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Cerebral Microvascular Dysfunction and Clinical Considerations of Systemic Arterial Hypertension

Jenny Kim¹, Rowena Mobbs², Antonio Di Ieva³

¹Department of Clinical Medicine, James Cook University, College of Medicine and Surgery, Mackay 4740, QLD, Australia, ²Department of Clinical Medicine, Specialist Clinician Neurologist, Macquarie University Hospital, Sydney 2109, NSW, Australia, ³Department of Clinical Medicine, Faculty of Medicine, Health and Human Sciences, Macquarie University and Macquarie Neurosurgery, Sydney 2109, NSW, Australia

Abstract

Hypertension is one of the most commonly diagnosed conditions in the general population. In 2017, the American College of Cardiology and American Heart Association lowered the threshold for hypertension diagnosis from 140 mmHg to 130 mmHg for systolic blood pressures. These new guidelines have brought into question the true prevalence of hypertension and overall risk of hypertensive complications. While the cardiovascular effects of hypertension have been a long-held concern, there is a growing awareness for the need to understand the extracardiac concerns of hypertension. Specifically, the brain and nervous system are vulnerable extracardiac targets of hypertensive damage. Hypertension is a well-known risk factor for ischemic and more so hemorrhagic stroke as well as cerebral small vessel disease (cSVD) including vascular dementia. However, hypertension may also have association to less-known neurological presentations which themselves may also pose risk for stroke and cSVD. This includes obstructive sleep apnea, posterior reversible encephalopathy syndrome, and neurogenic hypertension. We aim to present an overview of the contemporary literature in regard to hypertension and clinical consideration as it applies to the cerebrovascular system.

Key words: Arterial hypertension, cerebrovascular, hypertension, neurology, neurosurgery

Introduction

For decades, arterial hypertension has been a well-established health burden, notably for cardiovascular complications such as ischemic heart disease (IHD). Known as the silent killer, extracardiac complications of hypertension have become a primary concern for preventative healthcare.^[1] Ischemic and hemorrhagic stroke are archetypal examples that combined, have risen from fifth (1990) to third (2017) on the list of most prevalent causes of early death globally, after IHD and neonatal disorders.^[2]

The global prevalence of hypertension has been predicted to rise from 972 million in 2000 to 1.56 billion by year 2025.^[3] Current rates are already at an estimated 1.13 billion (2015).^[4] In 2017, the American College of Cardiology and American Heart Association lowered systolic pressure

thresholds that define hypertension, from 140 mmHg to 130 mmHg [Table 1].^[5] This was in response to a randomized clinical trial data demonstrating that lower cardiovascular events and mortality rates are associated with a systolic pressure target of <120 mmHg.^[6] These new diagnostic thresholds have been inconsistently implemented across clinical practice and research, making current prevalence predictions inaccurate and subsequent extracardiac consequences underestimated.^[7]

However, there is a growing body of research and clinical knowledge of hypertension-associated pathophysiology and clinical outcomes. In addition, traditional borders segregating the roles and functions unique to each clinical specialty are becoming multidisciplinary. Thus, there is a growing need to have an up-to-date knowledge base of hypertension-associated pathologies as it relates to their specialty. In the context of neurology, this knowledge refers to the impact of hypertension

Address for correspondence:

Antonio Di Ieva, Suite 201, Level 2, 2 Technology Place, Macquarie University, NSW, 2109, Sydney, Australia.

E-mail: antonio.dileva@mq.edu.au

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Table 1: American Heart Association classification of BP in adults^[5]

BP category	Unrevised BP thresholds (mmHg)		2017 revised BP thresholds (mmHg)	
	Systolic	Diastolic	Systolic	Diastolic
Normal	<130	<85	<120	<80
High normal	130–139	85–89	120–129	<80
Hypertension stage 1	140–159	90–99	130–139	80–89
Hypertension stage 2	160–179	100–109	≥140	≥90
Hypertensive crisis	>180	>110	>180	>120

BP: Blood pressure

to neurological presentations less known than cerebral small vessel disease (cSVD) and stroke.

This aim of this review is to provide an overview of the clinical impact of systemic arterial hypertension to microvascular brain pathophysiology by: (1) Outlining the pathophysiology of hypertension as it relates to clinical neurology, (2) summarizing the contemporary concerns and findings of arterial hypertension as it relates to the microvascular pathophysiology of neurological and neurosurgical presentations, and to (3) describe potential clinical recommendations and future direction for clinicians.

Literature Review Process

A literature review was conducted on Medline (Ovid) database on February 3, 2020, using the search terms, respective synonyms and MeSH headings: Neurology OR Neurosurgery AND hypertension AND microvascular. Full search criteria can be accessed in Appendix 1. Additional articles were identified perusing reference lists of included articles.

