Recent advances in the pathophysiology of arterial hypertension: potential implications for clinical practice

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ABSTRACT
Hypertension remains a major and growing public health problem associated with the greatest global rate of cardiovascular morbidity and mortality. Although numerous factors contribute to poor control of blood pressure (BP) and to pseudo-resistance (e.g., unawareness, lifestyle habits, nonadherence to medication, insufficient treatment, drug-induced hypertension, undiagnosed secondary causes), true resistant hypertension (RH) is reported in 10.1% of patients treated for elevated BP. While the mechanisms underlying RH remain complex and not entirely understood, sympathetic activation involved in the pathophysiology of hypertension, disease progression, and adverse complications is further augmented in patients with drug-resistant hypertension. The well-established contribution of neurogenic component of hypertension has led to the introduction of new alternative therapies aimed specifically at modulating central and neural reflexes mechanisms involved in BP control. Although clinical benefits of lowering BP with renal denervation, baroreflex activation therapy, carotid body denervation, central arteriovenous anastomosis, and deep brain stimulation have advanced our knowledge on uncontrolled hypertension, the variable BP response has prompted extensive ongoing research to define predictors of treatment effectiveness and further investigation of pathophysiology of RH. Very recently, research on the role of vasopressinergic neurons, masked tachycardia, and impaired brain neural activity has provided novel insights into hypertension. This review briefly summarizes the role of the centrally mediated sympathetic nervous system in hypertension, the therapeutic strategies that distinctively target impaired neural reflex mechanisms, and potential implications for future clinical research and therapies.

Introduction
Despite the well-recognized benefits of reducing major cardiovascular events and mortality through the control of blood pressure (BP), detection rates and control of hypertension remain low across all countries. Even though therapy is initiated in the vast majority of patients diagnosed with hypertension, treatment is suboptimal with a declined use of antihypertensive drugs over time. A large gap between the prevalence, awareness, treatment, and control of hypertension has been addressed in the multinational Prospective Urban Rural Epidemiology (PURE) study conducted in 628 communities, including high-income, upper-middle-income, low-middle-income and low-income countries. A low global control of BP was found among the treated hypertensive population. Notably, only 46.5% of participants were aware of their hypertension, with less than half (40.6%) medically treated and BP levels less than 140/90 mm Hg achieved in 1 in 3 individuals (13.2%). The global disparities in the prevalence, awareness, treatment, and control of hypertension have also been indicated in a recent meta-analysis of 135 population-based studies from 90 countries. Globally, the number of individuals with hypertension increased, reaching an estimated total of 1.39 billion adults with hypertension, including 349 million in high-income countries and 1.04 billion in low- and middle-income countries by 2010. The increased and highest prevalence of raised BP has been particularly noted in East Europe, Asia, Africa, and Latin America.
Among hypertensive patients, specific consideration was given to the high-risk cohort with hypertension that was difficult to treat, including patients with drug resistance or drug intolerance. Patients with RH commonly display a high prevalence of organ damage (ie, left ventricular hypertrophy, carotid intima-media thickening, carotid plaques, advanced retinal involvement, increased albumin urinary excretion) when compared to patients with controlled hypertension. The risk of cardiovascular events increases with ambulatory BP levels and is higher than in patients with controlled or white coat hypertension. Moreover, higher 24-hour BP levels predicted the composite endpoints of fatal and nonfatal cardiovascular events in hypertension. In addition to a higher risk of adverse cardiovascular outcomes, patients with RH are more likely to develop cardiovascular comorbidities (ie, ischemic heart disease, heart failure, chronic kidney disease).

The exact prevalence of RH remains unknown and data mainly derive from BP control population, outcomes, or retrospective studies in which medication adherence was not directly monitored. Nevertheless, pooled prevalence rates for uncontrolled RH account for 10.1% among treated patients. While the improvement of patient adherence to medication can considerably decrease the prevalence of RH, physician therapeutic inertia is a major contributing factor to the inadequate management and lack of BP control. A retrospective investigation revealed that only appropriate therapy intensification, but not therapy adherence, was associated with 1-year control of BP. These findings highlight the importance of tailoring drugs for lowering BP towards improving the control of BP. The observed 8.2% increase in death rate attributable to high BP and the actual number of deaths of 34.7% between 2003 and 2013 indicate an unmet need for collaborative efforts to combat the emerging incidence of hypertension.

