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HYPERTENSION AND THE BRAIN (S STOCKER, SECTION EDITOR)

# The Role of Central Nervous System Mechanisms in Resistant Hypertension

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**Abstract** Arterial hypertension remains a primary global health problem with significant impact on cardiovascular morbidity and mortality. The low rate of hypertension control and failure to achieve target blood pressure levels particularly among high-risk patients with resistant hypertension has triggered renewed interest in unravelling the underlying mechanisms to implement therapeutic approaches for better patient management. Here, we summarize the crucial role of neurogenic mechanisms in drug-resistant hypertension, with a specific focus on central control of blood pressure, the factors involved in central integration of afferent signalling to increase sympathetic drive in resistant hypertension, and briefly review recently introduced interventional strategies distinctively targeting sympathetic activation.

**Keywords** Resistant hypertension · Central sympathetic nervous system · Noradrenaline spillover · Muscle sympathetic nerve activity · Neural reflex mechanisms · Oxidative stress · Therapeutic intervention

## Introduction

The sympathetic nervous system (SNS) acts as a key regulator of blood pressure (BP), cardiovascular control (CV) and function of the majority of all internal organs. Slightly elevated BP, even in high-normal levels, when sustained over time alters autonomic neural balance resulting in sympathetic activation preceding subsequent arterial hypertension. Increased efferent postganglionic sympathetic excitation is causative of established hypertension and disease progression with adverse impacts on various peripheral organs. Of particular relevance is neural control of the kidney which plays a critical role in centrally mediated BP regulation via sensory afferent fibres originating from the kidney, influencing reflex neural mechanisms in the brain stem. The global burden attributable to uncontrolled hypertension, particularly resistant hypertension (RH), has led to a rapid development of mechanism-based novel approaches targeting the neurogenic component of this condition. While experience with interventional strategies attempting to restore autonomic balance along with improved BP control via stimulation of organ-specific homeostatic mechanisms (deep brain stimulation, carotid sinus baroreceptor activation) or ablation of renal nerves appear promising in drug-RH, only larger-scale clinical studies will define the long-term safety, effectiveness and patient outcomes associated with these therapies.

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## Role of the Sympathetic Nervous System in Human Hypertension

The sympathetic nervous system (SNS) is activated in human hypertension, with an increase in sympathetic outflow to the kidney, the heart and the skeletal muscle vascular bed as convincingly demonstrated by the use of isotope dilution method for quantifying noradrenaline (NA) spillover rates and postganglionic efferent sympathetic nerve recording with microneurography. NA spillover has allowed for assessment of regional differentiation of sympathetic outflow. While the rate of overflow of NA into plasma has been documented for

most internal organs, neurotransmitter release from the heart and the kidney is most relevant in initiating and maintaining arterial hypertension [1••, 2]. Increased NA release from the renal sympathetic nerves is present in patients with untreated essential hypertension (EH), particularly below the age of 40 [3••], and is a primary trigger for BP elevation [4]. Augmented cardiac NA spillover and reduced neuronal NA reuptake further contribute to sympathetic activation in EH [5].

In the healthy heart, the amount of adrenaline release from the sympathetic nerves is negligible as the majority (80 %) of adrenaline is secreted from the adrenal medulla into the blood stream, with only a small amount released from sympathetic nerve endings. However, in patients with untreated EH, adrenaline release has been reported from cardiac sympathetic nerves providing a possible additional mechanisms of potentiated NA release through adrenaline co-transmission [6••]. Additionally, stress *per se* induces adrenaline plasma release and is likely to enhance neuronal uptake of adrenaline in cardiac sympathetic nerve endings leading to discharge of adrenaline as co-transmitter supporting the 'adrenaline hypothesis' in EH [6••].

