

Blood pressure and the Brain: The Neurology of Hypertension

*Dearbhla M. Kelly¹ MBBChBAO MSc MRCPI, Peter M. Rothwell¹ MD PhD FRCP
FMedSci.*

*¹Center for Prevention of Stroke and Dementia, Nuffield Department of Clinical
Neurosciences, John Radcliffe Hospital, University of Oxford, United Kingdom.*

Corresponding author:

Dearbhla Kelly,

Center for Prevention of Stroke and Dementia, Nuffield Department of Clinical
Neurosciences, John Radcliffe Hospital, University of Oxford, United Kingdom.

Tel no: +441865231601

Email: dearbhla.kelly@ndcn.ox.ac.uk

Abstract

Hypertension affects more than one in four adults. The brain is an early target of hypertension-induced organ damage manifest as stroke, subclinical cerebrovascular abnormalities, and dementia. Hypertension-related small vessel disease can cause vascular dementia and potentiate Alzheimer's pathology to lower the threshold at which signs and symptoms manifest. Many hypertensive emergencies can also have a neurological presentation such as hypertensive encephalopathy, haemorrhagic stroke, or pre-eclampsia. In this review, we aim to highlight the importance of blood pressure in maintaining brain health and the role of the brain in controlling blood pressure.

Introduction

The global prevalence of hypertension is estimated to be 1.13 billion. Hypertension is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke.¹ Given that stroke accounts for the largest share of the neurological burden of disease, hypertension is increasingly recognized as a global neurological problem. In this review, we will explore the role of the brain in blood pressure (BP) control, the impact of hypertension on cerebral physiology, and some of the clinical consequences including cerebrovascular disease, dementia, and sleep disorders.

Is hypertension a neurological disease?

The brain plays an important role in BP homeostasis (see *Figure 1*). The cardiovascular center in the medulla oblongata is responsible for the regulation of cardiac output.² By mediating changes in heart rate, stroke volume or vascular tone via sympathetic or parasympathetic stimulation, it facilitates the short-term control of BP whereas renal regulation is more important for long-term control. The cardiovascular center responds to signals from baroreceptors that detect stretch and from chemoreceptors that detect changes in oxygen/carbon dioxide concentrations.

The rostral ventrolateral medulla and upper cervical spinal cord regions play a key role in central BP control. For example, high cervical spinal cord injury is associated with very erratic BP and dysregulated neural network dynamics in caudal pressor regions have been implicated in the development of hypertension.³

The brainstem control centers may also receive modulation from higher brain regions, such as the cerebral cortex, hypothalamus, and limbic system. Lesion studies of epilepsy surgery patients have given us greater insight into cortical cardiovascular control. In a study of five patients undergoing intraoperative insular stimulation prior to temporal lobectomy for seizure control, stimulation of the left insular cortex tended to produce bradycardia and depressor responses while stimulation of the right insular cortex resulted in tachycardia and pressor effects, suggesting a right-sided dominance for sympathetic cardiovascular effects.⁴ Because the insular cortex is located in the region of the middle cerebral arteries (MCA), it tends to be particularly susceptible to cerebrovascular disease, and right MCA infarction may disinhibit insular function, resulting in increased sympathetic cardiovascular tone and the cardiac consequences of stroke, including sudden death.⁵

Further supporting evidence of the role that the brain may play in the genesis and maintenance of hypertension is that BP starts to decrease 3 years before overt development of dementia and continues to decline afterwards.⁶ Subtle neurodegenerative lesions in these strategic locations of the brain that regulate BP may initiate this premorbid decline.

Pathophysiology of hypertension-induced brain injury

At ages 40–69 years, each difference of 20 mm Hg usual SBP (or, approximately equivalently, 10 mm Hg usual DBP) is associated with more than a twofold difference in the stroke mortality.⁷ Hypertension also worsens stroke outcomes as patients with

pre-existing hypertension have smaller penumbras and larger infarctions compared to normotensive patients.⁸