**Sympathetic activation in human hypertension**

The activation of the sympathetic nervous system (SNS) in human hypertension has been convincingly demonstrated through the use of isotope dilution method for quantifying noradrenaline (NA) spillover rates and postganglionic efferent sympathetic nerve recording with micro-neurography. NA is the main neurotransmitter of sympathetic nerves and the rates of its release from nerve terminals allow to measure sympathetic nerve activity. While the rate of NA overflow was documented for most internal organs, a selective increase in sympathetic outflow to the heart and the kidney is evident in primary hypertension, and is likely contributing to established hypertension. Augmented NA levels from the renal sympathetic nerves characterizes essential hypertension (EH), predominantly in adults below the age of 40 years, and is a prime mover for BP rise. Increased cardiac NA spillover and decreased NA neuronal reuptake further potentiate sympathetic activation in maintaining arterial hypertension.

Increased muscle sympathetic nerve activity (MSNA) was present even in high-normal BP. Our study corroborated these findings and further suggested that resting sympathetic excitation may precede overt arterial hypertension in very low risk patients with high-normal BP. Tonic sympathetic activation evident in patients with hypertension appears to contribute to time-related increase in BP and development of sustained hypertension and asymptomatic arterial stiffness. High levels of NA release from cardiac and renal sympathetic nerves accompanying elevated MSNA was linked to left ventricular hypertrophy and left ventricular dysfunction in hypertension. Sympathetically mediated rise in BP and induced organ damage are likely to contribute to the development of cardiac, renal, vascular, and cerebrovascular events. The magnitude of sympathetic excitation predicted mortality and cardiovascular outcomes.

The SNS is directly related to the renin-angiotensin-aldosterone system (RAAS). Both systems play an important role in the control of BP and blood volume, acting at different levels of the central nervous system and peripheral sites leading to the synthesis and release of angiotensin II and NA, the fundamental neurotransmitters involved in the development and progression of the disease. Sympathetic activation increases the activity of the RAAS through direct effects on the 3 renal neuroeffectors: 1) the juxtaglomerular granular cells that enhance renin release, 2) the renal tubular epithelial cells that increase sodium reabsorption, and 3) the renal vasculature that reduces renal blood flow. Consequently, it results in increased efferent renal sympathetic nerve activity (ERSNA). In physiological conditions, ERSNA stimulates afferent renal sensory nerves which, through the renal reflex mechanism, leads to a subsequent reduction in ERNSA and resultant diuresis and natriuresis. In the presence of elevated BP, increased signals arising from the injured and/or ischemic kidney through afferent renal sensory nerves is projected directly to the central integrative structure in the brainstem, rostral ventrolateral medulla (RVLM), potentiating sympathetic outflow to the periphery, causing end-organ damage and adverse sequelae.

The RVLM integrates neural reflex mechanisms from afferent arterial baroreceptors and afferent arterial chemoreceptors. Baroreflex is an important inhibitory regulatory mechanism induced by changes in BP mediated by the parasympathetic and sympathetic component. Reduced baroreflex sensitivity has been demonstrated in patients with hypertension and also patients with family history of hypertension and normal BP levels. Augmented gain of the cardiopulmonary baroreflex control of sympathetic activity was found in hypertension when compared to normal counterparts. This augmentation was not associated
with the attenuation of the arterial baroreflex. Further causative mechanism that leads to increased sympathetic activation in hypertension is the potentiated sensitivity of arterial chemoreceptors. Studies performed by Trzebski et al in the early 1980s for the first time demonstrated the contribution of increased sensitivity of arterial chemoreceptors to the pathogenesis of human hypertension. This concept was supported by microneurography studies demonstrating high sympathetic drive induced by hypoxia in hypertension. On the other hand, deactivation of peripheral chemoreceptors (hyperoxia) resulted in BP and MSNA reduction in EH.

Recent studies documented the underlying persistent neurohumoral activation in patients with RH. Direct microneurography recordings documented an increased activity of all properties of single-unit firing pattern and multi-unit MSNA in RH. Our own experience indicated that patients with RH were characterized by high levels of multi-unit MSNA (often 50–70 bursts/min) with burst activity synchronized with every heartbeat, often superimposed within one cardiac cycle (sharp “M” shape burst) due to high sympathetic nerve discharge when compared to healthy controls (<20 bursts/min) and to patients with untreated EH (25–40 bursts/min). Patients with RH displayed markedly elevated activity of single-unit muscle vasoconstrictor fibers, including firings within a cardiac cycle.