In fact, patients with uncontrolled hypertension are at high risk for developing heart disease and kidney disease with the progression to heart failure (HF) and kidney failure over time. Accordingly, the prognosis in HF has been directly linked to the magnitude of NA release from the cardiac sympathetic nerves [7••], while increased NA release from the renal sympathetic nerves has been shown to be a strong independent predictor of all-cause mortality and heart transplantation in HF patients [8••]. Clearly, elevated cardiac and renal sympathetic tones are core features of human hypertension and associated with disease progression and mortality. High levels of cardiac and renal NA spillover accompanying increased muscle sympathetic nerve activity (MSNA) measured by microneurography have been related to heart damage including left ventricular (LV) hypertrophy [9] and LV dysfunction [10] in untreated EH. However, it is not only elevated blood pressure (BP) and hypertension-related ventricular remodelling that is characterized by sympathetic activation but also increased rate of sympathetic nerve firing is evident in low risk subjects with high-normal BP [11], EH [5] with a further 2–3-fold increase in patients with true resistant hypertension (RH) irrespective of the combination of multi-drug therapy which supposed to oppose chronic sympathetic outflow [12••, 13, 14••]. Indeed, our own experience indicates that patients with RH are characterized by high levels of MSNA when compared to healthy controls and EH patients, with burst activity evident with every heartbeat, often superimposed within one cardiac cycle (*sharp* '*M*' *shape burst*) due to high sympathetic nerve firing. While there is an increased incidence of sympathetically mediated associated co-morbidities in patients with RH including diabetes, CKD, obesity and obstructive sleep apnoea (OSA) [15], the mechanism implicated in drug resistance are not fully understood. Sympathetic excitation is primarily derived from specific autonomic brain regions and/or impaired peripheral neural reflex mechanisms including arterial baroreceptors, arterial chemoreceptors and cardiopulmonary mechanoreceptors. The regulatory process underlying sympathetic activation in RH remains uncertain, though it is likely to involve an imbalance between catecholaminergic neurons widely distributed in the brain stem and possible loss of inhibition transmitted from non-catecholaminergic structures in the rostral and caudal ventrolateral medulla.

Despite substantial progress in the management of hypertension and a better understanding of the mechanisms controlling BP, one in every ten adults is likely to fail in achieving target BP with antihypertensive pharmacotherapy with true RH warranting alternative treatment options to minimize associated cardiovascular (CV) risk [16, 17]. Of clinical relevance, therapeutic approaches aimed at SNS inhibition via modulation of interrelated pathways appear pivotal for attaining BP control and reducing adverse complications associated with chronic elevation of sympathetic drive in neurogenic hypertension.

## Role of Autonomic Brain Regions in Sympathetic and Blood Pressure Control

Tonic sympathetic activation and tonic arterial pressure control critically depend on central integrative structures in the brain stem, specifically the rostral ventrolateral medulla (RVLM) (Fig. 1). Descending projections to the RVLM arise among others from the neurons in the peri-aqueductal grey (PAG) and hypothalamic paraventricular nucleus (PVN). The RVLM integrates reflex neural mechanisms from arterial baroreceptors, chemoreceptors and various afferent sensory visceral receptors via direct connection with the upper part of the medulla through the nucleus tractor solitarius (NTS) and PVN which modulate vasomotor sympathetic nerve discharge and BP. Evidence from experimental models has indicated that up to 70 % of spinally projecting RVLM neurons are sympathoexcitary C1 neurons. These play a critical role in tonic drive and reflex control of sympathetic vasomotor activity to the preganglionic motor neurons of the spinal cord, thereby directly modulating peripheral SNS activity. Consequently, chemical, electrical or photo stimulation of most of the RVLM neurons increases BP, which subsequently decreases with experimental cooling, destruction of the region or GABA agonists injection [18••, 19–21]. Under physiological conditions, arterial baroreceptors play a fundamental role in preventing excessive variation in BP levels. Afferent signals from baroreceptors stimulate the NTS in the upper part of the medulla in response to the distension of the vessel wall caused by transmural pressure. Subsequently, a signal arising from the NTS exerts a (1) parasympathetic vagal effect