Regulation of cerebral blood flow (CBF) in a normal brain is determined by a variety of intrinsic control mechanisms including myogenic/stretch, chemical, metabolic, and neurogenic control.⁹ Autoregulation ensures that CBF remains relatively constant over a wide range of BP changes (*Figure 2*). Autoregulation is impaired when extremes of BP exceed the compensatory vasoconstrictive or vasodilatory capacity. This usually occurs if the mean arterial BP (MAP) falls below 50 mmHg or rises above 150 mmHg in a normotensive person. However, this plateau phase may be shifted to higher BP values during chronic hypertension to maintain the same level of CBF. The exact mechanisms by which hypertension affects cerebral autoregulation are not completely understood but they likely include a combination of myogenic tone alterations and inward vessel remodelling with an increase in wall-to-lumen ratio in response to tangential stress on the artery wall.¹⁰

A role for angiotensin II in cerebral artery remodelling is supported by studies using angiotensinogen knockout mice¹¹ with a reduction in wall thickness and wall-to-lumen ratio in aged spontaneously-hypertensive rats (SHR) treated with angiotensin-converting enzyme inhibitors (ACE-Is).¹² Angiotensin II and aldosterone have been linked to the production of reactive oxygen species (ROS).¹³ ROS are key mediators of cerebrovascular dysfunction in hypertension, as they contribute to vessel rarefaction (loss of arterioles and capillaries) and structural remodelling of cerebral blood vessels with resultant chronic hypoperfusion of the brain. Hypertension also enhances blood-brain-barrier (BBB) permeability via ROS and impairs its ability to

regulate central nervous system homeostasis.¹⁴ The increased BBB permeability associated with hypertension may also be attenuated by ACE inhibition.¹⁵

Arterial stiffness and hypertension

Arterial stiffness is related to age, heart rate, and MAP, and in hypertensive diabetic subjects, to diabetes mellitus duration and insulin treatment.¹⁶ It is not fully understood whether stiffness is a cause or consequence of hypertension. Carotid artery stiffening was only seen to be elevated independently of BP in young hypertensive patients, and not in older ones¹⁷ and based on data from the Framingham Heart Study, higher aortic stiffness was associated with higher risk of incident hypertension and initial BP was not independently associated with risk of progressive aortic stiffening.¹⁸ However, hypertension may contribute to or worsen arterial stiffness as a result of increases in distension pressure, vascular thickness, and structural stiffening.¹⁹

Pulsatility

Trans Cranial Doppler (TCD) has been used to evaluate the haemodynamics of cerebral blood vessels including the MCA and the Pulsatility Index (PI) is calculated by subtracting the end diastolic velocity from the peak systolic velocity and then dividing by the time averaged (mean) velocity. In a study of patients with recent TIA or minor stroke, MCA-PI was the strongest physiological correlate of leukoaraiosis, independent of age and other parameters.²⁰ MCA-PI also strongly associated with

aortic pulsatility, DBP, and aortic stiffness, indicating that cerebral pulsatility is mainly dependent on aortic pulsatility and large artery stiffness rather than on distal small vessel resistance.

The Reykjavik study, a large community-based study of older males and females, also found that higher pressure, flow pulsatility, and carotid-femoral pulse wave velocity parameters were associated with diffuse microvascular brain lesions, including subcortical infarcts and greater white matter hyperintensity volume, and reduced scores in multiple cognitive domains.²¹ It would appear that significant proximal aortic stiffening in older people facilitates transmission of excessive pressure and flow pulsatility into the carotid circulation and that these abnormal pulsatile forces can cause flow-limiting small vessel damage and remodelling, cerebral ischaemia, and reduced cognitive reserve.

Prognostic value of BP variability

BP is characterized by short-term fluctuations occurring within a 24-hour period (beat-to-beat, minute-to-minute, hour-to-hour, and day-to-night changes) and also by long-term fluctuations occurring over more-prolonged periods of time (days, weeks, months, seasons, and even years).²² These variations may result from the interaction of environmental and behavioural factors as well as innate changes in cardiovascular regulatory mechanisms.