This is of particular significance as high sympathetic drive is a hallmark of RH despite the use of all available antihypertensive drug classes which target the efferent sympathetic component of the heart, kidney, vasculature, and central nervous system through different mechanisms. Notably, some specific agents (diuretics, calcium channel blockers, selective β-blockers, and α-blockers) result in increased or unchanged sympathetic activation instead of inhibition, particularly when given in a mixed-drug cocktail combination. An increased prevalence of sympathetically mediated comorbidities including diabetes, chronic kidney disease, obesity, and obstructive sleep apnea (OSA) in RH patients is likely to further potentiate high sympathetic drive.

Against this background, inhibition of the SNS and the RAAS were a major target for BP control. However, despite the availability of potent antihypertensive drugs, high-risk patients with hypertension that is difficult to treat remain a challenge from a clinical perspective. This triggered an increasing interest in the development of alternative therapies aimed at precise targeting of hypertension physiology.

**Role of central neuroplasticity in hypertension** A collective body of research documented that the brain has a powerful ability to adapt to new behavioral, physical, and physiological challenges and to alter existing neural pathways in response to stimuli over time. This process known as neuroplasticity (brain plasticity) involves molecular, functional, and structural modification of neural networks in association with central sensitization. While centrally mediated sensitization is integral for controlling many functions, particularly during early development (eg, memory formation), it occurs in various pathophysiological conditions in response to chronic pain, pleasure (eg, drug abuse), baroreceptor and chemoreceptor reflexes, intermittent hypoxia, exercise, and depression. It was suggested that changes in cellular and molecular components in the neural network involved in sympathetic control and control of BP can promote and potentiate pressor response to recurrent, sustained, or new stressors. Neuroplasticity underlining sensitization appears to play an important role in the long-term regulation of BP and hypertension. The pressor response to repeated infusion of angiotensin II can be substantially potentiated by small nonpressor doses of angiotensin II or aldosterone administered for several days. The hypertensive response sensitization mediated by the brain RAAS resulted in sustained neurochemical changes in the organum vasculosum of the lamina terminalis, which is an osmosensitive area of the brain involved in the regulation of NA release in the anterior hypothalamic nucleus.

Amongst numerous neurohumoral mediators involved in the central sensitization network (eg, dopamine, substance P), brain-derived neurotrophic factor (BDNF) plays a critical role in the neurogenesis and plasticity of the brain. Aside from neuroprotective role in preventing neuronal atrophy, age-related cognitive impairment and potentially Alzheimer disease, BDNF is involved in modulation of the central angiotensin signaling. Preclinical data demonstrate that overexpression of BDNF in the paraventricular nucleus (PVN) is associated with sympathoexcitation, elevation of BP and heart rate (HR), and weight loss that are largely mediated by modulation of angiotensin signaling in the PVN. Another study found that high-fat diet elicits augmented hypertensive response to subsequent angiotensin II administration, which is mediated by leptin through upregulation of the central RAAS and proinflammatory cytokines. These findings indicate that sensitization stems from permanent alterations in the brain RAAS and potentiated activation of markers associated with central plasticity which influence the long-term regulation of BP. Understanding the underlying mechanisms may have important implications for preventing and treating hypertension; however, this requires further investigation.

**Role of brain neural activity in hypertension** Increased NA release within the central nervous system was demonstrated in studies assessing the combined overflow of brain NA, its precursor dihydroxyphenylalanine, and its lipophilic metabolites into the internal jugular veins. Direct blood sampling from the internal jugular
veins and concomitant cerebral blood flow scans revealed that suprabulbar noradrenergic projections from the brainstem to the hypothalamus play a key role in neurogenic hypertension. Subcortical NA turnover in brain regions (not cerebral cortex) was found to be significantly higher in EH when compared to healthy patients, and directly related to neurochemical indices of the SNS activity and renal NA spillover in EH, supporting the notion that sympathetic activation in EH is of central nervous system origin that potentiate different sympathetic outflow to the periphery. Further studies revealed that the measurements of transcranial plasma NA spillover provide a valid tool for assessing the sympathetic nerve activity of the cerebral vessels (outside the blood-brain barrier) in a range of clinical settings and that the NA metabolites originate primarily from brain noradrenergic neurons. This technique, however, due to its need for arterial and venous catheterization, was used for research purpose only.

