortic root or arch and these tended to be those with surgery at an older age. Stewart et al emphasized the high incidence of late morbidity despite good integrity of the surgery and indicated the importance for long-term follow-up.²⁵ Walhout et al compared 18 surgical coarctation patients, age 0.30 to 14 years, median 0.63 years versus 28 balloon angioplasty coarctation patients, age 0.25 to 15 years, median 5.8 years.²⁶ Mean follow-up was 7.2 ± 2.4 years postsurgical and 5.4 ± 2.8 years for angioplasty. The authors noted immediate success for all postsurgical patients and in 27 of 28 angioplasty patients regarding a decrease in pressure gradient and there was no mortality. Subsequent recoarctation was noted in one surgical patient and in two angioplasty patients and aneurysm was not noted. In an independent Cochrane Database review, Pádua et al found insufficient evidence for a preference of surgical repair versus angioplasty and emphasized the importance of performing a randomized-controlled clinical trial.²⁷ In contrast, Wong et al in 2008 reviewed articles reporting treatment outcomes of coarctation from 1984 until 2005 and determined the

Table 1 Invasive treatment of hypertension

Open surgical repair of coarctation	Good initial results with significant long-term problems ^{24,27}
Balloon angioplasty of coarctation	Good initial results with significant long-term problems ^{24,27}
Adrenalectomy, usually performed by laparoscopy	Promising initial results but long-term evaluation essential ³¹
Renal artery stenting	Appears beneficial with renal dysfunction but other results are disappointing ³⁹
Renal artery denervation	Some promising results but still unproven ⁴³
Rheos carotid baroreceptor activation therapy	Some blood pressure decrease and reduced need for medications ⁵¹

baseline probabilities of success, complications, recoarctation, and formation of an aneurysm.²⁸ These authors reported that balloon angioplasty had a final mean preference score of 0.8999 with standard deviation of 0.0236, significantly higher than for surgery with a mean of 0.8873 with standard deviation of 0.0246. Looking at these reported numbers actually appears to emphasize even more the need for a randomized trial. Hypertension remains a common and significant problem following surgical repair of coarctation. Canniffe et al, after reviewing 26 full text articles, found a median prevalence of hypertension late after successful repair to have a median prevalence of 32.5% with range 25 to 68%.²⁹ On the contrary, Vohra et al ultimately assessed 11 articles on surgical repair which showed a consistent immediate postoperative BP on a consistent basis with the majority of patients normotensive and the others with decreased need for antihypertensive medications.³⁰ In summary, surgical repair or angioplasty of significant coarctation of the aorta are indicated but the results are far from ideal.

Adrenalectomy as a surgical approach to hypertension is now mainly involved with hormonally active adrenal masses. Such adrenalectomy is the standard of care for these adrenal masses which include as pheochromocytoma and hyperaldosteronism from aldosterone-producing adenomas.³¹ Minimally invasive techniques now dominate and laparoscopic partial adrenalectomy, when feasible and based on the pathologic anatomy, can spare patients from the requirement of chronic steroid replacement, especially important in patients with bilateral benign adrenal tumors, or a solitary adrenal gland.

Current Interventional Approaches

Renal artery angioplasty/stenting: Renal artery angioplasty alone was first performed by Gruntzig in 1978.³² Today, the routine use of stents has increased technical success rates compared with angioplasty alone and as previously noted, surgery is now rarely performed.³² Nevertheless, there are those proponents of surgery who question the predominance of endovascular intervention in atherosclerotic renal artery stenosis (RAS) and advance the need for randomized trials.³³ In addition, even though many case series have claimed benefit for BP control, no randomized, controlled, prospective evaluation of renal artery intervention has defined the effect on CV morbidity or mortality.³² In patients with RAS from fibromuscular disease, medical management appears less effective than a procedural approach, whereas the data may be less consistent with atherosclerotic disease.³⁴ With the use of percutaneous techniques, renal artery revascularization for treatment of atherosclerotic RAS has increased markedly. Currently accepted indications are significant RAS with progressive or acute deterioration of renal function, severe hypertension that is uncontrollable, decline in renal function in the presence of medications that block the renin-angiotensin system, and recurrent flash pulmonary edema.³⁵ Also, percutaneous renal revascularization, in addition to medical therapy for RAS, may decrease the intensive use of antihypertensive medications.³⁶ Although it appears that revascularization with stenting for RAS versus medical management

