Novel devices

Novel procedure- and device-based strategies in the management of systemic hypertension

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Despite the considerable advances in the treatment of hypertension that have been made over the past few decades, adequate management and control of this condition remains poor, and efforts are ongoing to develop new strategies to improve related outcomes. Novel therapeutic approaches to the management of systemic hypertension fall into two major categories: (i) those that seek to improve blood pressure-lowering efficacy using new therapeutic strategies in addition to standard non-pharmacological and pharmacological approaches and (ii) novel ways to optimize and improve the efficacy and utility of existing therapies. Novel procedure- and device-based strategies to control hypertension include renal sympathetic denervation and baroreflex sensitization. These two techniques will be the focus of the present review.

Keywords   Systemic hypertension • Renal sympathetic denervation • Baroreflex sensitization

Introduction

Systemic hypertension represents a major cardiovascular epidemic in the developed and developing world. Projections out to 2025 suggest that up to 50% of the adult populations of Western countries will meet standard guideline definitions of hypertension[1] and thus require therapeutic intervention, be it non-pharmacological or pharmacological. Hypertension is also a component of many other major co-morbidities contributing to the burden of cardiovascular disease. Based on this public-health epidemic, maximizing effective existing therapeutic strategies is a priority. In addition, development of novel additional approaches to hypertension management is also an urgent goal.

The management of hypertension has advanced considerably over the past few decades, in terms of both the efficacy of available treatments and their safety and tolerability profiles. The question therefore arises as to why new therapeutic approaches are required. Epidemiological studies of hypertension and analysis of completed randomized controlled trials have resulted in a continued lowering of blood pressure (BP) goals for both systolic and diastolic pressure.[2,3] For this reason, monotherapy alone is usually not able to lower BP to these target levels in most patients.

The use of multiple classes of agents within an individual patient has therefore become the norm.

Polypharmacy strategies for the treatment of elevated BP have identified populations of both resistant and difficult-to-treat hypertension. Resistant hypertension (BP above target despite the use of three agents from different classes including a diuretic[4]) and difficult-to-treat hypertension (patients whose pressures fail to get to target for reasons of therapeutic inertia, patient non-compliance, or non-persistence with the assigned therapeutic strategy) continues to grow. Failure to reach target BP levels despite therapeutic intervention leaves patients at risk for the complications of elevated BP. Moreover, chronic use of certain medications has been associated with the development of metabolic complications, such as glucose intolerance, dyslipidaemia, and worsening renal disease.[5] Based on the above, a not inconsiderable proportion of hypertension patients meet formal criteria as being refractory and difficult to treat despite current therapies. Such patients are clearly appropriate for consideration of newer therapeutic approaches.

Combining novel drug-, device-, and procedure-based strategies with improved utilization of existing therapies (including appropriate attention to diet, exercise, and weight control) should result in a major public-health impact on this cardiovascular epidemic.

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This review will focus on novel procedure- and device-based strategies in the management of refractory hypertension. A number of such approaches have been developed. This review will focus on two of the most promising of such approaches: renal sympathetic denervation and baroreceptor sensitization.

Renal sympathetic denervation

The contribution of renal sympathetic efferent and afferent nerve activity towards the development and progression of hypertension has been convincingly demonstrated in both preclinical and human studies involving models of hypertension, myocardial infarction, heart failure, chronic kidney disease, and diabetic nephropathy. Renal sympathetic efferent nerve activity participates in renin release, sodium retention, and reduced renal blood flow (RBF), which in turn contributes to the development and maintenance of hypertension (*Figure 1*).[6] Renal sympathetic afferents are recognized as seminal in conveying central sympathetic drive in patients with both chronic kidney disease and end-stage renal disease (ESRD). Reduction of renal afferent signalling may, therefore, decrease central sympathetic drive and significantly contribute to therapeutic benefits in the treatment of myriad clinical settings associated with a hyper-stimulated adrenergic system. Thus, inhibition of renal sympathetic efferent or afferent nerves (or both) represents an attractive target for the treatment of established hypertension as well as related disorders.