A total of 281 studies were found. For a broad scope, all non-animal English articles and reviews that examined arterial hypertension-associated pathology in neurological pathologies in the past 10 years (2011–2020) were included in this review.

For the limits of our aim, articles discussing hypertension only in association with cSVD or stroke were excluded. Application of the new hypertension thresholds in obstetric presentations is yet to be implemented, and thus peri-partum presentations including pre-eclampsia were excluded from the study. Due to differences in pathology and management, articles in pediatric settings were excluded. Articles discussing venous hypertension were excluded. Conference abstracts, case reports, non-English, animal, and opinion papers were excluded from the study.

Duplicates were removed and 275 articles screened. A total of 29 articles were chosen for review.

Cerebrovascular Autoregulation

The brain is a highly homeostatic dependent, and therefore vulnerable, organ, reliant on exquisite, autoregulatory control of cerebral perfusion, as measured by cerebral perfusion pressure (CPP):^[8]

$$\text{CPP (i.e., MAP-ICP)} = \text{CBF} \times \text{CVR}$$

Autoregulation of CPP is a homeostatic process which involves real-time changes in cerebral vascular resistance (CVR) in a pattern inverse to the rate of cerebral blood flow (CBF). As such, it ensures that when the mean arterial pressure (MAP) of the systemic circulation increases, CVR inversely increases. Therefore, a constant CBF sufficient to the cerebral metabolic demands must be maintained despite wider systemic flow variation.

Up to 75% of initial CPP elevations is believed to be relieved by vasodilatory control of large cerebral arteries,^[9] in effect, preventing the pulsatile arterial pressure from reaching small pial arteries and arterioles and penetrating arterioles, and thereby preserving the downstream microvasculature. The exact process and control of cerebral autoregulation are not completely understood. However, recent literature has emphasized it to be a more complex interplay between neurogenic, myogenic, as well as intrinsic microvascular metabolic and endothelial mediators.^[10] This autoregulation can be visualized as a triphasic curve; the limits of effective autoregulation are within CPP of 50 and 150 mmHg in a supine normotensive patient.^[9] However, in chronic hypertension, autoregulation sees a rightward shift (i.e., increasing the set point of regulated pressure range).^[9] This shift is thought to be neuroprotective by chronic resistance against high blood pressure (BP)-induced damage to the downstream microcirculation. While the etiology is unconfirmed, it has been hypothesized as a blunting of baroreceptors in response to ongoing tangential arterial wall stress.^[11]

Acute cerebral microvascular dysregulation

When the average systemic arterial pressures (i.e., MAP) causes CPP to surpass 150 mmHg, autoregulation is lost. Cerebrovascular resistance is fatigued and pial arteries and arterioles and penetrating arterioles receive unregulated pulsatile systemic flow. Specifically, MAP above 200 mmHg has been shown to cause irreversible cerebral damage.^[12] The vasogenic theory instructs unregulated hyperperfusion to create an increased capillary hydrostatic pressure, subsequent capillary rupture, and breakdown of the blood–brain barrier. Secondary injury cascades involve intrinsic pro-inflammatory markers, mass effect, and downstream ischemia causing white matter damage. The outcome of ischemic injury is also anatomically variable; a richer sympathetic innervation to the anterior cerebral circulation (ACC) as opposed to the posterior cerebral circulation. This provides ACC more protection against slight BP elevations by increasing the upper limit of the cerebral autoregulation.^[13]

Chronic cSVD and remodeling

cSVD is a collective term for pathological changes in the microvascular architecture; small arteries, arterioles, capillary beds, and small veins.^[14] Usually asymptomatic, chronic hypertension causes microatheromatous structural changes to increase risk of acute presentations of ischemic stroke and intracerebral hemorrhage (ICH) as well as chronic cognitive decline. Chronic benign hypertension induces hyaline arteriosclerosis, the thickening of the vessel wall due to replacement of intramural smooth muscle with fibrin and hyaline plasma materials (lipohyalinosis). In acute malignant hypertension, hyperplastic arteriosclerosis occurs whereby a rapid resistance is attempted against sudden increase in intraluminal pressure through concentric “onion-skin” hyperplasia of intramural smooth muscle. Rarefaction, vascular pseudo-calcification and microaneurysm (<0.9 mm diameter) development in basal ganglia, thalamus, and pons are less recognized changes in response to poorly regulated BP.^[15] Due to the inability to grossly visualize microvascular changes, secondary detection through magnetic resonance imaging (MRI) visual markers have been a commonly substituted tool. These markers include white matter hyperintensities (WMH, leukoaraiosis), lacunes, cerebral microbleeds, cerebral atrophy, and increased perivascular spaces.^[14] Often, the early stages of cSVD are asymptomatic and may therefore be neglected. However, such illustrative changes provide an opportunity to discuss vascular processes and to educate patients with regard to modifiable risk factors. However, these are only predicative markers of chronic small vessel disease and are not diagnostic markers.