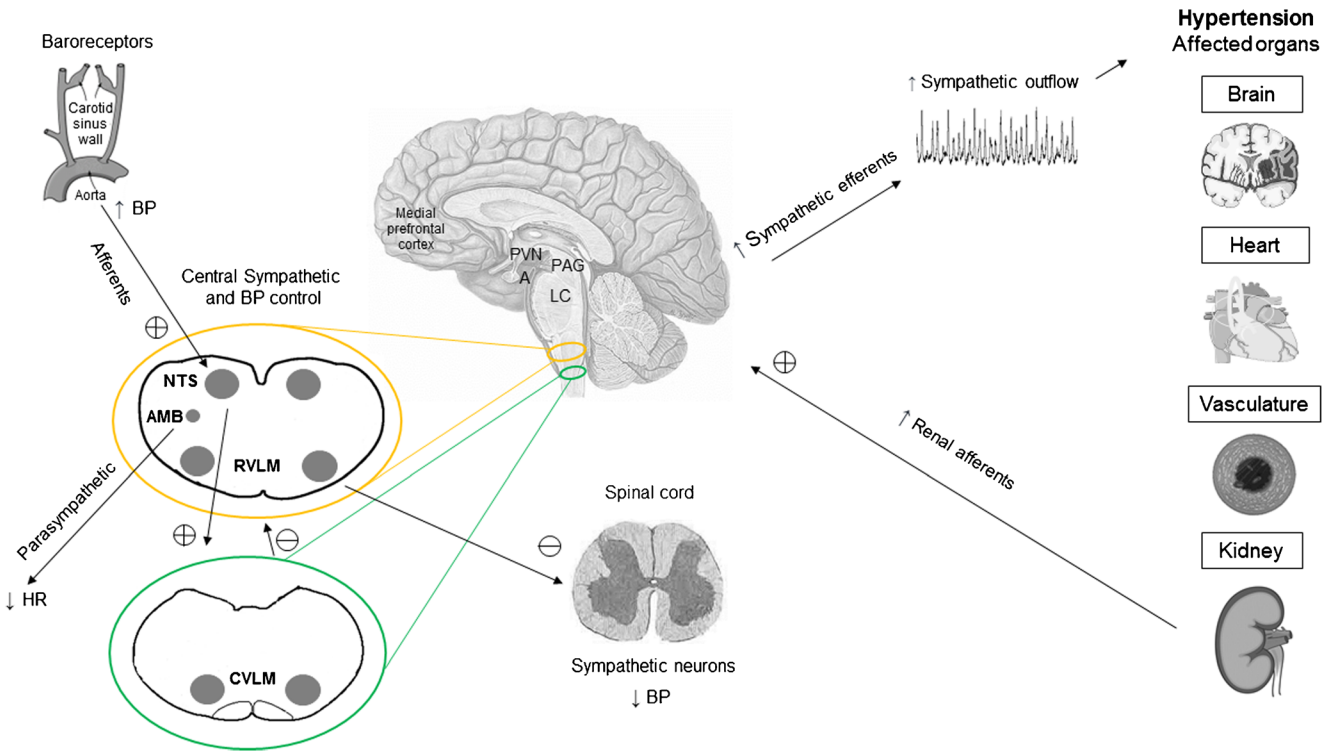


**Fig. 1** Central tonic sympathetic outflow and blood pressure (*BP*) control in central integrative structures in the brain stem; the upper part of the medulla, rostral ventrolateral medulla (*RVLM*), and lower part of the medulla, caudal ventrolateral medulla (*CVLM*). Parasympathetic outflow to the heart arises mainly from neurons in the nucleus ambiguous (*AMB*). Descending projections to the *RVLM* from the periaqueductal grey (*PAG*) and hypothalamic paraventricular nucleus (*PVN*). Projections from the amygdala (*A*) and locus coeruleus (*LC*) involved in behavioural, psychological and cognitive control

resulting in slowing HR and (2) direct activation of the lower caudal ventrolateral medulla (CVLM) (3) and reduced tonic sympathetic activity generated in the RVLM. Depressor neurons of the CVLM provide direct tonic inhibition to the RVLM neurons (Fig. 1). In this context, a reduction in tonic sympathoinhibitory function of the CVLM to RVLM is likely to contribute to the development of hypertension. In fact, the parasympathetic cardiac component of the baroreflex is impaired in patients with hypertension and a family history of hypertension [22]. While the lack of activity of depressor neurons of the CVLM on the RVLM has been shown to be attenuated in spontaneous hypertensive rats and renovascular hypertensive rats [23, 24], the activity of CVLM and RVLM neurons in human arterial hypertension has not been tested directly.