Renal denervation in the management of hypertension has previously been explored in man via surgical nephrectomy, and even radical surgical sympathectomy.[7] Surgical renal denervation has been shown to be an effective means of reducing sympathetic outflow to the kidneys, augmenting natriuresis and diuresis, and reducing renin release, without adversely affecting other functions of the kidney such as glomerular filtration rate (GFR) and RBF. However, these early surgical approaches (e.g. splanchnicectomy) were complicated by severe orthostatic hypotension, impotence,
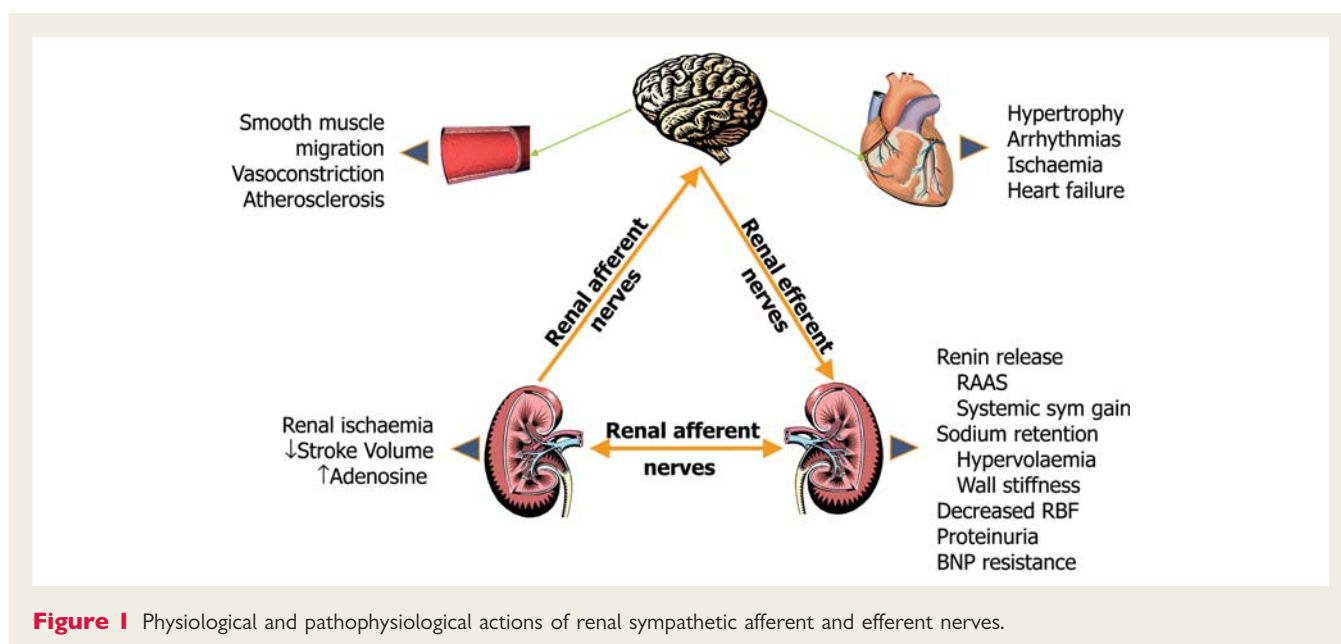
and incontinence (both urinary and faecal).[8] A minimally invasive, catheter-based approach to directly target sympathetic nerves adjacent to the renal artery has therefore been developed in an attempt to overcome the above, surgery-related problems.

Abridging afferent renal sympathetic nerves can reduce central sympathetic drive. Based on this early clinical and pre-clinical work, surgical nephrectomy and renal denervation would appear to be comparable in their impact on central sympathetic tone. Pre-clinical work on rhizotomy of partial nephrectomized rats has demonstrated reduction of BP and hypothalamic noradrenaline production.[9,10] Prior human clinical work has shown that nephrectomy in ESRD patients with renal transplant or on dialysis resulted in reduction of muscle sympathetic nerve activity (MSNA) and calf vascular resistance, confirming the similarity of the physiology.[11]

The renal denervation procedure itself involves femoral artery catheterization, with the tip of the catheter being placed in the distal renal artery. Radiofrequency (RF) energy is then applied to the endothelial lining, the catheter is drawn back 1–2 cm, circumferentially rotated, and a further RF energy is applied. This procedure is repeated 4–5 times in the individual renal artery and then the same RF energy is applied to the contralateral renal artery (*Figure 2*).