Based on analysis of data from multiple cohorts of patients with previous TIA or stroke and patients with hypertension, visit-to-visit clinic BP variability and 'episodic

hypertension' was predictive of an increased risk of vascular events, including stroke, myocardial infarction, heart failure, independent of mean BP.²³ BP variability increased with age and is higher in females, diabetics, smokers, and those with peripheral vascular disease, atrial fibrillation, or previous TIA or stroke.²²

In analyses of randomised trials of BP-lowering drugs, different drug-classes had similar effects on mean BP, but very different effects on visit-to-visit variability.²⁴ Calcium channel blockers and thiazide diuretics reduce variability whereas beta-blockers and ACE/ARB-based drugs increase variability. In an analysis of the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm, compared to the atenolol group, the amlodipine group had lower variability of BP from visit-to-visit, on 24-hour ABPM and on 3 measurements within a 10 minute clinic visit.²³ Treatment with amlodipine was associated with a lower risk of stroke and this association was almost completely attenuated after adjusting for within-individual BP variability. Similar drug class effects and correlations with outcome were found in the MRC trial of BP-lowering in older hypertensive patients.²³

Anti-hypertensive drugs should therefore be chosen to reduce variability as well as the mean level, particularly in the setting of stroke prevention. The deleterious impact of BP variability may potentially have implications for neurological conditions associated with dysautonomia such as Parkinson's disease, multiple system atrophy and spinal cord trauma. Spinal cord injury at or above T6 may be complicated by a phenomenon known as autonomic dysreflexia, whereby acute hypertension is generated by unmodulated sympathetic reflexes below the injury level that is often accompanied by baroreceptor-mediated bradycardia.²⁵ Typically, autonomic

dysreflexia is precipitated by noxious visceral or somatic stimulation below the level of injury that activates a massive sympathetic reflex causing widespread vasoconstriction and hypertension. The most common triggers include bladder distension, constipation, pressure sores, fractures, or occult visceral disturbances. Hypertensive episodes should be managed by sitting the patient up, removing tight-fitting garments, searching for potential noxious stimuli, and use of rapid-onset, short-duration antihypertensive agents such as labetalol or nitrates.

Small vessel disease

The term small vessel disease (SVD) encompasses all the pathological processes that affect the small vessels of the brain, including small arteries, arterioles, capillaries, and small veins.²⁶ There are several types but type 1 (arteriolosclerosis) is particularly related to hypertension and also affects the kidney and retina. Pathological type 1 SVDs are characterized by loss of smooth muscle cells from the tunica media, deposits of fibro-hyaline material, narrowing of the lumen, and thickening of the vessel wall. Postulated mechanisms of cerebral damage include chronic hypoperfusion, acute vessel occlusion, BBB damage, local subclinical inflammation, and oligodendrocyte apoptosis. The neuroimaging correlates of SVD are small deep infarcts, cerebral haemorrhages, microbleeds, white matter lesions (WML), dilated perivascular spaces, and cerebral atrophy (See an example in *Figure 3*). Clinical manifestations of hypertension-related SVD include stroke, depression, gait disturbance, cognitive decline, and dementia. An acute small vessel occlusion is the cause of about a quarter of all acute ischaemic strokes.²⁷

Hypertension is one of the most important risk factors for WML progression. Long-term hypertension results in medial lipohyalinosis, thickening of the vessel walls, and narrowing of the lumen of the arterioles and small perforating arteries that supply the deep white matter.²⁸ From the Rotterdam scan study²⁹, subcortical WML were associated with a 1.4 times greater risk of ischaemic stroke while periventricular WML were associated with 2-3 excess risk of ischaemic stroke. Deficiencies in gait and balance performance, and urinary urgency also correlate with the severity of these white matter changes.³⁰

Frequently associated with WML, lacunar infarcts are defined as hypointense foci (<15 mm) on MRI T1-weighted sequences, typically seen in locations such as the basal ganglia, internal capsule, thalamus, and pons. The overall prevalence of silent brain infarcts (most of which are lacunar infarcts) is about 28% in the general population.³¹ Apart from age, hypertension is the most widely accepted risk factor for silent brain infarcts.³² Silent brain infarcts also increase the risk of ischaemic and haemorrhagic stroke.³³