Central nervous system (CNS) NA turnover in humans can be estimated from the combined overflow of brain NA and its lipophilic metabolites into the internal jugular veins [25••, 26]. Indeed, direct blood sampling from the internal jugular veins and simultaneous cerebral blood flow scans revealed that CNS mechanisms involving suprabulbar noradrenergic projections from the brain stem to the hypothalamus play an important role in sympathetic activation in untreated EH [27]. Augmented NA release from subcortical brain regions but not cerebral cortex corroborates the critical contribution of sympathoexcitatory and pressor noradrenergic brain neurons to elevated BP in patients with EH [25••], mediating increased sympathetic outflow to the periphery. Subcortical NA turnover in brain regions is significantly higher in EH when compared to healthy subjects and directly related to MSNA in healthy subjects, total body NA spillover in normal and hypertensive subjects combined and renal NA spillover in EH [25••, 27]. Notably, among noradrenergic neurons in the brain stem, the locus coeruleus (LC) is the largest source of NA production [28, 27]. In this context, the role of kidney in centrally mediated cardiovascular regulation is of significant relevance. The kidney has a dense network of chemoreceptors and baroreceptors that transmit afferent signals to the brain stem. These afferent signals originating from unmyelinated renal sensory fibres travelling along arteries enter the dorsal roots and project to spinal and supraspinal neurons and the hypothalamus causing increase in BP and sympathetic outflow to peripheral organs [29, 30]. A series of experimental studies showed that kidney failure following 5/6 nephrectomy in rats causes subsequent hypertension through sympathetic activation. Dorsal rhizotomy in the dorsolateral part of the thoracolumblar vertebral bodies (T10-L2) led to a significant BP reduction and prevented an increase in NA turnover rate in the LC (A6), and posterior and lateral hypothalamus where the majority of brain NA-producing neurons reside [31••].

In humans, bilateral nephrectomy reduced or 'normalized' MSNA in hemodialysis patients [32••] and renal transplant recipients [33]. Furthermore, bilateral nephrectomy improved BP control in hemodialysis patients with RH [34••]. This observation affirms that afferent renal sensory fibres originating from the failing kidney cause sympathetic activation and BP elevation [32••, 33, 34••].

## Role of Central Processes in Sympathetic Outflow

The association between obstructive sleep apnea (OSA) and hypertension is well recognized [16]. Accordingly, OSA is associated with augmented sympathetic excitation contributing to neurogenic hypertension. Very recently, a study using functional magnetic resonance imaging (MRI) assessed brain activity and regional grey matter changes in OSA patients with simultaneous MSNA recordings [35••]. In comparison to healthy controls, high levels of MSNA in OSA patients appear to be 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 via the brainstem regulatory nuclei. Increased signal intensity in the medial prefrontal cortex and covariation with MSNA levels in OSA patients when compared to controls [35••] may have important implications for understanding the mechanisms involved in reduced baroreflex gain in OSA and RH. Accordingly, the medial prefrontal cortex has projections to the NTS and RVLM which are responsible for sympathetic and BP regulation [35••].

In view of recent meta-analysis demonstrating favourable effects of renal denervation (RDN) in reducing apnea-hypopnea index and BP in OSA patients [36], it is reasonable to speculate that interrupting afferent signalling from the kidney to brain stem via renal nerve ablation may reverse altered functional brain changes thereby improving outcomes in OSA patients. At this stage, the functional changes in blood oxygenation and flow in response to brain neural activity in RH patients remain unknown. Likewise, the potential impact of therapeutic interventional strategies opposing chronic sympathetic drive on brain functional imaging in RH needs to be determined.