An initial first-in-man experience has evaluated the efficacy and safety of this approach in patients with refractory hypertension. Considerable efforts were made in the study regarding appropriate patient selection as well as evaluation of relevant adverse events. Patients recruited in the BP range of 140–180 mmHg (despite three or more antihypertensive drugs, including a diuretic). Renal imaging was undertaken to exclude atherosclerotic renal artery disease prior to catheterization and a contrast renal angiogram performed at the time of catheterization (but pre-procedure) to ensure again that no major renovascular disease was present as well as to exclude dual renal arteries and other anatomical abnormalities.

Substantial and progressive reductions in office BP measurements were observed, beginning at the initial 1-month time point

Figure 1 Physiological and pathophysiological actions of renal sympathetic afferent and efferent nerves.

and continuing out to the final (12 month) visit[12] (*Figure 3*). This was paralleled by significant reductions in ambulatory blood pressure monitoring (ABPM) readings and accompanied by


Figure 2 Percutaneous renal denervation procedure. Graphic of catheter tip in distal renal artery. Reproduced with permission from Ardian Inc.
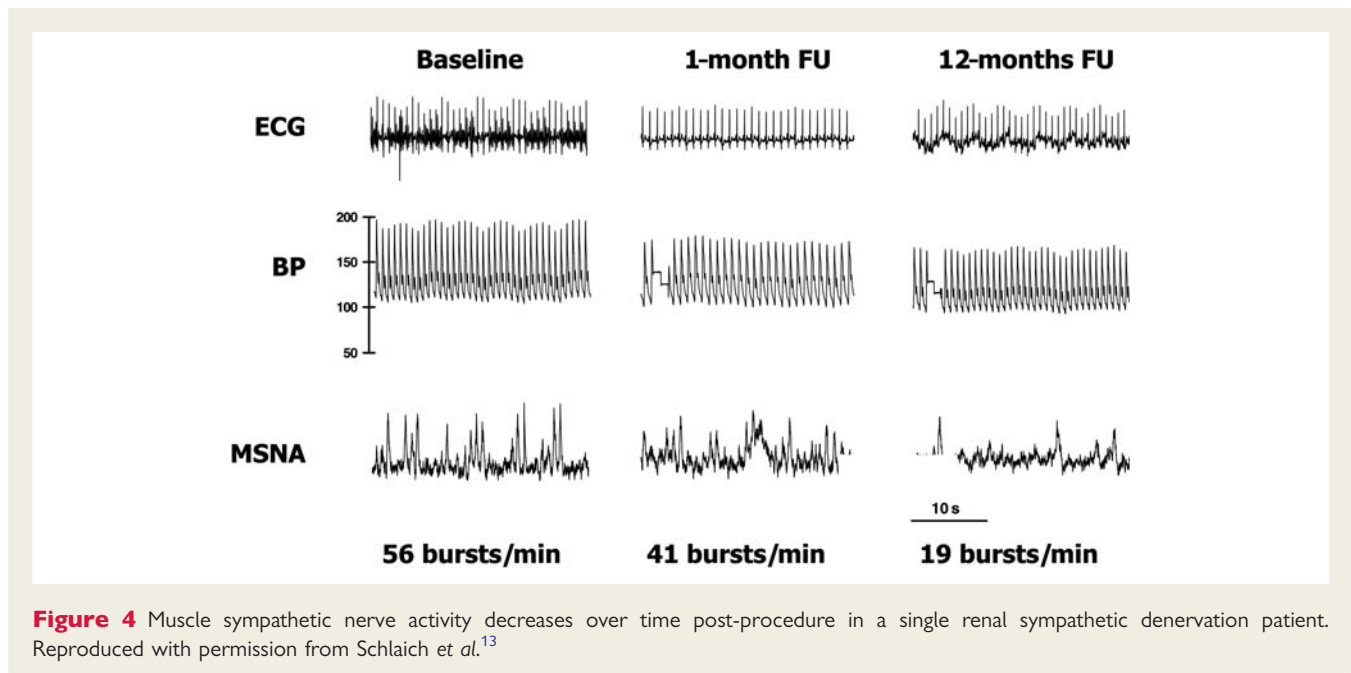
reductions in renal sympathetic activity, as assessed by the organ-specific noradrenaline spillover rate. Furthermore, MSNA studies suggest a reduction in afferent sympathetic activity, i.e. reduced central sympathetic drive[13] (*Figure 4*).