Posterior Reversible Encephalopathy Syndrome (PRES) and Microvascular Dysregulation

PRES is a rare phenomenon, characterized by an acute or subacute onset of global cerebral manifestations (i.e., seizures, visual disturbances, and nausea/vomiting).^[16] Clinically, PRES forms a growing differential among neurological presentations, but is poorly understood.

PRES manifestations are commonly brought about within a matter of hours by a known trigger, most commonly an acute rise in BP. Occurring in up to 80% of presentations, systolic BP has been recorded to peak up to 170–190 mmHg.^[17] As such, PRES has been commonly witnessed in groups with pre-existing risk of hypertension including; Guillain–Barre syndrome, illicit drug use, pre-eclampsia, and autoimmune/immunodeficient presentations. With no set diagnostic criteria, a clinicoradiological diagnosis through typical MRI findings of symmetrical cortical and/or subcortical edema in parieto-occipital regions that may “reverse” and disappear within a matter of weeks to months post onset.^[18]

The pathophysiology underlying PRES is controversial and has been held attributable to the vasogenic theory.^[17] The endovascular damage caused by pre-existing conditions in risk groups possibly lowering the thresholds for auto dysregulation

and subsequent syndrome development. However, this theory is difficult to reconcile hypertensive PRES presentations. Furthermore, contemporary literature has shown atypical presentations of grey matter change and non-posterior circulation patterns including the temporal lobes, central deep white matter, basal ganglia, as well as anterior watershed areas.^[19] In one retrospective study, 64.2% of patients presented with frontal white matter changes rather than posterior circulatory regions.^[20]

Contemporary studies have also made efforts to conceptualize the possible pathophysiology for this prevalence within the medical oncology and transplant subspecialties.^[21–24] The immunomodulation and pharmacological metabolic cascades in chemotherapy, in addition to fluid overload, have shown to provide possible theories to these anatomical patterns.^[19] This includes the potent vasoconstriction and vasospasm or direct endothelial damage due to pro-inflammatory cytokines from specific pharmacology (e.g., cyclosporin), direct endothelial damage by pro-inflammatory mediators in patients with chemotherapy as well as increased endothelial permeability, and microthrombotic damage due to vascular endothelial growth factors, and T cell activation in organ transplant patients.^[19,21–23] Overall, the contemporary theories postulate PRES as a primarily intrinsic endothelial dysfunction, whereas the reversible MRI markers are indicative of reversible endothelial damage rather than hypertensive ischemic damage. While this may explain the cause for PRES presentations in normotensive patients, further research is required to confirm these theories.

The absence of consensus diagnostic criteria has limited the literature to provide empirical data for the appropriate management of PRES. In addition to supportive management, contemporary literature has shown the rapid removal of a trigger to be associated with faster recovery and complications.^[17] As such, the use of IV or sublingual anti-hypertensives in the acute setting has been proven effective.^[25] While corticosteroids have been reported to precipitate as well as treat PRES, a retrospective study showed no significant association with vasogenic edema.^[26] However, its therapeutic impact still requires further evidence.^[17]

Sleep Disorders and cSVD

The literature has shown sleep disordered breathing disorders (SDBD) and sleep related movement disorders (SRMD) to have a bidirectional relationship with stroke and cardiovascular mortality/morbidity, whereby sleep disorders are risk factors for cardiovascular disease (CVD).^[27,28] This has been generally attributed to diurnal hypoxia-mediated autonomic and hemodynamic responses. However, recent literature has shown obstructive sleep apnea (OSA) to be an independent association to development of SCVD changes.

SDBDs

SDBD is an umbrella term for sleep-associated breathing disorders including obstructive (OSA), central or mixed sleep apnea and/or sleep-associated hypoventilation. OSA is most

prevalent among SBDB subtypes, affecting up to 34% males aged 30–70 years and 17.4% of women aged 30–70 years.^[29] Contemporary literature has also demonstrated that moderate-to-severe OSA is independently associated with microvascular changes, using MRI markers of cerebral ischemia.

Two recent meta-analyses have showcased no significant association with OSA and IHD (i.e., myocardial infarction and angina).^[27,30] In addition, included literature in our review has not shown any significant link between atrial fibrillation and stroke among OSA patients. These findings may indicate the pathophysiological impact of OSA on cerebral microvasculature to be independent of embolic or IHD pathophysiology. Furthermore, Butt *et al.* showcased patients with moderate-to-severe OSA to have significant brachial artery hyperactivity, independent of a pre-existing arterial BP.^[31] This supports the belief that there may be a localized endothelial dysfunction mediated by OSA, independent to systemic BP, rather than an exacerbation of BP. This is in line with previous hypotheses that chronic cerebral microvasculature changes such as capillary rarefaction may be present in OSA patients, as such changes have been recorded in forearm of OSA patients.^[32] In addition, there is insufficient knowledge of the impact of hypertensive management and its impact on the microvascular changes from OSA independently. Nevertheless, the qualitative impact of pre-existing hypertension to the degree of microvascular change has yet to be determined and requires further investigation.