is yet to be resolved,³⁷ RAS causing renal dysfunction can be safely managed with endovascular stenting and a rapid decrease in renal function is associated with a positive response to stenting. This appears to be key in identifying patients for renal salvage.³⁸ Unfortunately, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study just published found that the addition of renal artery stenting did not result in significant benefit regarding prevention of clinical events when compared with comprehensive, multifactorial medical therapy alone.³⁹ The CORAL study involved 947 patients with atherosclerotic RAS and either systolic hypertension on two or more antihypertensive medication or chronic kidney disease that were continued on medical management plus placement of a renal artery stent versus management with only medical therapy.

Renal artery denervation: The kidney has been shown to combine blood volume regulation with maintenance of a balance of sodium and water by mechanisms of natriuresis and diuresis. When this regulation is abnormal in the presence of a defect in renal excretory function, hypertension can occur as a result of the need for an increase in arterial pressure to offset abnormal natriuresis and diuresis and thereby maintain sodium and water balance.⁴⁰ There is accumulating evidence that an important etiology of the defect in renal excretory function in hypertension results from an increase in renal sympathetic nerve activity (RSNA). There is convincing evidence of an increased RSNA in animal models as well as in humans with hypertension. Furthermore, increased RSNA causes reduced renal excretory function due to effects on the renal vasculature, renal tubules, and the juxtaglomerular cells.⁴⁰ The elevated RSNA appears to be of central nervous system origin, and a possible stimulus could be from angiotensin II. This angiotensin II can act on brain stem nuclei important in the control of peripheral sympathetic vasomotor tone and thereby increase the basal level of RSNA, impairing its arterial baroreflex regulation.

As the role of renal sympathetic nerves as a link between the central sympathetic nervous system and the kidney in the development of hypertension became better understood, the concept of targeting and interrupting signaling through such nerves to control hypertension evolved.⁴⁰ Recognizing the course of these sympathetic nerves in the adventitia of renal arteries meant that they are accessible to the rapidly advancing endovascular techniques, particularly the availability of ablation catheters used in other areas of the CV system.

Of all the catheter-based renal denervation systems the most developed to date are those based on delivery of radio frequency (RF) energy from the luminal aspect of the renal artery, reaching the sympathetic nerve fibers embedded in the adventitia. By creating multiple transmural "lesions," the neural plexus surrounding the renal artery is damaged and the sympathetic signaling is interrupted. The SIMPLICITY-HTN-1 (Medtronic, Minneapolis, MN) is the device that has undergone the most clinical investigation so far (► Fig. 2). This is a unipolar RF delivery catheter with a deflectable tip connected to a generator and a grounding pad. It can be inserted into the renal artery via a 6F introducer and used to

Fig. 2 The Symplicity renal denervation catheter (Medtronic Inc., Minneapolis, MN). This is a unipolar RF catheter with controls for rotation and deflection of the tip (inset). After advancing the catheter into the renal artery, the tip is positioned in contacts with the wall and RF energy is delivered from an external generator. After delivering 5 to 8 W over 120 seconds, the tip is rotated and withdrawn to create a second lesion. Eventually four to six lesions are created in a spiral distribution to complete the process of denervation.

create multiple RF lesions within each renal artery in a helical fashion. The generator display provides continuous monitoring of resistance (indicating contact with the wall), energy delivered, and temperature at the tip of the catheter.