Patients were carefully evaluated for peri-procedural problems. The main problem to emerge at the time of RF energy application was that of loin pain. This was treated with prophylactic use of intravenous analgesia. Potential longer-term complications such as vessel thrombosis have been mitigated with the prophylactic use of aspirin and clopidogrel. Evaluation of development of catheter-related complications to the treated vessel was performed using various angiographic techniques, including computed tomography and magnetic resonance angiography. There was one peri-procedural complication among the initial reported cohort: a renal artery dissection upon placement of the catheter for RF energy delivery in that artery.

In addition to the therapeutic implications of the procedure, renal sympathetic denervation also offers insights into the interaction between central and renal sympathetic drive. The above findings suggest that renal sympathetic afferent and efferent fibres are comingled in an arcade about the renal artery, and ablation results in simultaneous reduction of both pathways as evidenced by the reduction of renal noradrenaline spillover and
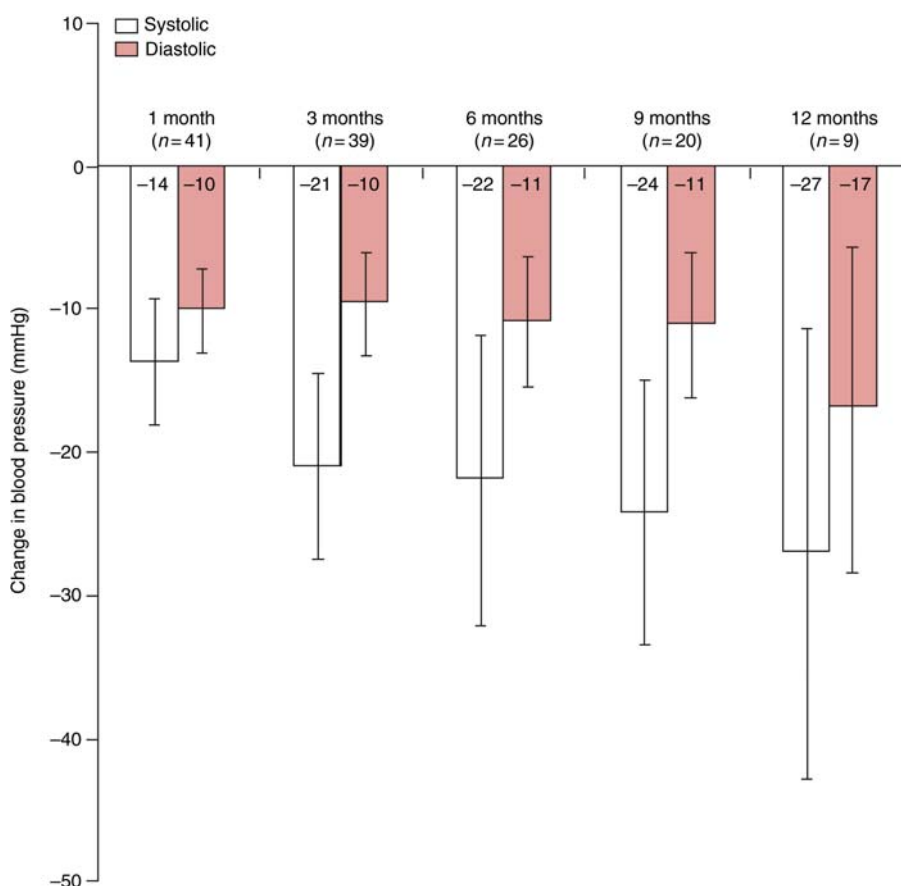
Figure 3 Blood pressure-lowering effects of renal sympathetic denervation. Change from baseline in office blood pressure at 1, 3, 6, 9, and 12 months with 95% confidence intervals. Changes in systolic and diastolic blood pressure were highly statistically significant ($P < 0.001$) at all time points post-procedure, except the 12-month diastolic blood pressure change which was $P = 0.02$. Reproduced with permission from Krum *et al.*[12]

Figure 4 Muscle sympathetic nerve activity decreases over time post-procedure in a single renal sympathetic denervation patient. Reproduced with permission from Schlaich *et al.*[13]

total body noradrenaline spillover. The reduction of renal afferent signalling is additionally expected to reduce efferent sympathetic drive, including that to the kidney itself. Furthermore, a reduction in central sympathetic drive via central integration of altered signalling from the denervated kidney is expected to beneficially influence sympathetic outflow to other organs, with attendant (potential) benefits. These benefits may theoretically include: reduction of insulin resistance, reduction of central sleep apnoea, improvements in perfusion to exercising muscle in heart failure, reduction of left ventricular hypertrophy, reduction of ventricular rates in patients with atrial fibrillation, abrogation of lethal arrhythmias, and slowing of progression of deterioration of renal function in chronic kidney disease. A reduction in renal renin release was also observed in our initial study. Therefore, suppression of renin–angiotensin–aldosterone system (RAAS) activity may be anticipated post-denervation. This may be of particular relevance to diseases characterized by a marked RAAS activation such as chronic heart failure.