SRMDs

Similarly, there is empirical evidence to support periodic limb movements (PLM) as an independent risk factor to CVD, independent of its known cerebrovascular covariation. Boulos *et al.* has shown an increase in PLM ($\geq 5/h$) to be significantly associated with increased WMH burden for first minor stroke or TIA presentations.^[33] An association significant when age, apnea/hypopnea, and cerebrovascular risk factors (including hypertension) are controlled.

PLM has a common association of up to 15% of restless leg syndrome (RLS) cases.^[34] Furthermore, an association with long-standing RLS to WMH burden is recognized. In a prospective study, Ferri *et al.* showcased long-standing RLS (>10 year duration) to have an independent association to asymptomatic and thus subclinical cSVD.^[35] Another prospective study executed by Gupta *et al.* found that pre-stroke RLS to only be a predictor for subcortical as opposed to cortical strokes (22.83% vs. 2.74%, $P < 0.001$).^[36] Ferri *et al.* did not assess MWH burden within cortical regions and only within subcortical, deep nuclear regions including pons and thus cannot confirm Gupta's findings.^[35] Boulos *et al.* showed there to be no significant association between diagnosed RLS and WMH burden ($P = 0.046$).^[33] However, the close epidemiological association between PLM and RLS is of note.^[33,34]

Overall, the pathophysiology behind PLM CVD risk is theoretical and under-investigated. Contemporary literature suggests the pathophysiology behind PLM CVD risk is multifactorial. However, the main attribution has been

deemed as the nocturnal sympathetic hyperactivity causes a high variation in heart rate, vasomotor and thus, arterial BP. Triggering a cascade of mechanical endothelial stress congruent to the mechanisms of cSVD as mentioned above. Ferri *et al.* also postulated this cerebral hemodynamic instability to produce transient intracerebral hypoxia-mediated damage.^[35] The hypercoagulable and oxidative stress which may contribute to the rise of pro-inflammatory biomarkers including CRP and Lp-PLA2 to have significant levels in PLM patients.^[37,38]

While Boulos *et al.* identified a qualitative assessment for trends of WMH burden, the specific trends of WMH burden to intracerebral location was not investigated.^[33] They theorize PLM to have an unrecognized cerebral network which may allow WMH aggregation along these pathways. In turn, WMH themselves may make interconnected pathways that may increase PLM vulnerability to ischemic insult and thus increase risk of CVD. This theory is congruent with Gupta *et al.*'s findings, whereby among the 35 patients with pre-stroke RLS, 8 presented strictly unilateral, and 16 patients had asymmetrical RLS involvement.^[36] All 24 patients showing symptom predominance on the motor aspect associated (contralateral) to the stroke affected cerebral hemisphere. Further prospective studies are required to confirm the nocturnal BP changes and determine if transient cerebral hypoxia episodes are confirmed. As well as confirm whether anatomical location of WMH is associated with PLM location.

Neurosurgical Considerations of Hypertension

Peri-operative complications

The contemporary literature has showcased growing concern for hypertension as a significant variable to peri-operative complications and subsequent surgical prognosis. Perioperative hypertension is characterized as a 20% or greater increase of the patient's BP baseline from that of their pre-operative BP.^[39] In addition to surgical stress associated Renin-Angiotensin-Aldosterone System (RAAS) and sympathetic nervous system activation and intraoperative fluid overload, sympathetic stimulation from surgical handling of the deep white matter as well as metabolic stress from cerebral activation.^[40]

A literature review in 2011 stated the presence of isolated or combined pre-, intra-, and/or post-operative hypertension to increase intra- and post-operative ICH and hematoma formation at and remote from the operating site.^[41] Perioperative bleeding, especially at pressures of more than 160/90 mmHg, has been associated with microvascular damage subsequent to the acute hypertensive damage.^[41] In addition, surgical disruption of the BBB at the surgical site causes uncompensated vasogenic edema and subsequent secondary injury cascades. The surgical considerations toward preventing and reducing these hemorrhagic complications are still in question. Soghomonyan *et al.* stated up to 50.8% of survey responders aim to reduce such complications by performing permissive hypotension for cerebral aneurysm clipping.^[42] In addition, the literature

has recommended slow weaning from anesthesia to effectively suppress surgical stress-induced hypertension and bleeding tendency.^[41] In contrast, other studies have stated concern for intraoperative hypotension among pre-existing hypertensive patients due to anesthesia-induced vasodilation in an already constricted blood volume, causing ischemic microvascular damage. Overall, empirical data to support the best perioperative management of hypertension are poor and cannot be appropriately evaluated until further investigation.

