Kardiologia Polska 2013; 71, 5: 441–446; DOI: 10.5603/KP.2013.0089 ISSN 0022–9032

Sympathetic nervous system and arterial hypertension: new perspectives, new data

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EPIDEMIOLOGY OF HYPERTENSION

Over the past decade, arterial hypertension has become recognised as a major killer, accounting for the greatest proportion of global cardiovascular (CV) morbidity and mortality. Despite clinical and research advances in hypertension prevention and management [1], high blood pressure (BP) is present in one in three adults, with a growing incidence and prevalence worldwide [2]. Recent data from the cross-sectional analysis of the United States National Health and Nutrition Examination Survey has shown that 150 million (32%) Americans have hypertension when categorised according to the 2007 American Heart Association task force's updated BP goals, with the greatest proportion of uncontrolled BP in diabetes, followed by chronic kidney disease (CKD) and CV disease [3]. Despite the increase in hypertension awareness and the use of BP lowering drugs, patients with a higher CV risk have lower rates of controlled BP when compared to average risk patients [3]. The global prevalence of hypertension is comparable between men (33.6%) and women (33.4%), with the highest occurrence among African-American adults (44%) [4]. Patients with apparent treatment resistant hypertension (RH) [5] are at very high risk for CV events [6]. Determining the prevalence of RH is complex; data available from USA and Europe has indicated that RH occurred in 13% of patients treated already for high BP [5]. Similarly, 12–13% of Polish adults are unresponsive to BP lowering drugs [7]. A recent meta-analysis showed that one in 50 patients with newly detected hypertension failed to respond to drug therapy following a median treatment period of 1.5 years [8]. 205,750 patients with incident hypertension were monitored retrospectively over a four-year period; 3,960 patients from this cohort developed RH within 18 months following initial treatment. Drug-RH occurred more often in males, older subjects and patients with diabetes when compared to patients who achieved BP control [8]. Additionally, patients with RH had a two-fold increased risk for adverse CV events, primarily attributable to CKD, compared to patients with controlled BP. Further retrospective investigation of the relationships between medical adherence, treatment intensification and BP control [9] revealed that only therapy intensification, not therapy adherence, was associated with BP control at one year. Of note, the use of several antihypertensive drug classes declined after 12 months of therapy, with a diuretic being ceased first in the majority of patients (> 90% patients at baseline vs. 78% patients at one year follow-up) [9]. Although treatment intensification is a promising approach to improving BP control, further clinical trials are warranted to delineate the long-term CV benefits resulting from therapy intensification.

Achievement of BP control is the most cost-effective way of reducing major CV hypertension-related diseases including heart disease and stroke [4]. Given the accumulating evidence for increased renal and CV risk for every rise in BP level [10], pharmacological approaches, in combination with alternative therapies including device- or procedure-based strategies to improve hypertension outcomes, are compulsory.

ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN HYPERTENSION

The contribution of the sympathetic nervous system to hypertension development, progression and complication has been extensively investigated over the past 40 years. Enhanced sympathetic activation is the core of human hypertension pathophysiology, and its deleterious CV consequences are well recognised [11–14]. Increased muscle sympathetic nerve activity (MSNA) [15] and augmented cardiac and renal noradrenaline (NA) release from the sympathetic nerves [11, 16, 17] feature in patients with essential hypertension. Sympathetic activation is evident even in very low risk subjects with high-normal BP [13]. Our recent findings not only confirmed elevated MSNA in high-normal BP, but demonstrated that resting sympathetic excitation may precede overt arterial hypertension as the sympathetic, pressor and cardiac responsiveness to stress tests

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remained unchanged [18]. The magnitude of sympathetic overactivity has been closely related to hypertension-related end organ damage [14, 19, 20]. Furthermore, sympathetic excitation predicts mortality and CV outcomes [21].