A key issue with this RF energy denervation approach is whether anatomical and/or functional re-growth of renal sympathetic nerves occurs, abrogating the BP-lowering benefits observed for 12 months. Such re-growth has been observed in other conditions where sympathetic nerves have been disrupted, such as in organ transplantation.[14] In this regard, longer-term (24 month) data are currently being collected and will be presented soon at major meetings. Maintenance of the BP reduction post-procedure raises hypotheses about resetting of disordered regulatory systems and reversal of vascular remodelling as well as the possibility of continued functional denervation.

A randomized, controlled study in refractory hypertension (Symplicity II) is currently underway. If successful, application of this procedure could be considered for patients with less severe hypertension and for lowering the overall absolute cardiovascular risk.

Baroreflex sensitization

Abnormalities of the baroreflex in the setting of systemic hypertension have long been recognized.[15] Arterial baroreceptors are rapidly reset in response to sustained BP elevations, but they also buffer short-term fluctuations in BP. As BP increases, there is an increase in firing of baroreceptor afferents. However, in the setting of sustained elevations of BP, despite their adjustment, the baroreceptor response diminishes over time and a new threshold for activation becomes established. Thus, baroreceptors become less sensitive to any given change in BP in the chronic hypertension setting. The reasons for this baroreceptor re-setting are complex but may include both peripheral and central contributions.

Based on the above considerations, the concept of re-setting the baroreflex to a lower set point via exogenous stimulation, thus restoring carotid sinus nerve activity, has been a holy grail of hypertension therapeutics for some decades. In animal models, activation of central baroreflex pathways results in the suppression of medullary sympathoexcitatory cells in both acute and chronically hypertensive dogs as well as the inhibition of renal sympathetic nerve activity, thus inducing beneficial effects such as natriuresis as well as sustained reductions in BP and heart rate.[16]