Hypertension undoubtedly creates deleterious acute and chronic consequences on the cerebrovascular architecture. Lifestyle and pharmacological management have been successful endeavors by medicine. However, up to 35.3% of current hypertensive presentations are diagnosed as resistant hypertension, whereas BP is perceived and/or confirmed as unresponsive to diuretic-containing triple drug combination.^[43] Up to 50% of such presentations have been likely attributed to an undiagnosed neurogenic etiology rather than a true pharmacological resistance.^[44]

The brain-heart axis requires complex multi-level processing. The brainstem contains the nucleus of solitary tract, a cardiovascular center which processes mechano- and chemo-peripheral baroreceptor and vagal inputs to deliver parasympathetic control to vascular tone, heart contractility, and rate.^[45,46] A similar process is seen in the rostral ventrolateral medulla (RVLM) to deliver sympathetic output.^[45,46] While the left RVLM has an additional function for receiving input from the baroreceptors of the left atrium. First hypothesized in the 1970s by Jannetta *et al.*, the vascular compression of the RVLM and adjacent root entry zone (REZ) of the glossopharyngeal (CNIX) and vagal (CNX) nerves to be a neurogenic etiology of hypertension.^[47] The pulsatile compression by adjacent vasculature activate residing RVLM sympathoexcitatory C1 neurons creating transient episodes of sympathetic and RAAS metabolic cascades, resulting in microvascular endothelial inflammation and remodeling.^[48]

Studies have shown success in the use of microvascular decompression (MVD) as a therapeutic treatment of the above hypothesis. Lu *et al.* identified a significant mean BP reduction when the left trigeminal nerve, RVLM, and REZ were decompressed (experimental group) as compared to trigeminal nerve decompression alone (control group).^[49] The experimental group found up to 83.3% of the experimental group to have an improvement or resolution of their hypertension ($P\Delta SBP < 0.001$; $P\Delta DBP < 0.001$), with an overall significant decrease in the mean SBP and DBP.^[49] While only the control group saw no significant improvement in BP ($P\Delta SBP = 0.131$; $P\Delta DBP = 0.078$).^[49] These trends were confirmed by Sindou *et al.* who prospectively determined a 79.2% effective rate among its 48 patient pool with combined RVLM and REZ decompression.^[50] No cases of elevated or rebound BP post-operative were reported. Except for transient vertigo, no post-operative complications were reported.

However, the indication for MVD for resistant hypertension remains controversial. The hypothesized pathophysiology

would foresee further antihypertensive effect upon left-sided decompression. Studies show inconsistencies as to the location of the decompression itself. Lu *et al.* showed the successful antihypertensive effect of concomitant left RVLM and REZ decompression at least 6 months postoperatively.^[49] Legrady showcased no significant difference in the location of left-sided decompression (i.e., RVLM or REZ).^[48] However, this study used a 1 week post-operative follow-up, which may be too short a time frame, considering a maximum anti-hypertensive effect has been shown at 1 year.^[48,49] If we consider the duration of post-operative assessment as a variant for result validity, results by Sindou *et al.* would deem most valid. With a mean follow-up of 7 years (2–16 years), the side of decompression (of REZ and RVLM) was ipsilateral to concomitant facial nerve spasm.^[50] These results showcased left- and right-sided decompression to have no significant difference in efficacy.^[50] The efficacy of the right-sided decompression may be accountable by Lu *et al.*'s theory where an associated cranial nerve symptom (e.g., trigeminal neuralgia or facial spasm) may enhance anxiety-induced sympathetic activation.^[49] Nevertheless, the results of the contemporary study are inconsistent and more prospective studies with long-term follow-up are required.

All three studies consistently suggest MVD to only be indicated in patients presenting with resistant hypertension that has MRI confirmed NVC at REZ and/or RVLM. Nevertheless, detection of an elongated arterial loop on MRI is only a presumptive diagnosis. The neurogenic nature of the MRI finding cannot be confirmed. While internationally recognized as a modality for hypertensive treatment, there remains no unified criterion for diagnosing neurogenic hypertension and thus the patient selection for MVD.

Greater research into long-term prognostic outcomes, cost-efficacy, and patient selection is likely to be of benefit; however, the literature on these factors is sparse. MVD was indicated for primary cranial nerve disorders including hemifacial spasm and trigeminal neuralgia rather than for resistant hypertension. As such, the etiology and identification of resistant hypertension as well as post-operative reduction in hypertension were not pursued. Until all such factors are investigated and evaluated, the benefit of therapeutic surgery for hypertension will remain uncertain.