Although there is evidence to suggest an increased prevalence of obesity, diabetes, sleep apnoea, and CKD in patients with RH [3, 5], the mechanisms mediating drug resistance remain elusive. Neurohumoural activation appears pivotal in this condition. Recent findings have demonstrated for the first time an increased sympathetic activity in patients with refractory hypertension as evidenced by increased MSNA and augmented renal NA spillover [22, 23]. This is of particular importance as potentiated sympathetic activation of single-unit vasoconstrictor fibres and multi-unit nerve discharge characterises patients with RH despite the use of a median of five antihypertensive drugs [23] designed to oppose efferent sympathetic drive.

Sympathetic activation in arterial hypertension stems from either disturbed peripheral regulatory mechanisms or a primary increase in sympathetic outflow within the central nervous system [24]. Peripheral modulators of sympathetic activation and CV function entail arterial baroreceptors, cardiopulmonary mechanoreceptors and arterial chemoreceptors. Baroreceptor dysfunction has been demonstrated not only in patients with hypertension, but also in subjects with a family history of hypertension and normal BP levels [25]. Likewise, increased gain of the cardiopulmonary baroreflex control of sympathetic activity is higher in hypertensive patients when compared to their normal counterparts and the augmentation is not associated with attenuation of the arterial baroreflex [26]. An additional causal mechanism leading to increased sympathetic activation is potentiated sensitivity of arterial chemoreceptors. Studies performed by Trzebski et al. [27] showed for the first time that impairment of arterial chemoreceptors importantly contributes to the pathogenesis of human hypertension. Studies based on microneurography have confirmed an exaggerated hypoxic sympathetic drive in hypertension [28], where deactivation of peripheral chemoreceptors resulted in BP and MSNA reduction in essential hypertension [27, 29]. Studies using regional NA spillover techniques showed increased neurotransmitter release within the brainstem [30] supporting the concept of an augmented central contribution to the efferent sympathetic outflow.

Persistent generalised sympathetic activation evident in arterial hypertension is critical in disease progression leading to increased CV morbidity and mortality. In particular, the dominant role of the kidney in the long-term BP regulation is well established. Both efferent renal sympathetic nerves and afferent renal sensory fibres are relevant in the initiation, development and maintenance of elevated BP [31]. The activation of efferent renal sympathetic nerves potentiate sodium retention, reduce renal blood flow, and increase renin release with ensuing stimulation of the renin–agniotensin–aldosterone system. Signals arising from afferent renal sensory fibres in response to intra-renal ischaemia and/or renal injury directly enhance the substantial contribution of central sympathetic outflow to the periphery with deleterious consequences on various organs [31]. In this context, strategies aimed at distinctively targeting chronic sympathetic drive via modulation of closely interrelated pathways appear an attractive approach for attaining BP control, restoring existing CV autonomic imbalance, retarding disease progression, and improving the clinical benefit in patients with uncontrolled BP.

DEVICE-BASED INTERVENTIONAL STRATEGIES

The most recent developments in the management of drug-RH have been directed at modulation of the sympathetic nervous system. Alongside pharmacological therapy, device-based approaches have demonstrated beneficial effects on BP control. Based on accumulating support for improved BP control from a treatment involving renal sympathetic nerve ablation, the current European Society of Hypertension position statement recommends the procedure for patients who are resistant to drug therapy with office systolic BP (SBP) ≥ 160 mm Hg (≥ 150 mm Hg in the presence of type 2 diabetes) and estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73 m^2 despite the use of at least three antihypertensive drugs at adequate doses including a diuretic [32]. Additionally, effective treatment of drug-RH has been shown with device-based therapies including carotid sinus baroreceptor and deep brain stimulation. Given the ample evidence for increased sympathetic activity in all hypertensive phenotypes [32] and direct involvement in CV and renal disease, therapeutic methods which attenuate overall sympathetic outflow are of significant importance.

We summarise below the most recent clinical advances related to device-based interventions including the non-pharmacological approach for hypertension management.