Devices for baroreceptor stimulation have been commercialized and are currently undergoing pre-clinical and clinical testing. The Rheos (CVRx, Minneapolis, MN, USA) implantable carotid sinus stimulator (*Figure 5*) has been studied in patients with severe hypertension refractory to drug therapy.[17] Implantation of Rheos involves both carotid sinuses being surgically exposed and electrodes placed around the carotid adventitial surface bilaterally. The leads are subcutaneously tunnelled and connected to an implantable stimulation device placed in the subclavian subcutaneous position on the anterior chest wall. Electrical baroreflex activation is then initiated on both carotid sinuses simultaneously with
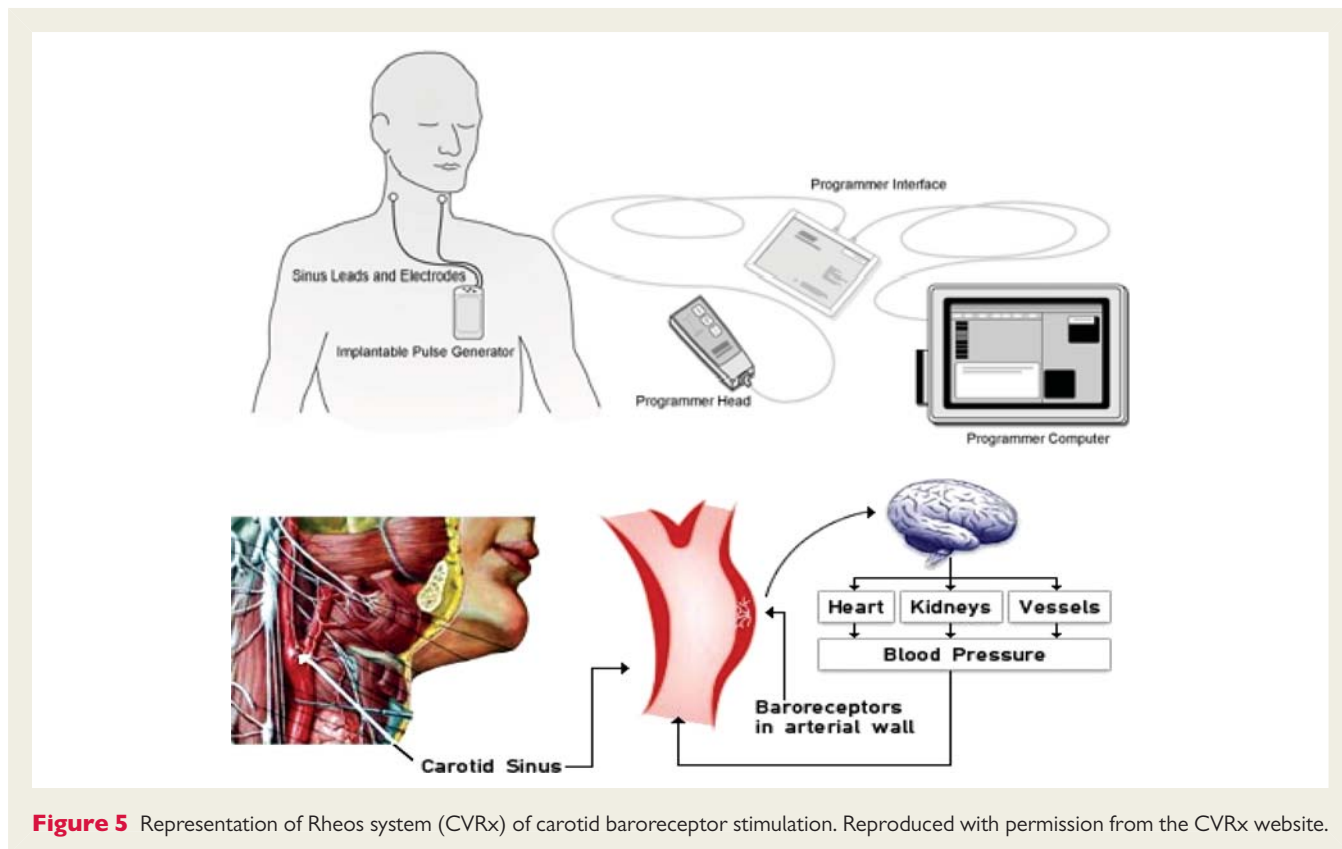
Figure 5 Representation of Rheos system (CVRx) of carotid baroreceptor stimulation. Reproduced with permission from the CVRx website.

incremental voltage increases until the chronic stimulation level is achieved.

An experienced surgeon can perform the operation within 2.5–3 h, but the patient needs hospitalization for a few days for the usual post-operative care. Wound infection may occur but is uncommon in experienced hands. Caution is needed not to harm adjacent nervous tissue as paraesthesias and even tongue paresis have been observed as complications.

In the Baroreflex Activation System Study, 11 normotensive patients who underwent carotid endarterectomy were briefly stimulated under local or general anaesthesia through 1 min incremental intervals.[18] In this study, systolic BP fell from 144 to 131 mmHg, directly related to the intensity of stimulation.

Following these early clinical observations, DEBUT, a multi-centre feasibility study in patients with treatment-resistant hypertension demonstrated a clinically and statistically significant reduction in office BP of over 20 mmHg systolic after 3 months of stimulation in 37 participants. A cohort of 17 participants were followed for up to 3 years, with BP reductions found to be sustained,[19] *Figure 6*. Ambulatory BP measurements have confirmed a decrease in BP during device therapy, with reductions both during daytime and night-time. Recent data indicate that lowering of BP during activation of the device is associated with a reduction of MSNA.[20]

The safety of the procedure to implant the Rheos system needs attention. Altogether, 7 out of 42 subjects experienced a procedure-related adverse event and one a device-related event. There was one case of fatal angioneurotic oedema (cause unknown) a few days after the operation but prior to device activation. Prior to activation three subjects had the device explanted due to infection. Three
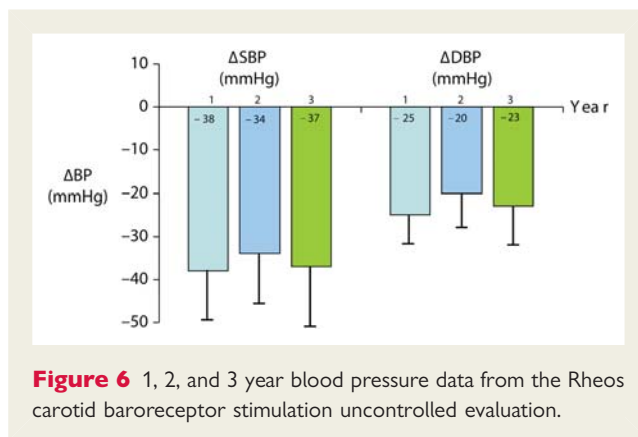