Numerous studies investigated the link between hypertension and the brain and its relevance for the development of cerebrovascular disease and aging-related cognitive impairment. Studies applied functional magnetic resonance imaging (fMRI), which has the capacity to measure neuronal activity of the brain noninvasively by detecting changes associated with cerebral blood flow. Hypertension was found to be associated with cerebral hypoperfusion and reduced cortical thickness independently of the use of antihypertensive drugs. The presence of type 2 diabetes in patients with hypertension appeared to accelerate these abnormalities further. Cerebrovascular reactivity assessed by MRI dependent on the level of blood oxygenation and cortical thickness estimated from MRI images were reduced in patients with type 2 diabetes. Moreover, coexisting hypertension, when compared to age-matched hypertensive individuals, suggested that brain regions affected by the combined effects of both comorbidities may undergo cognitive impairment. While these findings were intriguing, the underlying mechanistic insights have not yet been elucidated. The situation was even more complex with the findings indicating a continued atrophy with the shrinkage of regional gray matter despite reducing BP to normotensive levels over 12 months therapy in newly treated patients with hypertension.

More recently, 2 studies aimed at unravelling BP-dependent and independent structural and functional characteristics of the brain provided novel insights into disease physiology. Micro-neurography recordings and simultaneous assessment of brain neuronal activity using fMRI documented that high levels of MSNA in OSA patients is associated with functional (not anatomical) changes within the higher cortical and subcortical brain regions, which are involved in the modulation of sympathetic outflow and BP through the brainstem regulatory nuclei, when compared to healthy controls. Increased signal intensity in the medial prefrontal cortex and its relation to MSNA in OSA may have important implications for understanding the neural reflex regulation of BP (ie, reduced baroreflex gain) in OSA (condition characterized by high sympathetic activity), which often coexists with hypertension and shares its multiple physiological and cardiovascular consequences. Notably, the medial prefrontal cortex has projections to the nucleus tractus solitarius and RVLM, which are responsible for basal and reflex sympathetic activity and cardiovascular function. A novel finding linking functional neural reorganization to the history of hypertension comes from a recent study of a total of 40 middle-aged patients (20 patients with EH, 20 healthy matched controls) who underwent a comprehensive assessment of fMRI during a Stroop color interference task and structural evaluation based on a modified Fazekas scale. There were no differences in white matter lesions, distribution of punctuate white matter, and task performance between patients with hypertension and control group. However, there were substantial variations in brain activation between both groups during the demanding task processing irrespectively of the task difficulty. Importantly, this functional reorganization occurred in a reasonably controlled hypertensive cohort, in the absence of previous history of cardiovascular disease, diabetes, drug or alcohol abuse, cerebral damage, brain injury, and factors influencing functional reorganizations at neuronal level. This study for the first time revealed that neuroplasticity occurs in the course of human hypertension. The functional reorganization in the brain neuronal network in relation to stress and demand may further impair brain plasticity leading to cognitive decline at a later age. This, however, merits further studies in arterial hypertension. Likewise, it remains unknown if lowering the BP per se may facilitate neuroplasticity of certain brain areas, thereby favorably affecting cognitive function. Consistent findings indicated that hitherto physical exercise is associated with neurocognitive benefits by enhancing brain plasticity, as well as structural and functional alterations. Results from fMRI studies demonstrated that exercise training increases the size of the anterior hippocampus, hippocampal volume, and BDNF levels, which leads to improvement of spatial memory increased neuronal efficiency during "executive and memory task".

In this context, further larger studies are warranted to determine whether physical exercise may alter brain functional connectivity and improve neuronal processing in hypertension irrespective of BP control and whether this is mediated by BDNF signaling.

Potential surrogate markers in the clinical management of hypertension Copeptin Clinical interest was focused on testing plasma copeptin, a peptide derived from preprohormone arginine...
vasopressin (AVP) produced by the hypothalamic PVN. Unlike AVP, which is an unstable molecule with short half-life and quite complicated measures, copeptin is considered a vasopressin surrogate. Diagnostic benefits of measuring copeptin levels were documented in acute cardiovascular events, including acute coronary syndrome. An independent and prognostic value of copeptin levels for unfavorable outcomes and mortality was evidenced in patients with hemorrhagic and ischemic stroke. Elevated copeptin was also found in septic shock, suggesting its potential use in guiding clinical therapy and reversing vasodilatory shock states that are unresponsive to standard catecholamine therapy.