SLOW BREATHING TECHNIQUE

Non-pharmacological approaches are recommended for all individuals with hypertension, regardless of drug therapy. Among several behavioural interventions, the device-guided slow breathing (SLOWB) exercise using RESPeRATE (Intercure, Ltd. Northern Industrial Area, Israel) has been introduced as a non-pharmacological approach in the prevention or treatment of elevated BP. It has been suggested that a decrease in breathing frequency may have beneficial effects on BP and autonomic CV regulation through the modulation of central mechanisms at the brainstem integrating cardiopulmonary receptors, arterial baroreceptors and efferent sympathetic outflow [33]. RESPeRATE aims to lower BP with ad hoc regular paced therapeutic breathing (slow and deep breathing) below 10 breaths per minute accumulating ≥ 40 min of therapeutic breathing training per week. In contrast to the previous findings indicating that SLOWB acutely reduces BP

and MSNA [34], we recently demonstrated that sympathetic activation was not influenced by reduced breathing frequency over eight weeks [35]. In this study, ten patients with untreated newly diagnosed essential hypertension received RESPeRATE and were asked to breathe effortlessly and gradually at home over an eight-week period. While the acute effect of SLOWB decreased MSNA, long-term SLOWB home exercise had no impact on sympathetic activity [35]. In contrast to the reduced office BP (SBP: 155 ± 3 vs. 137 ± 3 mm Hg, $p < 0.001$), after eight weeks of SLOWB home therapy, 24-h daytime (SBP: 145 ± 2 vs. 145 ± 3, $p = 0.92$; DBP: 86 ± 3 vs. 89 ± 3 mm Hg, $p = 0.13$) and 24-h night-time (SBP: 122 ± 3 vs. 125 ± 3, $p = 0.27$; DBP: 62 ± 4 vs. 64 ± 4 mm Hg; $p = 0.56$) BP profile remained unchanged [35]. In addition to the office BP decrease, SLOWB home exercise selectively attenuated pressor and tachycardic responses to mental stress which may favourably influence physiological stress reduction. Whether the device-paced breathing represents an adjunctive treatment to state-of-the-art drug therapy for hypertension requires further clinical investigation in a larger patient cohort. However, given that ambulatory BP and sympathetic activation remained unaltered after eight weeks of SLOWB therapy, this method appears unlikely to reduce sympathetic activity alone over the longer term.

RENAL DENERVATION

Most recent interventional procedures aimed at treating pharmacotherapy-RH have focused on renal sympathetic nerve ablation. Bilateral sympathetic renal denervation (RDN) using the Symplicity™ catheter has been shown to have a favourable safety profile leading to substantial and continued BP reduction in patients with RH [36–38]. Recently, expanded results from the SYMPLICITY HTN-1 trial including a total of 153 patients across 19 centres in Australia, Europe and the United States were displayed at the American College of Cardiology Annual Meeting 2012. These findings indicated an average BP reduction of –33/–19 mm Hg out to 36 months ($n = 24$) from baseline ($p < 0.001$) with no deterioration of renal function following the procedure.

In addition to BP lowering effects, RDN may lead to regression of hypertension-related target organ damage. Recent results from a study of 46 RH patients who underwent bilateral RDN indicated not only a BP fall in the treatment group (–27.8/–8.8 mm Hg, $p < 0.001$) after six months, but also that the procedure resulted in a rapid and substantial improvement in left ventricular (LV) diastolic function. RDN reduced intraventricular septum thickness (14.1 ± 1.9 to 13.4 ± 2.1 and 12.5 ± 1.4 mm, $p = 0.007$) with a corresponding improvement in LV mass index (112.4 ± 33.9 to 103.6 ± 30.5 and 94.9 ± 29.8 g/m^2, $p < 0.001$) and mitral valve lateral E/E' (9.9 ± 4.0 to 7.9 ± 2.2 and 7.4 ± 2.7, $p < 0.001$) at one and six months after the procedure, respectively. Isovolumic relaxation time shortened (109.1 ± 21.7 vs. 85.6 ± 24.4 ms, $p = 0.006$) and ejection fraction increased (63.1 ± 8.1% vs. 70.1 ± 11.5%) at six month follow-up [39]. As expected, there were no changes in echocardiographic parameters in 18 patients who underwent repeated measurements without having undergone the procedure [39].