Cerebral microbleeds (CMBs) are seen as small, homogeneous, round foci of low signal intensity on MRI gradient echo T2 sequences. The prevalence of CMBs is 5% in healthy adults, 34% in people with ischaemic stroke, and 60% in people with ICH.³⁴ Hypertension-associated cerebral microbleeds are typically located in basal ganglia, thalamus, brain stem, and cerebellum, while a lobar distribution is frequently linked to cerebral amyloid angiopathy (CAA).³⁵ The Modified Boston Criteria are helpful to distinguish CAA from SVD that is more likely to be related to hypertension.³⁶ The presence of CAA should be suspected clinically in patients over

the age of 55 who have multiple lobar hemorrhages in the absence of an obvious alternative cause. Lobar lacunes are also more likely to be associated with CAA, whereas deep lacunes are more frequent in hypertensive SVD.³⁷ It can be challenging to manage anti-platelet therapy in patients with CMBs as the relative risk of ICH increases as the CMB burden increases. However, a recent pooled analysis of individual patient-level data has shown that in those with recent TIA or ischaemic stroke, regardless of the CMB number, distribution, and presence of anti-coagulant/antiplatelet treatment, the absolute risk of ischaemic stroke is consistently substantially higher than that of ICH.³⁸ Similarly, in the REstart or STOP Antithrombotics Randomised Trial (RESTART), restarting antiplatelet therapy in patients with prior ICH did not seem to increase recurrence, even in the presence of microbleeds.³⁹

Cognitive Impairment and Dementia

Higher BP is associated with smaller total brain volume and reduced regional brain volumes in AD brain regions.⁴⁰ While the mechanisms underlying these associations are unclear, some evidence suggests that cortical neuronal apoptosis related to subcortical vascular pathology and abnormalities in CBF underlie brain atrophy.⁴¹

In addition to its casual role, the presence of hypertension appears to augment the clinical significance of SVD. The progression of periventricular WML in hypertensive patients is related to cognitive impairment (especially executive function), whereas there is no association between baseline periventricular WML and cognitive dysfunction.⁴² High home BP and multiple lacunar infarcts have been

shown to be significantly independent predictors for the progression of both cognitive impairment and stroke recurrence.⁴³ Hypertensive vasculopathy and CAA may also combine to cause cognitive decline with variable phenotype depending on the location and number of CMB.⁴⁴

Cerebrovascular disease appears to interact with and augment neurodegenerative pathologies. At autopsy, hypertensive older adults have evidence of greater AD pathology in the brain, including neurofibrillary tangles and neuritic amyloid-beta (A β) plaques.⁴⁵ Positron emission tomography studies have shown that the extent of A β deposition in the brain is positively associated with higher BP.⁴⁶

The duration of hypertension may be a stronger risk factor for cognitive dysfunction than age. Multiple studies have indicated that midlife hypertension and persistence of elevated blood pressure into late life are leading risk factors for late-life dementia.⁴⁷

In contrast, studies of late-life BP suggest that only the extremes of BP (SBP>180mmHg, DBP <70mmHg) increase the risk for dementia.⁴⁸

Large artery disease

Hypertension is an important risk factor for atherosclerosis with a significant dose-response relationship. A 10mmHg increase in BP increases the risk of complex aortic atherosclerosis (protruding atheroma, ulcerated plaques, mobiles debris) by about 40% and is highly predictive of ischaemic strokes.⁴⁹ Atherosclerotic lesions are observed at sites of turbulent flow, such as the carotid bifurcation and cause stroke by releasing fragments with artery-to-artery embolism, or by rupture and/or haemorrhage

resulting in acute cerebrovascular occlusions (see an example in *Figure 4*). Carotid atherosclerosis can progress silently with increasing SBP and hypertension is also a risk factor for large artery intracranial stenosis.⁵⁰

Hypertensive patients are therefore high-risk for the development of large vessel atherothrombotic stroke which may make them candidates for thrombolytic therapy. However, special considerations apply to BP control in this setting. According to the 2018 ASA/AHA guidelines⁵¹, patients with elevated BP who are otherwise eligible for thrombolysis should have their BP carefully lowered to < 185/110 mmHg and kept <180/105 mmHg for the first 24 hours after treatment. This recommendation is based on observational studies that higher BPs are associated with greater risk of haemorrhage but the exact BP at which the risk of haemorrhage after thrombolysis increases is unknown. Treatment options include IV labetalol, nicardipine or clevidipine. In patients with BP \geq 220/120 mmHg who do not receive thrombolysis or endovascular therapy, the benefit for initiating or reinitiating treatment of hypertension within the first 48-72 hours is uncertain. The guidelines suggest that it may be reasonable to lower BP by 15% during the first 24 hours after onset of stroke.