Apart from the benefits of monitoring copeptin in acute clinical scenarios, data from animal studies suggested that stress-mediated release of AVP from the hypothalamus plays a critical role in triggering BP and sympathetic outflow through activation of the brain RAAS. On the contrary, chronic infusion of angiotensin antagonists acting in the PVN prevented BP rise induced by sleep apnea. In this context, interesting were the findings from a study on young healthy adults in whom copeptin independently predicted nighttime hypertension among men, but not women. Previous studies indicated that the copeptin level is higher in healthy men than in women. While the sex-related association between copeptin and MSNA has not yet been determined, it is likely that lower copeptin paralleled MSNA levels, in line with our previous findings of lower BP and MSNA in younger women than men counterparts. Likewise, female sex hormones may attenuate stress-induced vasopressin release and prevent BP-related disease and sympathetic activation in women; however, this merits further clinical research.

Recent findings determining the impact of antihypertensive therapy on copeptin levels in patients with RH were also clinically relevant. Following a 4-week treatment (irbesartan, hydrochlorothiazide, and amlodipine), patients with RH were randomized to the sequential neprilysin blockade group (spironolactone, furosemide, amlodipine) or the sequential RAAS blockade group (ramipril, bisoprolol) if home BP was greater than or equal to 135/85 mm Hg. Following 12-week therapy, baseline plasma copeptin was positively associated with men, plasma osmolality, BP, and inversely with glomerular filtration rate. Plasma copeptin levels were nearly 2-fold higher in RH patients than in patients with controlled BP after adjustment for plasma osmolality. Importantly, plasma copeptin remained significantly higher in patients whose BP was controlled by sequential neprilysin blockade or sequential RAAS blockade than in patients with controlled hypertension. Given that in hypervolemia in physiological conditions hypertension and hyperosmolality inhibit AVP secretion, these findings suggested that RH was associated with impaired biosynthesis and chronic stimulation of vasopressinergic neurons, subsequent release of AVP despite hypervolemia, and resultant resistance to antihypertensive drugs. In view of these findings, it would be relevant to explore whether blocking AVP may restore neuroendocrine imbalance and overcome the centrally mediated resistance in hypertension.

**Tachycardia** Amongst numerous risk factors influencing patient prognosis and used for patient stratification of total cardiovascular risk, elevated HR gained important prognostic recognition. The association between tachycardia and the development of hypertension, metabolic abnormalities, atherosclerosis, and cardiovascular disease is well established. A strong independent relationship between tachycardia and all-cause cardiovascular morbidity and mortality was documented in the general population, patients with prehypertension, patients with hypertension, cardiovascular disease, and heart failure. Elevated HR predicted cardiac events in high-risk patients with hypertension when compared to patients with the lowest HR. The negative impact of elevated HR on patient prognosis was unrelated to BF control suggesting that even patients with reasonably well-controlled hypertension but presence of tachycardia display high risk for cardiac events. The prognostic value of resting HR was also demonstrated in RH patients in whom not only fast (>75 bpm or >70 bpm for nighttime HR) but also slow HR (<60 bpm or <55 bpm for nighttime HR) were predictors of cardiovascular mortality. Notably, therapy with β-blockers had an impact on prognosis related to HR. While fast HR was a significant risk marker in patients using β-blockers, slow HR was also a predictor in those not using β-blockers suggesting an overall U-shaped phenomenon between the levels of HR and outcomes in RH.

Recent findings which provided the first clinical evidence for the important independent predictive role of masked tachycardia for risk stratification in patients with untreated hypertension were clinically relevant. A novel finding is that masked tachycardia defined as normal office HR (≤85 bpm) and nighttime HR (≥76 bpm) increased both the risk of excess major adverse cardiovascular events and mortality in hypertension. In contrast, patients with sustained tachycardia (elevated office and nighttime HR) presented a greater risk for major adverse cardiovascular events only, but not for all-cause death, whereas white coat tachycardia bore no association with any cardiac events or all-cause mortality. Importantly, the prognostic significance of masked tachycardia and sustained tachycardia in future major adverse cardiovascular events was independent of β-blocker use. The mechanisms through which β-blockers were unable to prevent cardiovascular events in patients with out-of-office tachycardia have not yet been determined.