## Role of Renal Denervation

In view of the well-established contribution of the SNS and renal nerves to the initiation, development and maintenance of elevated BP, the interruption of renal sympathetic and afferent nerves appears as a reasonable treatment approach to improve BP control in RH and renal failure patients. Accordingly, RDN has improved BP control over the longer term [37••, 38••] and has been introduced to clinical practice [16]. The recent Symplicity HTN-3 study was unable to confirm a BP-lowering effect above that of the sham control [39••] although it has been questioned whether RDN was actually achieved in this study [40••]. In an initial proof-of-concept pilot study of a total of 12 patients with end-stage renal disease (ESRD) and uncontrolled BP [41••], eight out of nine patients from the study cohort who had eligible anatomy of renal arteries to ablate the nerves experienced a substantial improvement in BP control. The reduction in renal NA spillover directly after bilateral RDN and in MSNA at follow-up was observed in the two patients who also underwent assessment of sympathetic activation [41••]. The reduction of whole body NA spillover, renal NA spillover and postganglionic efferent multi-unit MSNA in addition to BP improvement has also been demonstrated in patients with RH in the short term [42••, 12••, 13] and longer term [14••] out to 12 months post RDN. Interestingly, the reduction in multi-unit MSNA after RDN was accompanied by even more pronounced reduction in all properties of single active vasoconstrictor neurons including firing rate, firing probability and the incidence of multiple spikes within one cardiac cycle which may be reflective of central mechanisms integrating afferent signalling from the kidneys and efferent sympathetic outflow resulting in sympathetic inhibition and BP control [12••].

Additional relevant findings involving brain noradrenergic neurons, hypothalamic and amygdala projections in behavioural responses mediated autonomic activation were observed after RDN [43••, 44]. Patients with RH experienced a significant improvement in health-related quality of life aspects including the mental components (i.e. the vitality, social function, role emotion, mental health). These effects were unrelated to the BP-lowering effect post procedure. Additionally, symptoms indicative of depression including sadness, tiredness and libido were considerably attenuated with RDN [43••]. The potential impact of RDN to favourably modulate brain regions involved in cognitive processing was confirmed in another study demonstrating a substantial reduction in anxiety, depressive symptoms, the intensity of headache and stress tolerance after the procedure [44].

## Role of Neurovascular Compression in Resistant Hypertension

Pulsatile vascular compression between arterial and neural tissue in the medulla has been shown to be implicated in sympathetically mediated hypertension. Neurovascular compression (NVC) related to hypertension results from the compression and subsequent irritation of the left RVLM regions at the levels of the C1 neurons and/or the root entry zone of cranial nerves by looping arteries, mostly posterior inferior cerebellar artery (PICA) and/or vertebral artery [18••]. Among several proposed theories for the association between NVC on the left side and BP rise, oxygen deficiency resulting from the compression of nerve IX and X is likely to cause deafferentation of the NTS leading to loss of inhibitory effect transmitted