After extensive and successful swine experiments demonstrating the impact of renal denervation on RSNA and BP, a clinical proof-of-concept study was conducted using the Symplicity catheter in 50 patients, who were then followed for 1 year.⁴¹ With evidence of significant reduction in BP and safety of the procedure, investigations continued and a series of 153 patients with resistant hypertension were enrolled in the Renal Sympathetic Denervation in Patients with Treatment-Resistant Hypertension SIMPLICITY-HTN-2 study.⁴² Postprocedure office BPs were reduced by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg at 1, 3, 6, 12, 18, and 24 months, respectively ($p < 0.01$ compared with baseline BP at all time points). Procedural complications were infrequent and there were no long-term consequences. In addition to providing further evidence of efficacy, this observational study extended the follow-up to 2 years, which also demonstrated the durability of the initial result. A significant number of SIMPLICITY-HTN-2 patients have now been followed up for 3 years, with persistence of the favorable effect on BP seen early after the procedure.

The SIMPLICITY-HTN-3 study was a multicenter, randomized, controlled trial of renal denervation in 106 patients with resistant hypertension in 24 centers in Australia and Europe. The primary effectiveness end point was a change in office measurement of systolic BP at 6 months. In the renal denervation group, BP measurements were reduced by 32/12 mm Hg ($\pm 23/11$ standard deviation, $p < 0.0001$), whereas they did not differ from baseline in the control group (change of 1/0 mm Hg $\pm 21/10$, $p = 0.77$ systolic and $p = 0.83$ diastolic). At 6 months, 41 (84%) of 49 patients who underwent renal

denervation had a reduction in systolic BP of 10 mm Hg or more, compared with 18 (35%) of 51 controls ($p < 0.0001$). While such results demonstrated excellent efficacy, it was also very important that there was no report of any serious adverse events related to the denervation therapy.⁴³ The study patients were followed up for an additional 6 months, with those receiving placebo therapy at the onset allowed to crossover to active therapy at the end of the first 6 months (**Fig. 3**). At 12 months after the procedure, the mean fall in office systolic BP in the initial renal denervation group (-28.1 mm Hg; 95% CI, -35.4 to -20.7 ; $p < 0.001$) was similar to the 6-month fall (-31.7 mm Hg; 95% CI, -38.3 to -25.0 ; $p = 0.16$ vs. 6-month change). The mean systolic BP of the crossover group 6 months after the procedure was significantly lowered (from 190.0 ± 19.6 to 166.3 ± 24.7 mm Hg; change, -23.7 ± 27.5 ; $p < 0.001$). The crossover group included one procedure-related complication.⁴⁴

SIMPLICITY program is designed in a similar fashion, but intended to be the pivotal trial for approval of the device in the United States. It is designed as a prospective, randomized, masked procedure, single-blind trial evaluating the safety and effectiveness of catheter-based bilateral renal denervation for the treatment of uncontrolled hypertension, despite compliance with at least three antihypertensive medications of different classes (at least one of which is a diuretic) at maximal tolerable doses. The primary effectiveness end point is measured as the change in office-based systolic BP from baseline to 6 months.⁴⁵ The study enrolled 530 patients who were randomized in a 2:1 fashion, favoring denervation. The one-third of patients who underwent a sham procedure at entry will be allowed to crossover to receive active denervation at 6 months. Enrollment has been completed and follow-up is ongoing with still much data to be analyzed. Unfortunately, there is now some concern regarding the status of Symplicity HTN-3 since it appears to have

Fig. 3 Six and 12 months change in office-based blood pressure seen in Symplicity HTN-2 trial. Both the initial renal denervation (RDN) group and the crossover group denervated at 6 months after randomization experienced significant drops in systolic blood pressure (SBP) and diastolic blood pressure (DBP). A $p < 0.001$ for SBP and DBP change after renal denervation; $p = 0.025$ for SBP change from baseline; and $p = 0.055$ for DBP change from baseline for the crossover group before denervation at 6 months. Adapted with permission from Esler et al.⁴⁴

failed to achieve its primary efficacy end point.⁴⁶ The company involved, Medtronic, Inc., plans to meet with all involved on the future of the SIMPLICITY-HTN-4 program and has stated that it plans to suspend enrollment in SIMPLICITY-HTN-4.