**Nonpharmacological therapeutic interventions for hypertension management** Recent advancements...
in the treatment of RH were directed at inhibiting the relevant neurogenic pathways underlying the physiology of hypertension. The effect of BP lowering was demonstrated through the modulation of the SNS activity through interruption of afferent signaling arising from the kidney (RDN), carotid arterial baroreceptors (BAT), and carotid arterial chemoreceptors (CBD) projected to the RVLM, which controls BP and sympathetic outflow. Although clinical experience with deep brain stimulation (DBS) is limited to case reports of severe RH, direct stimulation of the ventrolateral periaqueductal gray (PAG) has potential to favorably alter brain activity resulting in sympathoinhibition and BP reduction. While central iliac AV anastomosis does not directly influence sympathetic nerve activity, it is likely to activate pulmonary arterial mechanoreceptors and alter mechano-circulatory properties of the arteries, providing a novel therapeutic approach to uncontrolled hypertension.

Renal denervation While most interventional advancements for the treatment of drug-RH focused on renal nerve ablation since the first in-man proof of concept Symplicity HTN-1 trial, its broad clinical utility has not yet been fully established. Evidence from the unblinded studies applying catheter-based RDN demonstrated a significant decrease of around 10 to 15 mm Hg in mean ambulatory systolic BP and around 15 to 25 mm Hg in office systolic BP. The BP lowering following RDN has been linked to attenuation of hypertension-induced organ damage in RH patients. Although expectations were high for the first prospective randomized double-blind sham-controlled Symplicity HTN-3 study designed for assessing true ambulatory BP lowering effects, unexpectedly this trial failed to meet its primary and secondary efficacy endpoints. The negative results surrounding the Symplicity HTN-3 trial triggered preclinical and clinical studies for further exploration of the RDN technique, including both procedural and anatomical factors. Evidence from human autopsy studies broadened our knowledge and provided a more comprehensive understanding of renal nerve localization to the renal artery lumen, potentially explaining the high variability in BP and renal NA spillover rate in response to RDN. Conflicting results derive from other sham-controlled trials of RDN. In patients with mild to moderate RH, RDN failed to demonstrate significant changes in the primary efficacy endpoint of 24-hour systolic BP at 6 months postprocedure between the RDN and sham-controlled groups. Another sham-controlled, double-blinded randomized, single-center trial assessing the efficacy of RDN on ambulatory BP levels in patients with RH demonstrated comparable reductions in daytime systolic BP at 3- and 6-month follow-up between both groups. However, these studies did not indicate whether the sufficient circumferential renal nerves ablation was actually achieved.

On the contrary, the recently reported renal denervation for hypertension study, a prospective, open-label randomized controlled trial with blinded 24-hour ambulatory BP endpoint evaluation in patients with RH demonstrated that effectiveness in BP lowering is greater when RDN is added to a standardized stepped-care antihypertensive treatment when compared to the same medication alone. The 6-month primary efficacy endpoint which was a reduction in daytime systolic BP was met (–15.8 mm Hg in the RDN vs –9.9 mm Hg in the control arm). Furthermore, extended analysis of the renal denervation for hypertension study identified baseline nighttime BP as a predictor for the reduction of daytime systolic BP 6 months after RDN. Higher nighttime BP variability prior to RDN was associated with greater daytime systolic BP lowering at 6 months postprocedure in responders. In contrast, controls neither nighttime BP nor its variability predicted 6-month BP response to standardized antihypertensive drugs, which therefore precluded the prediction of response to antihypertensive drug therapy.

In order to overcome the confounding factors encountered in the Symplicity HTN-3 study (ie, medication adherence, study population, procedural variability, insufficient renal nerve ablation), currently ongoing SPRYRAL HTN Global Clinical trial further evaluates the potential efficacy of RDN. The trial uses the next generation RDN multi-electrode Symplicity Spyrал catheter, which delivers radiofrequency energy treatment to all 4 renal artery quadrants and is likely to provide sufficient nerve ablation circumferentially. This global randomized sham-controlled program includes 2 studies aimed to determine the effects of RDN on BP control in patients with hypertension who are drug naive or who are able to discontinue existing pharmacological therapy (SPYRAL HTN OFF-MED study) and patients with moderate to high-risk hypertension on 3 antihypertensive drugs (SPYRAL HTN-ON MED study).