Discussion

Overall, contemporary research has shown its growing efforts to investigate the direct association of hypertension and neurological outcomes. By providing a broad overview of multiple neural pathologies, we can see the negative effects of hypertension as it influences multiple pre-existing acute and chronic neurological and neurosurgical concerns.

Specifically, on a microvasculature level, the association of hypertension to neurological pathologies seems to be based upon overriding compensatory adaptations made within the intrinsic endothelial rather than systemic vascular environment.

However, there is an overarching lack of detailed knowledge to support this pathophysiological basis. With many associations and trends being theorized by the literature, we can also see that the subsequent efficacy of management is put into question.

In addition, none of the contemporary studies had appropriately evaluated hypertension as per the new hypertension thresholds. Instead the trends and associations of hypertension was under the definition of a BP greater than or equal to 140/90 mmHg. Thus, the findings of contemporary literature cannot be guaranteed applicable to all hypertensive patients, as these trends are yet to be confirmed prevalent in BP values between 130–140 mmHg and 80–90 mmHg, systolic and diastolic, respectively.

Conclusion and Future Perspectives

There is growing contemporary evidence that supports hypertension as an important risk factor and etiology to multiple neurological pathologies. Nevertheless, we have been able to see several gaps in the literature. This has made it difficult to determine the true impact of BP optimization to each neural pathology. Future research should reinvestigate the contemporary concerns of hypertension as mentioned above, but in the context of the new hypertensive thresholds. This will reconfirm contemporary concerns and thus determine a true qualitative value of hypertension to each neuropathology. Research must be executed through more in-depth analysis, for example, examining if associations of hypertensive severity to microvascular damage and autoregulatory loss.

We believe it is also crucial for respective clinicians to advocate and implicate hypertension prevention and intervention into their subspecialty practice. Thus, we believe it is important for clinicians involved in neurological care (e.g., neurologists, neurosurgeons, neuroradiologists, and neuropsychologists) to recognize the gravity of hypertension to the morbidity and mortality of their patients. Specialty clinicians must begin to change their perceived role in patient management from treatment and symptom reduction to complication prevention and on-going optimization of BP. We also suggest researchers and clinicians to begin to identify current clinician knowledge, perception, and concerns regarding hypertension. This will allow barriers, limitations, and potential solutions to the integration of hypertension care to be identified. In hopes to create an appropriate standardized guidelines of the role of each specialist to the management of hypertension.

This review is to provide a broad umbrella of up-to-date knowledge and recommendations for patients, health professionals, health service providers, and researchers in the context of rapidly developing vascular knowledge. Furthermore, the knowledge we present is focused on the unidirectional direct impact of arterial hypertension toward neural complications. We iterate that the relationship of arterial hypertension and neurological/neurosurgical conditions is increasingly understood to be bi-directional. Future research should explore the complex and unique impact of neurological/neurosurgical conditions to arterial hypertension.

References

1. American Heart Association. Why High Blood Pressure is a “Silent Killer.” American Heart Association. Available from: <https://www.heart.org/en/health-topics/high-blood-pressure/why-high-blood-pressure-is-a-silent-killer>. [Last accessed on 2020 Feb 03].
2. Institute for Health Metrics and Evaluation. Findings from the Global Burden of Disease Study 2017. Seattle, WA: Institute for Health Metrics and Evaluation; 2018.
3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: A pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017;389:37-55.
4. The World Health Organisation. Hypertension The World Health Organisation. Available from: <https://www.who.int/news-room/fact-sheets/detail/hypertension>. [Last accessed on 2020 Feb 01].
5. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., Collins KJ, Himmelfarb CD. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol* 2018;71:e127-248.
6. The SPRINT Research Group. A randomised trial of intensive versus standard blood-pressure control. *J Med* 2015;373:2103-16.
7. Betjemann J, Hemphill JC, Sarkar U. Time for neurologists to drop the reflex hammer on hypertension. *JAMA Neurol* 2019;76:1277-8.
8. Morton R, Ellenbogen RG. Intracranial Hypertension Clinicalgate; 2015.
9. Shekhar S, Liu R, Travis OK, Roman RJ, Fan F. Cerebral autoregulation in hypertension and ischemic stroke: A mini review. *J Pharm Sci Exp Pharmacol* 2017;2017:21-7.
10. Armstead WM. Cerebral blood flow autoregulation and dysautoregulation. *Anesthesiol Clin* 2016;34:465-77.
11. Hemanshu P, Zulfiqar A. Textbook of Neuroanesthesia and Neurocritical Care. 1st ed. Singapore: Springer Singapore; 2019.
12. Bartynski WS. Posterior reversible encephalopathy syndrome, part 2: Controversies surrounding pathophysiology of vasogenic edema. *AJNR Am J Neuroradiol* 2008;29:1043-9.
13. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990;2:161-92.
14. Shi Y, Wardlaw JM. Update on cerebral small vessel disease: A dynamic whole-brain disease. *Stroke Vasc Neurol* 2016;1:83-92.
15. Shoamanesh A, Kwok CS, Benavente O. Cerebral microbleeds: Histopathological correlation of neuroimaging. *Cerebrovasc Dis* 2011;32:528-34.
16. Price RS, Kasner SE. Hypertension and hypertensive encephalopathy. *Handb Clin Neurol* 2014;119:161-7.
17. Roth C, Ferbert A. The posterior reversible encephalopathy syndrome: What's certain, what's new? *Pract Neurol* 2011;11:136-44.
18. Le EM, Loghin ME. Posterior reversible encephalopathy syndrome: A neurologic phenomenon in cancer patients. *Curr Oncol Rep* 2014;16:383.
19. McKinney AM, Jagadeesan BD, Truwit CL. Central-variant posterior reversible encephalopathy syndrome: Brainstem or basal ganglia involvement lacking cortical or subcortical