from the NTS and sympathoexcitation of C1 neurons. While NVC may potentially involve various cranial nerves in that area (i. e. V, VII, VIII, XII), compression of the cranial glossopharyngeal and vagus nerves appear to predominantly contribute to BP elevation. Visceral afferent fibres of the IX nerve provide sensory information from the carotid body baroreceptors to the NTS while a signal arising from the aortic body baroreceptors is transmitted via X afferent fibres modulating BP control. While screening for posterior fossa NVC in the management of RH is not routinely performed, it should be noted that neurovascular pulsatile compression, commonly present on the left side at the RVLM, has been documented in patients with RH. Previous studies have demonstrated a substantial decrease in BP and antihypertensive regimens in seven out of eight patients with uncontrolled BP 3 months following microvascular decompression (MVD) of IX and X cranial nerves root entry zone causing pulsatile neurovascular compression, with sustained BP reduction in four patients who were followed out to 12 months post procedure [45]. Additional interesting observation for a beneficial effect of a single MVD comes from a case report of a 72-year-old woman demonstrating typical clinical symptoms including trigeminal neuralgia, hemifacial spasm and tinnitus in addition to hypertension and paroxysmal supraventricular tachycardia (PSVT) caused by vertebral artery and subsequent compression of cranial nerves V, VII, VIII, IX and X. Of note, decompression of the posterior cranial fossa alleviated all symptoms immediately after the surgery with corresponding BP improvement and the absence of PSVT out to 8 months post procedure [46]. Further proof for a favourable BP-lowering effect and improved sensitivity to antihypertensive medication after successful neurosurgical decompression of the brain stem has been documented retrospectively in nine patients with severe primary hypertension not responding to conventional drug therapy and seven non-operated patients with neurovascular compression who were followed over a 2-year period [47]. While MVD resulted in a significant and permanent fall in BP accompanied by an improved response to medication over 2 years following the procedure, there were no noticeable changes in BP in controls at that point in time [47]. Additional retrospective analysis of 13 patients with RH revealed that MVD independently of the types of NVC (brain stem and/or the nerves IX–X) and/or side (left and/or right) led to a reduction in BP in all types of NVC, with a more pronounce BP-lowering effect when NVC affected both the brain stem and the nerves on the left side [48]. Whether NVC of its origin is a leading contributor to sympathetic activation and thereby causing BP elevation or remains a secondary cause of HT is debated. Nevertheless, studies based on microneurography have shown that NVC is associated with augmented MSNA in both normotensive and hypertensive subjects [49••]. Moreover, the prevalence of NVC and the magnitude of MSNA was greater in EH when compared to normal BP and high-normal BP suggesting that pulsatile compression may play a critical role in triggering sympathetic activation and may precede the development of hypertension [49••]. Further observation has shown that only hypertensive patients with signs of NVC of the RVLM on the MRI have high MSNA but not hypertensives without deformation or only vascular contact visible on the MRI [50]. While MVD results in sustained reduction in BP, MSNA and medication use from baseline to 12-month follow-up in RH, surprisingly it appeared that resting MSNA returned to the baseline BP and MSNA levels from 18 to 24 months post procedure [51]. Whether the rebound of hypertension and sympathetic activation in RH is associated with counter-regulatory neurohumoral mechanisms, increased hyper-responsiveness of beta-adrenergic receptors during sympathetic inhibition, occurrence of other sympathetically mediated co-morbidities or long history of primary hypertension requires further investigation.

In view of available data, NVC of the RVLM by a looping artery could be a potential underpinning cause of drug-RH when BP remains elevated despite multi-drug antihypertensive combination therapy, medication adherence and patient compliance. Furthermore, NVC associated with hypertension is often not accompanied by clinical symptoms such as cranial rhizopathies. At this stage, there is no supportive evidence for MVD in long-term BP control in RH. Nevertheless, therapy with clonidine appears to be a useful approach in NVC associated with drug-hypertension with drug-RH and CKD [52] and should perhaps be offered to patients until a suitable group of RH patients who may benefit from the MVD procedure can be identified.

## Deep Brain Stimulation

Deep brain stimulation (DBS) is a promising interventional therapy designed to alter pathological and sympathetic activity within the CNS and has gained significant recognition in the treatment of Parkinson's disease. In addition to a wide range of neurological disorders, DBS of the ventrolateral (PAG)/periventricular grey matter has been successfully demonstrated in RH [53••, 54]. While the central grey is the primary control centre for descending pain modality, it also sends descending projections to the RVLM. DBS was initially performed to treat chronic central pain syndrome unresponsive to pain relief drugs; however, it unexpectedly produced a sustained BP reduction in the two patient cases. While the effect of DBS of MSNA in RH is unknown, more recently acute DBS of specific midbrain nuclei and ventrolateral PAG improved acutely vasomotor baroreflex sensitivity, reduced MSNA and BP in patients with chronic neuropathic pain and Parkinson's disease [55]. Although costly and associated with a potential 1 % stroke risk, DBS appears to be an alternative therapeutic approach for treating severe forms of uncontrolled hypertension and/or possibly patients unresponsive

to other currently available interventional strategies. However, whether BP control achieved with DBS may improve patient outcomes needs to be investigated further.