Numerous other ablation devices have been in various stages of development over the past several years.⁴⁷ The goal of second-generation devices is to continue to demonstrate efficacy and safety, while making the procedure easier to perform, for example, by reducing procedure time, radiation exposure, and flank pain experienced by most patients during denervation. Several of the newer devices have been undergoing clinical testing in Europe and Australia. Most of the new devices continue to use RF energy to create the transmural renal artery lesions, although additional and more innovative devices are based on delivering other forms of energy for ablation. The RF-based devices include an ablation catheter

with a basket-like deflectable tip that has four electrodes for simultaneous contact and energy delivery to the arterial wall (EnligHTN multielectrode renal denervation system, St. Jude Medical, Minneapolis, MN) (► **Fig. 4**) and a denervation balloon with multiple bipolar electrodes on its surface (Vessix Denervation System, Boston Scientific Corp., Natick, MA). The OneShot RF catheter from Covidien Inc. (Mansfield, MA) is another balloon device with a helical electrode on its outer surface and with tip irrigation to reduce heat generation. Other investigators have used standard electrophysiology RF ablation catheters in the renal arteries with evidence of successful denervation.

Other more innovative catheters depend on delivery of ultrasound energy to cause nerve fiber damage. These include the PARADISE denervation system (ReCor Medical Inc., Ronkonkoma, NY) which comprises an ultrasonic transducer

Fig. 4 The EnligHTN catheter (St. Jude Medical Inc., St. Paul, MN) has four electrodes distributed over a basket-like catheter tip (left). As the catheter is placed in the renal artery (right), the basket design and the multiple electrodes all for simultaneous energy delivery to four sites along the endoluminal surface of the artery, which reduces treatment time significantly. The basket is available in two sizes to allow treating renal arteries of varying diameters and has been approved for use in Europe since 2012.

that is centered in the renal artery lumen with the aid of a balloon catheter. The transducer delivers energy circumferentially to ablate the renal sympathetic nerves. The ultrasonic sound waves emitted from the central core of the balloon produce frictional heating of soft tissues outside of the artery while the fluid-filled balloon cools the endoluminal surface of the artery. Another emerging approach is that of pharmacologic ablation using local directed-delivery systems. An example of such technology is the Bullfrog microinfusion catheter (Mercator MedSystems Inc., San Leandro, CA) which is equipped with a microneedle and protective balloon system. As the balloon catheter is positioned and inflated within the renal artery, the needle becomes unsheathed and penetrates the vessel wall, allowing for perivascular delivery of the therapeutic agent.

Recently, a meta-analysis of several randomized and non-randomized trials of renal denervation was published in an effort to provide an overview of all the ongoing clinical research, and to overcome the small number of patients included in each of the individual studies.⁴⁸ In controlled studies (two randomized and one observational study with a control group), there was a reduction in mean systolic and diastolic BP at 6 months of -28.9 mm Hg and -11.0 mm Hg, respectively, compared with medically treated patients ($p < 0.0001$ for both). In nine uncontrolled observational studies, the 6-month reduction in mean systolic and diastolic BP was -25.0 and -10.0 mm Hg, respectively, compared with predenervation values ($p < 0.00001$ for both). No specific difference could be detected among the used devices and the overall procedural safety was excellent.

These data represented the basis of the consensus statement of the European Society of Cardiology,⁴⁹ which endorsed renal denervation as a therapeutic option in patients with resistant hypertension whose BP cannot be controlled by a combination of lifestyle modification and pharmacological therapy, according to current guidelines. The fact that renal denervation also reduces whole-body sympathetic nerve activity suggests that this therapy may also be benefi-

cial in other clinical states characterized by sympathetic nervous system activation—this may ultimately lead to new indications.

Available Device Approaches to Hypertension

Device approaches to managing hypertension can be simple and noninvasive such as device-guided slow breathing exercises. A specific example (RESPerATE, InterCure Ltd., Lod, Israel) includes a belt-type respiration sensor worn on the clothing.⁵⁰ It is connected to a computerized box that generates musical patterns listened to through earphones. The patient is interactively guided to slow their breathing with a relatively prolonged expiration by synthesis to real-time musical patterns with differentiated inspiration and expiration sounds. The patient voluntarily slows breathing, inhaling, and exhaling in synchrony with the musical sounds. There is an associated relaxation and a reduction in hypertension.