- cerebral edema. *AJR Am J Roentgenol* 2013;201:631-8.
20. Pereira PR, Pinho J, Rodrigues M, Rocha J, Sousa F, Amorim J, *et al.* Clinical, imagiological and etiological spectrum of posterior reversible encephalopathy syndrome. *Arq Neuropsiquiatr* 2015;73:36-40.
 21. Munoz J, Kumar V, Hamilton J, Pasche LJ, Langford LA, Taggart MW, *et al.* Posterior reversible encephalopathy syndrome: More than meets the eye. *J Clin Oncol* 2013;31:360-3.
 22. Hugonnet E, Da Ines D, Boby H, Claise B, Petitcolin V, Lannareix V, *et al.* Posterior reversible encephalopathy syndrome (PRES): Features on CT and MR imaging. *Diagn Interv Imaging* 2013;94:45-52.
 23. Aradillas E, Arora R, Gasperino J. Methotrexate-induced posterior reversible encephalopathy syndrome. *J Clin Pharm Ther* 2011;36:529-36.
 24. Floeter AE, Patel A, Tran M, Chamberlain MC, Hendrie PC, Gopal AJ, *et al.* Posterior reversible encephalopathy syndrome associated with dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) chemotherapy. *Clin Lymphoma Myeloma Leuk* 2017;17:225-30.
 25. Shao PJ, Sawe HR, Murray BL, Mfinanga JA, Mwafongo V, Runyon MS. Profile of patients with hypertensive urgency and emergency presenting to an urban emergency department of a tertiary referral hospital in Tanzania. *BMC Cardiovasc Disord* 2018;18:158.
 26. Parikh NS, Schweitzer AD, Young RJ, Giambone AE, Lyo J, Karimi S, *et al.* Corticosteroid therapy and severity of vasogenic edema in posterior reversible encephalopathy syndrome. *J Neurol Sci* 2017;380:11-5.
 27. Loke YK, Brown JW, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: A systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2012;5:720-8.
 28. Lisabeth LD, Sánchez BN, Lim D, Chervin RD, Case E, Morgenstern LB, *et al.* Sleep-disordered breathing and poststroke outcomes. *Ann Neurol* 2019;86:241-50.
 29. Parvey JE, Pengo MF, Drakatos P, Kent BD. Epidemiological aspects of obstructive sleep apnea. *J Thorac Dis* 2015;7:920-9.
 30. Dong JY, Zhang YH, Qin LQ. Obstructive sleep apnea and cardiovascular risk: Meta-analysis of prospective cohort studies. *Atherosclerosis* 2013;229:489-95.
 31. Butt WW, Gow R, Whyte H, Smallhorn J, Koren G. Complications resulting from use of arterial catheters: Retrograde flow and rapid elevation in blood pressure. *Pediatrics* 1985;76:250.
 32. Prasad A, Dunnill GS, Mortimer PS, MacGregor GA. Capillary rarefaction in the forearm skin in essential hypertension. *J Hypertens* 1995;13:265-8.
 33. Boulos MI, Murray BJ, Muir RT, Gao F, Szilagyi GM, Huroy M, *et al.* Periodic limb movements and white matter hyperintensities in first-ever minor stroke or high-risk transient ischemic attack. *Sleep* 2017;40:zsw080.
 34. Natarajan R. Review of periodic limb movement and restless leg syndrome. *J Postgrad Med* 2010;56:157-62.
 35. Ferri R, Cosentino FI, Moussouttas M, Lanuzza B, Aricò D, Bagai K, *et al.* Silent cerebral small vessel disease in restless legs syndrome. *Sleep* 2016;39:1371-7.
 36. Gupta A, Shukla G, Mohammed A, Goyal V, Behari M. Restless legs syndrome, a predictor of subcortical stroke: A prospective study in 346 stroke patients. *Sleep Med* 2017;29:61-7.
 37. Trotti LM, Rye DB, De Staercke C, Hooper WC, Quyyumi A, Bliwise DL. Elevated C-reactive protein is associated with severe periodic leg movements of sleep in patients with restless legs syndrome. *Brain Behav Immun* 2012;26:1239-43.
 38. Bekci TT, Kayrak M, Kiyici A, Ari H, Teki T, Maden E, *et al.* The relation between Lp-PLA2 levels with periodic limb movements. *Sleep Breath* 2012;16:117-22.
 39. Howell SJ. Preoperative hypertension. *Curr Anesthesiol Rep* 2018;8:25-31.
 40. Rabelo NN, Filho LJ, Passos GS, Junior LA, Pereira CU, Dias LA, *et al.* Acute arterial hypertension in patients undergoing neurosurgery. *Arq Neuropsiquiatr* 2016;35:296-303.
 41. Seifman MA, Lewis PM, Rosenfeld JV, Hwang PY. Postoperative intracranial haemorrhage: A review. *Neurosurg Rev* 2011;34:393-407.
 42. Soghomonyan S, Stoicea N, Sandhu GS, Pasternak JJ, Bergese SD. The role of permissive and induced hypotension in current neuroanesthesia practice. *Front Surg* 2017;4:1.
 43. Noubiap JJ, Nansseu JR, Nyaga UF, Sime PS, Francis I, Bigna JJ. Global prevalence of resistant hypertension: A meta-analysis of data from 3.2 million patients. *Heart* 2018;105:96-7.
 44. DiBona GF, Esler M. Translational medicine: The antihypertensive effect of renal denervation. *Am J Physiol Regul Integr Comp Physiol* 2010;298:R245-53.
 45. Ardell JL, Andresen MC, Armour JA, Billman GE, Chen PS, Foreman RD, *et al.* Translational neurocardiology: Preclinical models and cardioneural integrative aspects. *J Physiol* 2016;594:3877-909.
 46. Tahsili-Fahadan P, Geocadin RG. Heart-brain axis: Effects of neurologic injury on cardiovascular function. *Circ Res* 2017;120:559-72.
 47. Jannetta PJ, Segal R, Wolfson SK Jr. Neurogenic hypertension: Etiology and surgical treatment I. Observation in 53 patients. *Ann Surg* 1985;201:391-8.
 48. Legrady P, Voros E, Bajcsi D, Fejes I, Barzo P, Abraham G. Observations of changes of blood pressure before and after neurosurgical decompression in hypertensive patients with different types of neurovascular compression of brain stem. *Kidney Blood Press Res* 2013;37:451-7.
 49. Lu W, Wang H, Yan Z, Wang Y, Che H. Microvascular decompression for the treatment of neurogenic hypertension with trigeminal neuralgia. *BMC Neurol* 2019;19:341.
 50. Sindou M, Mahmoudi M, Brinzeu A. Hypertension of neurogenic origin: Effect of microvascular decompression of the CN IX-X root entry/exit zone and ventrolateral medulla on blood pressure in a prospective series of 48 patients with hemifacial spasm associated with essential hypertension. *J Neurosurg* 2015;123:1405-13.