Baroreflex activation therapy Electric stimulation of carotid sinus baroreceptors through modulation afferent signaling is another attractive approach for the treatment of RH. The safety and efficacy in substantial and durable BP-lowering effect with the CVRx Rheos System was demonstrated in the initial proof of concept study (DEBuT-HT Trial). The implantation of the first generation device was associated with procedure-related serious adverse events and the short-term battery life, which limited its utility. The next generation minimally invasive BAROSTIM neo led to a significant BP reduction in RH patients at 3- and 6-month follow-up, even in a subset of patients previously treated with RDN, and was associated with less device-related side effects. Further proof for additive BP lowering and antiproteinuric effects achieved by BAT was demonstrated.

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in 28 patients presenting with elevated BP despite previous RDN performed 5 months earlier.92

Two recent case reports that demonstrated the beneficial clinical utility of BAT in acute clinical scenarios deserve to be mentioned. Generally, the BAT device is activated between 2 and 4 weeks after surgical implantation to allow the site to heal. Its immediate activation in a young man with hypertensive crisis following aortic dissection due to RH that was unresponsive to sympatholytic agents resulted in a rapid, significant, and sustained BP reduction out to 12 months after procedure with no further incidence of hypertensive crisis.93 While the application of BAT in an emergency situation may not be feasible, the potential of this treatment option should be emphasised.

Clinical utility of the second generation Barostim neo was demonstrated in the first in-man treatment of severe BP variability greater than 30 mm Hg in a patient diagnosed with a progressive central and peripheral dysautonomia secondary to Sjögren syndrome and impaired cardiovascular reflex regulation.94 While initially no significant improvement was observed following the procedure, cessation of all antihypertensive medication revealed the true effect of BAT – the improvement of BP variability and associated symptoms. This observation suggested that drugs acting on different mechanisms (short acting central sympathectyics [clonidine and/or methyldopa], α-blocker [prazosin] and β-blocker [metoprolol]) were likely to potentiate neural baroreflexes, thereby interfering with BAT in this patient. Nevertheless, this case report highlights further clinical applicability of BAT in severe forms of difficult to manage hypertension.

**Carotid body denervation**  The association between potentiated tonic chemoreflex sensitivity and increased sympathetic activation in hypertension pathophysiology encouraged the initiation of studies investigating the feasibility and efficacy of a therapeutic intervention directed at modulation of peripheral arterial chemoreceptors located in the carotid body.95 The clinical benefits associated with resection of unilateral carotid body was first described in the early 1960s as a surgical approach for the management of asthma in patients who failed to respond to conventional therapy.96 Data from rat model of neurogenic hypertension demonstrated that CBD results in sustained reduction in BP and sympathoinhibition with a more pronounced lowering of BP when combined with RDN, which suggested independent afferent inputs to disease process.97 The results from the first in-human proof of concept study of a total of 15 patients with RH who underwent unilateral carotid body removal came from Gdansk’s group.98 Histology material revealed the finding of glomus cells in resected tissue in 14 out of 15 treated patients confirming the feasibility of the surgical approach. There were no significant changes in office, home, and ambulatory BP at follow-up. However, when patients were divided according to the reduction in daytime systolic BP greater than or equal to 10 mm Hg from 3 months after the procedure, eight out of 15 patients showed a significant and sustained reduction in daytime and nighttime BP accompanied by a reduction in MSNA and in number of antihypertensive medication out to 12 months follow-up. Interestingly, all patients who showed a decrease in BP underwent carotid body removal on the right side. In a patient previously treated with RDN who had the left carotid body removed, no short-term and long-term BP changes were noted after the procedure. Another novel finding was the association between the BP responses and increased chemoreflex sensitivity which indicated the underlying contributing mechanism of RH. While these finding were promising and BP lowering effects appeared higher when compared to RDN, this approach requires general anesthesia. Based on the results of a surgical removal, currently ongoing clinical trials are aimed at determining the effects of CBD through an arterial- or venous-based catheter approach for the treatment of difficult to control hypertension.