Figure 6 1, 2, and 3 year blood pressure data from the Rheos carotid baroreceptor stimulation uncontrolled evaluation.

additional procedure-related adverse events included: perioperative stroke with minimal residual effects; tongue paresis (no abnormalities on brain magnetic resonance imaging)—most likely due to injury to the hypoglossal nerve; and moderate pulmonary oedema, which resolved within 6 days. *Figure 7* presents functional and safety measures. Since most complications occurred early during the study, it is conceivable that a greater experience with the technique will reduce the number of adverse events.

Walk distance at 6 min hall walk at 1 year significantly rose by 48 m ($P = 0.01$) in 14 participants in whom this was measured. At the start of the trial, renal function was still in the normal range in all patients. Serum creatinine had significantly increased after 1 year of therapy in 22 participants, although the rise was <20%. In the others, it remained stable or even improved. None
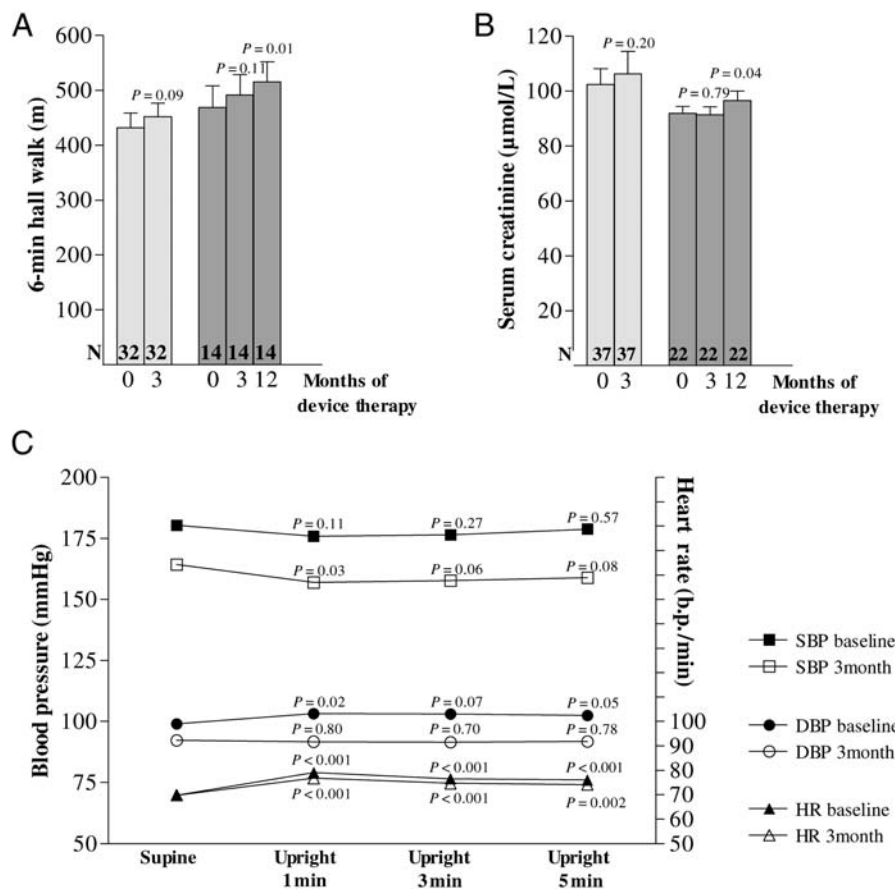
Figure 7 Functional and safety results following 3 months and 1 year of Rheos carotid baroreceptor stimulation device therapy. (*A* and *B*): Distance walked during the 6 min hall walk test and serum creatinine, respectively. Number of participants is shown in the bars. Means ± standard errors; *P*-values refer to the changes at each time point compared with baseline. (*C*): Orthostatic blood pressure readings at baseline and following 3 months of device therapy for 28 participants. Reproduced with permission from Scheffers *et al.*[21]

of the patients had developed carotid artery stenosis at the 1-year visit. No evidence for orthostatic hypotension was found, and no events of collapse or syncope were reported in the 32 participants with readings at baseline and following 3 months of device therapy. So far, there are no published data on circulating catecholamines during device therapy but preliminary data from DEBUT suggest no major alterations.