Evidence suggesting the beneficial effects of RDN on large artery function has been shown in 21 patients with RH [40]. Not only did peripheral SBP decrease by 6.1% ($p < 0.05$), but a parallel reduction in central SBP by 7.0% ($p < 0.05$), aortic augmentation index (AIx) by 9.5% ($p < 0.05$) and pulse wave velocity (PWV) by 10.4% ($p < 0.05$) was observed following the procedure. In this study, subgroup analysis revealed that, in the responders, peripheral SBP decreased by 16.1% ($p < 0.01$), central SBP by 18.3% ($p < 0.01$), aortic AIx improved by 19.2% ($p < 0.02$), and PWV by 13.7% ($p < 0.05$) [40]. Given the extensive evidence for a causal link between hypertension-induced organ damage and CV morbidity and mortality, these results appear reassuring given that LV hypertrophy, central haemodynamics and arterial stiffness were considerably diminished six months following RDN. Whether this improvement is sustained over time and has prognostic implications in this patient cohort remains to be elucidated.

Additional evidence of reduced BP with RDN has been shown in the first treated patient with renovascular hypertension resistant to antihypertensive regimens and percutaneous transluminal angioplasty for left renal artery stenosis with stent placement [41]. Ablation of renal nerves decreased office systolic and diastolic BP from 174/67 to 155/68, 148/75, 143/70, and 144/73 mm Hg at one week, and one, three, and six month follow-up, respectively. This report supports the concept that sympathetic activation is pivotal in renovascular hypertension, with the contributions of renal afferent sensory fibres and efferent sympathetic nerves. Whether RDN should be offered as an additional approach in renovascular hypertension remains to be determined.

Further evidence for the potential beneficial effect of RDN has recently been demonstrated in a very common condition: obstructive sleep apnoea in patients with RH [42]. In addition to the BP reduction after six months (–34/–13 mm Hg, $p < 0.01$), the apnoea–hypopnoea index decreased (16.3 vs. 4.5 events per hour, $p = 0.059$) in these patients, confirming that enhanced sympathetic drive is a major contributor to sleep apnoea severity. RDN was also associated with an improvement in glucose metabolism in this patient cohort [42].

The preliminary findings on the effects of catheter-based RDN on glycaemic control in patients with RH have recently been reviewed in detail [43].

While all patients treated with RDN in the initial clinical trials had an estimated eGFR ≥ 45 mL/min/1.73 m^2, potential support for beneficial effects of this procedure has also been derived from investigations of yet another high risk group of patients. This first in human pilot study including a total of 15 patients with moderate to severe CKD demonstrated that

RDN is a safe and effective procedure in this cohort [44]. Office systolic and diastolic BP were significantly reduced by –34 ± 13/–14 ± 13, –25 ± 20/–11 ± 10, –32 ± 18/–15 ± 12, –33 ± 20/–19 ± 20 mm Hg at one, three, six, and 12 months following RDN, respectively ($p < 0.001$). RDN decreased night-time ambulatory BP ($p = 0.01$) at three month follow-up resulting in improved dipping pattern. Importantly, no deterioration of renal function, reduction in eGFR or electrolyte disturbances were encountered in the following 12 months irrespective of CO_2-angiography use during the procedure to minimise contrast exposure. Moreover, an improvement in AIx associated with RDN in CKD patients may be of clinical relevance [44]. These findings indicate that ablation of renal nerves appears a promising approach to attenuate disease progression which may directly influence the mechanisms linking sympathetic activation to high CV morbidity and mortality.