Importantly, patients with extracranial or intracranial large artery stenoses may require a slower reduction in BP and to a less aggressive BP target, as some degree of BP elevation may be necessary to maintain cerebral perfusion to ischaemic brain regions.

Cerebral Hypertensive Emergencies

Patients with hypertensive emergencies present with significantly elevated BP (usually SBP ≥ 180 and/or DBP ≥ 120 mmHg) and signs or symptoms of acute target-organ damage. They can develop in patients with or without known pre-existing hypertension. Neurological emergencies account for approximately 30% of patients presenting with severe acute hypertension, and the majority of those who die.⁵² Most are due to cerebral infarction with hypertensive encephalopathy and ICH also accounting for many. 20–40% of cases may be attributable to secondary causes and most often consist of renal parenchymal disease and renal artery stenosis.⁵³

Hypertensive encephalopathy is defined as an acute organic brain syndrome occurring as a result of failure of the upper limit of cerebral vascular autoregulation.⁵⁴ The degree of hypertension necessary to trigger encephalopathy can vary and the rate of BP increase appears to be more important than the absolute BP value with rapidly developing, fluctuating, or intermittent hypertension in younger patients being particularly high risk. It is also associated with poorly controlled hypertension and secondary causes such as immunosuppressive therapy, erythropoietin use, and thrombotic thrombocytopenic purpura.

Proposed mechanisms for hypertensive encephalopathy include brain endothelial dysfunction, BBB disruption with increased permeability, cerebral oedema, and microhaemorrhage formation.⁵²

The diagnosis is a clinical one, relying on the presence of neurological symptoms in a patient who is severely hypertensive, supported by additional imaging.⁵⁵ Symptoms may include headache, visual disturbance, somnolence, lethargy, partial or generalised seizures. Focal neurological lesions are rare and should raise the suspicion of an acute stroke. If not adequately treated, hypertensive encephalopathy can progress to cerebral haemorrhage, coma, and death. Physical examination should focus on cardiovascular as well as neurological assessment. A proposed pathway of evaluation is outlined in *Table 1*. BP should be measured in both arms and in the lower limbs to detect pressure differences caused by aortic dissection.

Proposed evaluation in patients with suspected hypertensive emergency
<p>History-taking</p> <ul style="list-style-type: none"> • Symptoms (headache, confusion, somnolence, visual disturbance, seizures, focal neurological deficits) • Pre-existing hypertension, current treatment, withdrawal, compliance, previous control • Over-the-counter medication use (e.g. NSAIDs, sympathomimetics) • Recent steroid exposure • Recreational drug use (e.g. cocaine) • Co-morbidities (e.g. kidney disease, renal artery stenosis) <p>Diagnostic examination</p> <ul style="list-style-type: none"> • BP both arms • Radio-femoral delay • Signs of heart failure (gallop rhythm, raised JVP, bibasal crepitations, peripheral oedema) • Detailed neurological exam • Fundoscopy (papilloedema, haemorrhages) • ECG (ischaemia, arrhythmias, left ventricular hypertrophy) • Urinalysis (proteinuria, haematuria) <p>Further investigations as indicated</p> <ul style="list-style-type: none"> • Troponin-T, CK, CK-MB • Peripheral blood smear (for assessment of schistocytes) • Chest X-ray (volume overload) • Transthoracic echocardiography (cardiac structure and function) • CT/MRI-brain (ICH) • CT-angiography of thorax and abdomen (acute aortic disease) • Renal ultrasound (postrenal obstruction, kidney size, asymmetry suggestive of renal artery stenosis) • Secondary hypertension work-up (Renal profile, 24-h urine metanephrines/catecholamines or spot plasma metanephrines, plasma renin and aldosterone, 24-h urinary cortisol, TSH)

Table 1: Proposed diagnostic studies in patients with suspected hypertensive emergency