Pivotal studies are currently being conducted to validate these clinical hypotheses and identify the patient population who might receive greatest benefit from this implantable device strategy for the treatment of recalcitrant hypertension. A large (300 patient) pivotal trial[22] of baroreflex sensitization has randomized patients to have the device implanted, and then half have it turned on while the other half have it turned off for 6 months. Endpoint evaluations (efficacy and safety) are performed at this time point, and then all patients have the device turned on for longer-term follow-up.

Ultimately, the benefits of BP reduction and neurohormonal inhibition will have to be weighed against the cost and level of invasiveness of the procedure. However, for some patients, the opportunity to reduce the intensity of polypharmacy may prove

attractive, and this approach to device-based intervention may have a logical role in both recalcitrant and difficult-to-treat hypertension.

Summary and conclusions

Despite the considerable advances in the management of hypertension that have occurred over the past few decades, hypertension remains one of the major epidemics in the western world. Thus, efforts are ongoing to develop new strategies to combat this condition. Novel therapeutic approaches to the management of systemic hypertension fall into two major categories: (i) those that seek to improve BP-lowering efficacy using new therapeutic strategies in addition to standard non-pharmacological and pharmacological approaches and (ii) novel ways to optimize and improve the efficacy and utility of existing therapies.

The real explosion in the last few years has been that of procedure- and device-based approaches to hypertension, which mirrors such developments in other cardiovascular disease states. Some of these devices are fairly invasive, requiring complex procedures with intensive follow-up, e.g. the first

generation Rheos system. In that setting, the risks of the surgical procedure as well as the cost of the device have to be weighed against potential benefits. Less invasive approaches such as renal sympathetic denervation may offer a more attractive risk/benefit relationship, although this has to be weighed against possible re-growth of the nerves.

Both approaches may offer important advantages over conventional pharmacologically based strategies. For example, preservation of renal function following both renal denervation and baroreceptor stimulation remain critical endpoints. In reported series of both treatments, serum creatinine, estimated GFR, and proteinuria remained relatively stable or improved, despite presumed reductions in renal perfusion pressure. This is different from the findings seen in patients who experience similar dramatic falls in BP with pharmacologic agents, which are frequently associated with significant falls in renal perfusion and worsened renal function. These findings together suggest that reduction of renal efferent drive is a critical component of protecting renal function when BP is reduced.

Another consideration is cost. However, cost-effectiveness of these two strategies compared with current drug-based approaches is difficult to determine as, by definition, patients are refractory to these drugs. The reduction of BP achieved is expected to be associated with a direct linear reduction of expected cardiovascular morbidity and mortality. The cost per anticipated life year saved can only be estimated after the durability of the two procedures is better defined in terms of the need for repeat procedures (and their frequency) as well as the costs associated with hardware, implantation, and inpatient stay. Modelling of quality-adjusted life years gained with the procedure is currently being performed.

Implementation of these strategies must continue to be on a background of lifestyle management involving weight loss, dietary sodium-intake reduction, alcohol restriction, and exercise as well as individualized choice of drug therapy.

The next few years will determine which of these approaches meets with the greatest success and enters the clinic. In particular, controlled clinical trials are soon to be reported with both the renal sympathetic denervation and the baroreflex sensitization approaches. These newer approaches seem very likely to impact favourably on the overall burden of disease in the years to come.

Note added in proof

The Symplicity HTN-2 study has recently reported findings of a randomized controlled trial of renal denervation in resistant hypertension patients. Fifty-two patients underwent renal denervation and 51 served as controls. The primary endpoint at 6 months was office-based blood pressure (BP) measurements. BP was reduced by 32/12 mm Hg in the renal denervation group (baseline 178/96 mm Hg), but did not differ from baseline in the control group (change of 1/0 mm Hg, baseline 178/97 mm Hg). Between-group differences in blood pressure at 6 months were 33/11 mm Hg ($P < 0.0001$).[23]

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