Accordingly, recent findings have indicated that RDN markedly decreases whole body NA spillover, renal NA spillover and postganglionic efferent multi-unit MSNA beyond BP lowering effect in refractory hypertension [22, 23, 36]. Moreover, RDN results in a rapid and substantial reduction in all properties of single active vasoconstrictors neurons including firing rate, firing probability and the incidence of multiple spikes within a cardiac cycle which may have important clinical implications with regard to sympathetic inhibition and BP control [23].

The importance of assessing other patient outcomes such as the quality of life following RDN has been recently demonstrated in patients with RH [45]. Significant improvements in mental components such as vitality, social function, role emotion and mental health were noted three months post procedure. In addition, symptoms associated with depression such as sadness, tiredness and loss of libido were considerably diminished after RDN. The improvement in the quality of life associated with RDN was unrelated to the BP lowering effect.

Currently ongoing, the SYMPLICITY HTN-3 (NCT01418261 at http://www.clinicaltrials.gov/) clinical trial involving 530 patients from 87 centres across the United States differs from previous studies in its design. In this study patients are randomised in a two to one ratio to receive either RDN or a sham procedure, with obligatory 24-h BP assessment to further define the safety and effectiveness of RDN in patients whose BP is uncontrolled despite the use of at least three antihypertensive drugs at maximum tolerated doses. The final data collection for the primary outcomes in this study was due in March 2013.

Although the commonly used single-electrode Symplicity™ catheter allows the ablation of only one treatment site at a time, numerous point-by-point ablations are performed in each treated artery in an attempt to perform the procedure. Each ablation treatment lasts 120 s, with the overall time of the procedure and exposure to contrast prolonged. In contrast, the first-in-man study with RDN using a new generation spiral multi-electrode catheter (Medtronic, Inc.) system with advanced radiofrequency (RF) generator has recently been performed (http://wwwp.medtronic.com). A total of nine patients with RH were successfully treated bilaterally with the investigational catheter which features four unipolar electrodes on a spiral-tipped catheter that delivers RF energy through a 6 French sheath. The single 60 s therapy for each treated artery will certainly reduce ablation time, and may possibly enable the treatment of varying renal artery anatomy. The safety and efficacy of this multiple electrode catheter is currently being investigated in a prospective single-arm non-randomised and open label study (NCT01699529 at http://www.clinicaltrials.gov/).

In the past year, limited clinical data has been presented at the Transcatheter Therapeutics 2012 Meeting from trials investigating the utility of alternative renal denervation devices including the St. Jude Medical's EnligHTN™ system, Vessix's V2™ Renal Denervation System, Covidien's OneShot™ system, Recor's Paradise™ system and the KONA system with externally focused ultrasound therapy. These different technologies are currently being evaluated, with no randomised controlled and long-term data yet available.

BARORECEPTOR STIMULATION

The importance of baroreflex mechanisms in short-term BP regulation is well recognised. Given that in the presence of sustained BP elevation over time, arterial baroreceptors are less sensitive to mediate changes in sympathetic activity to the heart and blood vessels, the role of baroreflex in the long-term regulation of BP is more debatable and still under investigation. The recent development of a novel implantable device to electrically stimulate carotid sinus baroreceptors has provided a unique insight into human baroreflex physiology. Indeed, the safety and efficacy of device-based chronic electric baroreceptor stimulation with the CVRx Rheos System (DEBuT-HT Trial) has been demonstrated in a multi-centre non-randomised trial of 45 high CV risk patients with RH. Mean BP significantly decreased –21/–12 mm Hg three months following device implementation and was reduced –33/–22 mm Hg in patients who completed two year follow-up ($n = 17$). Despite the safe and substantial BP lowering effect demonstrated in this study cohort, eight patients experienced procedure-related serious adverse events [46]. Recent results of the long-term follow-up in the Rheos Pivotal Study have shown that 244 (76%) out of 322 implemented patients were classified as clinical responders, with an average BP decrease –35/–16 mm Hg, of whom 55% achieved target BP (< 140 mm Hg or < 130 mm Hg in diabetes and kidney disease) following baroreflex activation therapy [47]. In regards to the sympathetic activity, only the acute effect of carotid sinus baroreceptors stimulation has so far been determined in a group of 12 patients with RH showing an instant decrease in BP and MSNA when the stimulator was switched 'on', returning to baseline level when the device was 'off' [48]. In view of the dominant role of the

kidney in long-term BP regulation and the evidence for the potential of RDN to directly influence peripheral tissue, further clinical studies are warranted to determine the applicability of baroreceptor stimulation with regard to hypertension-associated co-morbidities.

DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) is an exciting interventional therapy designed to modify pathological activity within the sympathetic nervous system. This approach has gained significant recognition in the treatment of Parkinson's disease, recently entering clinical practice. Besides the promising therapeutic effects in a wide range of neurological disorders, DBS of the ventrolateral periadeuquotal grey/periventricular grey matter has been successfully demonstrated in refractory hypertension [49, 50]. While this approach was primarily performed to treat chronic central pain syndrome that was unresponsive to pain-relief drugs, there was also an unexpected effect of sustained BP lowering. Indeed, a 55 year-old man with symptoms of left-side weakness due to ischaemic stroke and office BP of 145/69 mm Hg on four antihypertensive drugs developed a severe left-sided hemibody central pain syndrome that was resistant to drug therapy three years thereafter. The patient underwent DBS to treat his pain. This intervention alleviated pain levels for four months, which then returned to the level seen before the procedure. However, there was a gradual decrease in BP of approximately 80/53 mm Hg that terminated his anti-hypertensive medication. After 33 months, BP averaged 118/70 mm Hg with medication withdrawal postoperatively. Further proof for the beneficial effect of DBS has been reported in a yet another 58 year-old man, who initially underwent DBS to relieve his neuropathic facial pain resistant to other regimens. In accordance with previous results, stimulation of periaqueductal grey resulted in sustained 24-h daytime BP reduction at 12 month follow-up (–12.6 mm Hg for SBP and –11.0 mm Hg for DBP) with corresponding decreases in heart rate variability and pulse pressure. In both cases, the most pronounced BP lowering effects were seen when the patients were switched 'on' DBS rather than when the device was switched 'off'. While costly, and associated with a 1% stroke risk, DBS appears to be an attractive approach for treating severe forms of uncontrolled hypertension and perhaps patients unresponsive to device-based interventional strategies. Whether DBS may be offered widely as a therapeutic tool to improve CV outcomes in patients with treatment RH clearly merits further investigation. The effect of DBS on sympathetic activity is unknown.

FUTURE DIRECTIONS

As the global burden of hypertension and associated diseases (obesity, diabetes and CKD) grows, the prevalence of treatment RH is projected to rise. Despite the wide range of non-pharmacological and pharmacological BP lowering approaches available, poorly controlled hypertension worldwide has a substantial impact on morbidity and mortality.

In this context, additional strategies to complement the current management of hypertension are required. The well established contribution of sympathetic overactivity to human hypertension has led to the development of novel device-based and procedural interventions that favourably modulate autonomic neural mechanisms underlying hypertension. An additional approach currently being investigated to attain BP control in patients with RH is carotid body removal (NCT01729988 at http://www.clinicaltrials.gov/). Given the invasiveness, the cost of device-based strategies, and the different responsiveness of different patients, pre-procedural markers to stratify patients for the specific approach need to be identified. At this time point, renal nerve ablation has been introduced into clinical practice to treat only RH and has been investigated, with promising results, in other co-morbidities. Future large scale clinical trials will determine the long-term safety and effectiveness of these various antihypertensive approaches in terms of BP control, hypertension-related end organ damage, and hard CV endpoints including death, myocardial infarction and stroke.

Conflict of interest: *Professor Krzysztof Narkiewicz has received grants, lecture and consultancy fees from Medtronic, Inc. Doctor Dagmara Hering was awarded a Research Fellowship by the Foundation for Polish Science KOLUMB/2010-1.*

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