### Baroreceptor Stimulation

Arterial baroreceptors are an important centrally mediated mechanism involved in the short-term BP regulation. However, in the presence of sustained BP elevation, baroreflex control becomes less sensitive in mediating changes in sympathetic activity to the heart and blood vessels. In this context, prolonged electric stimulation of baroreflex afferent nerves has been shown to be associated with a marked BP-lowering effect via baroreceptor-induced central sympathoinhibition [56]. Although the role of baroreflex control in long-term regulation is not entirely understood in humans, recent data from electrical stimulation of carotid sinus baroreceptors via an implantable device has provided novel insights into baroreflex physiology in RH patients. Indeed the safety and efficacy of device-based chronic baroreflex activation therapy (BAT) with the CVRx Rheos System (DEBuT-HT Trial) was demonstrated in high CV risk patients with RH. The magnitude of the fall in BP 3 months following device implementation was maintained in patients who were followed out to 53 months post procedure [57••, 58]. While safe and effective in terms of BP control, BAT with the CVRx Rheos System was associated with serious procedure-related adverse events and short-term battery life when compared to new generation device, the BAROSTIM neo which produced a significant BP reduction at 3- and 6-month follow-up, even in patients previously treated with RDN, with less device-related side effects [59]. Regarding sympathetic activity, the acute effect of BAT has only been determined in 12 patients with RH indicating a rapid reduction in BP and MSNA when the stimulator was switched on, returning to baseline level when switched off [60]. In view of the dominant role of the kidney in long-term BP and MSNA improvement [14••], further clinical studies need to determine the applicability of BAT on hypertension-induced end organ damage and neural function.

### Role of Oxidative Stress in Central Brainstem

Oxidative stress is implicated in the progression of CV disease. There is also supportive evidence from numerous experimental and clinical studies linking oxidative stress to the development and maintenance of hypertension [61]. Recently, increased oxidative stress has been suggested to promote transition from pre-hypertension to established hypertension [62], while therapy with nebivolol via inducing endothelium-dependent vasodilation via nitric oxide (NO) pathway led to a substantial increase in nitric oxide production in pre-hypertension and arterial hypertension [63]. While the mechanisms inducing the reduction in NO, bioavailability or impairment NO-mediated vasodilation in hypertension are not entirely understood, supportive evidence from experimental models is indicative of a bidirectional interaction between NO and SNS in modulating BP levels [61]. Accordingly, central production of oxidative stress in autonomic brain regions, particularly in the RVLM, increases central sympathetic activation thereby triggering BP elevation [64]. In this context, a better understanding of brain mechanisms linking oxidative stress to human neurogenic hypertension may help to implement novel therapies for drug-RH.

## Conclusion

Arterial hypertension remains a growing and challenging clinical problem. Special attention should be given to drug-RH affecting ~10 % of hypertensive adults. Currently available clinical interventional therapeutic strategies that have the potential to favourably modulate autonomic neural mechanisms such as RDN and carotid baroreceptor stimulation, if performed by experienced operators, can be offered to RH patients in the case of ineffective drug therapy. Given the importance of neurogenic hypertension, unravelling the CNS mechanisms implicated in human RH is likely to have a substantial impact in the application of specific treatment approaches for attaining BP control and reducing adverse complications associated with chronically elevated sympathetic drive.

#### Compliance with Ethics Guidelines

**Conflict of Interest** Dagmara Hering declare no conflicts of interest. Markus Schlaich is supported by career fellowships from the NHMRC, is an investigator in studies sponsored by Medtronic, serves on scientific advisory boards for Abbott (formerly Solvay) Pharmaceuticals, BI, Novartis Pharmaceuticals, BI, and Medtronic and has received honoraria and travel support from Abbott, BI, Servier, Novartis, and Medtronic. The laboratories of Dr. Schlaich receive research funding from Medtronic, Abbott Pharmaceuticals, Otsuka and Servier Australia.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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