**Deep brain stimulation**  Implanting electrodes within certain areas of the brain nuclei modulates local pathological activity involved in a specific disease process. Therapeutic effects of DBS have been successfully demonstrated in a wide range of neurological disorders (eg, Parkinson disease, chronic pain syndrome resistant to analgesics, major depressive disorder, dystonia, epilepsy, schizophrenia). The long-term DBS was found to restore local brain structural connectivity and global functional connectivity (eg, Parkinson disease).99 The first clinical evidence that demonstrated an effective BP reduction after DBS was reported in a patient who primarily underwent a stimulation of the ventrolateral PAG/periventricular gray matter to treat his chronic central pain syndrome that was unresponsive to pain-relief drug.100 While DBS alleviated pain levels for 4 months which then returned to the same level as before the procedure, there was a gradual decrease in BP up to 33 months after DBS with medication withdrawal postoperatively. These results indicated that the site in the brain (PAG) can be a target for sympathetic BP control and center for pain modulation. Further proof for sustained BP reduction with corresponding decreases in HR variability and pulse pressure following stimulation of PAG was documented in a man, who initially underwent DBS to relieve his neuropathic facial pain resistant to other regimens.101 Very recently, DBS led to a pronounced reduction in BP and MSNA in a resistant hypertensive patient with BP readings of 300/170 mm Hg, despite taking 8 antihypertensive drugs and previous device therapies, including chronic BAT and bilateral RDN.102 This observation indicated that DBS has the potential to treat severe forms of uncontrolled hypertension in which available
pharmacological approach failed, and presumably to treat nonresponders to device-based or interventional strategies. It is yet to be established whether DBS may be associated with neuroplasticity over long periods in patients with hypertension that is difficult to treat.

Central arteriovenous anastomosis The ROX Coupler device is another therapeutic option for achieving BP reduction. The creation of a 4-mm anastomosis between the iliac artery and iliac vein diverges a defined amount of arterial blood (~800 ml/min) into the venous system, which leads to beneficial hemodynamic alterations (eg, a reduction in total vascular resistance, an increase in arterial compliance and oxygen delivery to tissues) and immediate and sustained reduction of BP. Evidence for the feasibility and efficacy of the ROX system comes from a multicenter controlled trial in which RH patients were randomized to either interventional creation of anastomosis in addition to concomitant medication, or to BP-lowering medication alone. The primary efficacy endpoint was met, which was a significant reduction in office systolic BP and 24-hour daytime systolic BP at 6-month follow-up in the anastomosis group when compared to the control group. However, implantation of the AV coupler was associated with a number of adverse events (ie, anemia, transient bradycardia, deep venous thrombosis, intimal dissection of the iliac artery, lower limb pain) and late ipsilateral venous stenosis in 12 out of 42 patients that required venoplasty or stenting. Given the associated high postprocedural risk and potential in improving BP control, the ROX anastomosis device should be considered particularly in the absence of other options available, in patients who failed or are not eligible for RDN (ie, inappropriate renal anatomy) or CBD (ie, invisible or difficult access to the carotid body). Further studies need to determine the long-term safety and efficacy of this intervention and define the mechanisms underlying BP-lowering effects.

Perspectives Increasing the awareness of hypertension and cardiovascular risk associated with it is a global imperative for reducing the burden of disease connected with raised BP. The substantial increase in morbidity and mortality attributable to poorly controlled hypertension worldwide can be considerably reduced by improving patient medication adherence and physician therapeutic inertia. However, despite the wide range of available pharmacological approaches to BP lowering, there is still a portion of patients who remain resistant to drug therapy. Innovative device-based and procedural interventions that directly manipulate the mechanisms underlying hypertension successfully demonstrated their ability to lower BP in a vast majority of patients. The high variability in BP response to these therapies indicates that the pathophysiology, including complex neural reflexes that may trigger a disease in an individual, is still not completely understood. Nevertheless, the available data suggest a disturbed regulatory process underlying BP and sympathetic regulation at the central and peripheral levels, including augmented activity of the sympathetic, vasopressinergic, and renin-angiotensin-aldosterone systems. This abnormal function may further impair brain neuronal activity, as well as compensatory functional and structural reorganization. Understanding the underlying mechanisms and neuroplasticity in hypertension may open a new arena for future therapies and therefore clearly warrants further studies.

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