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Appendix

Appendix 1: Medline (OVID) search criteria

- S1 Intracranial hypertension/or hypertension.mp. or essential hypertension/or hypertension/or hypertension, malignant/or hypertension. mp
- S2 (hypertension or “arterial hypertension” or “hypertension in neurosurgery” or “hypertension in neurology”).m_titl.
- S3 1 or 2
- S4 (neurology or neurosurgery or “neurological surgery” or “surgical neurology” or cerebrovascular).m_titl.
- S5 Cerebrovascular.mp. or cerebrovascular trauma/or cerebrovascular disorders/
- S6 neurosurgery.mp. or Neurosurgery/
- S7 neurology.mp. or Neurology/
- S8 4 or 5 or 6 or 7
- S9 Cerebral small vessel diseases/or “small vessel disease”.mp.
- S10 (microvascular or “small vessel disease” or “cerebral small vessel disease” or microneurosurgery or microaneurysm or “microvascular brain damage” or microaneurysm).mp.
- S11 (PRES or “posterior reversible encephalopathy syndrome” or “hypertensive encephalopathy” or “hypertensive crisis” or “hemorrhagic stroke” or “hemorrhagic stroke” or AVM or “arteriovenous malformation”).mp.
- S12 9 or 10
- S13 11 or 12
- S14 3 and 8 and 13
- S15 Limit 14 to (English language and humans and yr=“2011-2020”)
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