The Rheos Pivotal Trial (Rheos Hypertension Therapy System CVRx, Inc., Minneapolis, MN) uses a new surgically implantable device designed to administer baroreflex activation therapy (BAT) via electrical stimulation of the carotid baroreceptors (▶ Fig. 5).⁵¹ Stimulation of baroreceptors sends impulses to the hind brain, and as a consequence, the vasomotor center is stimulated, resulting in vasodilation. Also, there is resultant vagal stimulation resulting in bradycardia. This stimulus also increases diuresis and natriuresis via the kidney. It appears that BAT favorably alters sympathovagal balance that is frequently abnormal in patients with resistant hypertension. In a double-blind trial of 265 patients with the device implanted and randomized 2:1 at 1 month after implantation, it appeared that after 12 months there was more than a 50% success in achieving systolic BP ≤ 140 mm Hg.⁵¹ In subsequent follow-up of the Rheos Pivotal Trial of 322 patients implanted with the device, 245 patients (76%) were clinically significant responders.⁵² Among the long-term

Fig. 5 Baroreceptor activation therapy (BAT) using the Rheos system. This system includes two electrodes implanted in the carotid bulb bilaterally, which are then connected to a subcutaneous pulse generator. BAT can then be accomplished by an external programmer (left panel). In the pivotal trial, and after 6 months, achieving a systolic blood pressure (SBP) < 140 mm Hg was more frequently seen in patients who received BAT after implantation (group A) compared with those in whom electrodes were implanted but BAT was deferred (group B). At 12 months, when both groups were receiving BAT for at least 6 months, there was no difference in the percentage of patients with controlled SBP. Adapted with permission from Bisognano et al.⁵¹

responders receiving BAT, the mean BP decrease was 35/16 mm Hg, medication use was reduced, and 55% achieved goal BPs (< 140 mm Hg; this goal was < 130 mm Hg in DM or kidney disease).⁵² There is another Food and Drug Administration–approved clinical trial with a smaller device and single lead that is in the planning stages, known as the Neo Baroreflex Activation Therapy System.⁵³ This system has been found to be effective in a subset of patients with renal denervation.⁵⁴

Some of the variable and potential problems with baroreflex stimulation need to be considered. It appears that African American men have significantly lower baroreceptor sensitivity stress responses as compared with Caucasian men as described by van Lill et al in a study of 82 African American teachers and 100 Caucasian teachers.⁵⁵ The lower baroreceptor sensitivity stress response may be a significant health risk for development of α -adrenergic-driven hypertension and greater risk for CV disease. Evaluation of their response to BAT would also be relevant and of interest and could reflect variable and adaptive baroreceptor responses. In addition, not all hypertensive patients respond to BAT⁵⁶ and this may also reflect variability and adaptive changes in human baroreflex physiology. In addition, a potential role of cardiopulmonary receptors must be mentioned. Reyes del Paso et al reported on brief respiratory training characterized by breathing at six breaths per minute, time of expiration twice that of inspiration, predominantly abdominal respiration, and with pursed lips as a promising intervention to improve baroreceptor function in hypertension.⁵⁷

Of interest to the consideration of hypertension is that at least two statins, atorvastatin and simvastatin have been shown to increase baroreceptor sensitivity in patients with hypercholesterolemia and systemic arterial hypertension.^{58,59} This may be a beneficial additional effect of statins in such patients.

Conclusion

Resistant hypertension represents a major and frustrating clinical problem. When all reasonable medical therapy has failed and the patient still has clinically significant and organ- and life-threatening hypertension, the availability of procedures that can ameliorate the clinical situation is essential. Renal denervation and BAT appear to offer significant contributions to management of these difficult hypertensive patients and further intensive investigation is warranted.

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