Apart from acute BP lowering in stroke patients, there are no randomized controlled trials that have examined different treatment strategies for most hypertensive emergencies with recommendations instead based on consensus opinion. Large reductions in BP (exceeding a >50% decrease in mean arterial pressure) have been associated with increased risk of ischaemic stroke and death.⁵⁶ The most recent recommendations of the European Society of Cardiology (ESC)⁵⁵ are summarized in

Table 2. Because patients are often volume depleted as a result of pressure natriuresis, IV saline infusion can be used to correct precipitous BP falls if necessary. In patients with hypertensive encephalopathy, IV labetalol may be preferable as it leaves CBF relatively intact for a given BP reduction compared with nitroprusside.⁵⁷

Hypertensive Emergency	Timeline and Target BP	First-line Treatment	Alternative
Hypertensive encephalopathy	Immediate, MAP –20% to –25%	<ul style="list-style-type: none"> • Labetalol • Nicardipine 	Nitroprusside
Acute ischaemic stroke and BP >220 mmHg systolic or >120 mmHg diastolic	1 h, MAP –15%	<ul style="list-style-type: none"> • Labetalol • Nicardipine 	Nitroprusside
Acute ischaemic stroke with indication for thrombolytic therapy and BP >185 mmHg systolic or >110 mmHg diastolic	1 h, MAP –15%	<ul style="list-style-type: none"> • Labetalol • Nicardipine 	Nitroprusside
Acute haemorrhagic stroke and systolic BP >180 mmHg	Immediate, systolic 130<BP <180 mmHg	<ul style="list-style-type: none"> • Labetalol • Nicardipine 	Urapidil
Eclampsia and severe pre-eclampsia/HELLP	Immediate, systolic BP < 160 mmHg and diastolic BP <105 mmHg	<ul style="list-style-type: none"> • Labetalol or Nicardipine and Magnesium sulphate 	

Table 2. European Society of Cardiology-recommended treatment strategies for hypertensive emergencies.⁵⁵

Posterior Reversible Encephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome (PRES) is a clinico-radiological disorder of heterogeneous aetiologies characterised by the sudden onset of neurological symptoms associated with potentially reversible lesions on brain imaging.⁵⁸ There is substantial overlap between the clinical syndrome of hypertensive encephalopathy and PRES, and it is unclear whether they represent distinct entities. The pathogenesis of PRES appears to be related to cerebral autoregulatory dysfunction with subsequent dilation of cerebral arterioles and extravasation of plasma and red blood cells leading

to vasogenic oedema. MRI typically shows symmetrical oedema primarily in the cortex and subcortical white matter of the parieto-occipital regions. The lower level of sympathetic innervation in the posterior cerebral arterial circulation may lead to less effective damping of BP oscillations, contributing to the susceptibility to hyperperfusion and vasogenic oedema during acute BP elevation.⁵⁹

Hypertension from renal disease has been reported to be a significant cause of PRES accounting for over 25% of cases in one study of both paediatric and adult patients, implicating a role for volume expansion or uraemia.⁵⁸ There is also a clustering of other well-known risk factors in this population including autoimmune disease, solid-organ transplantation, and immunosuppression.

The clinical syndrome, characterized by headache, altered consciousness, visual disturbances, and seizures, is identical to that of hypertensive encephalopathy. Unfortunately, there are no established and validated diagnostic criteria for PRES, and it is important to rule out other important differential diagnoses such as posterior circulation stroke and viral or autoimmune encephalitis. A diagnostic algorithm for PRES has been proposed that requires at least one acute neurological symptom (seizure, altered mental state, headache, visual disturbances), one or more risk factors (severe hypertension, renal failure, immunosuppressant drugs or chemotherapy, eclampsia, autoimmune disorder), and neuroimaging with bilateral vasogenic oedema, cytotoxic oedema with patterns of PRES or normal brain imaging; and no other alternative diagnosis.⁶⁰

The four most common patterns of brain involvement are the parieto-occipital pattern with vasogenic oedema predominantly in the parieto-occipital lobes, the superior frontal sulcus pattern with oedema mainly along the anterior and media watershed region located in the deep superior frontal sulcus, the holohemispheric watershed pattern, with oedema located in both anterior and posterior, medial and lateral watershed zones, and the central pattern with vasogenic oedema located predominantly in the deep white matter, basal ganglia, thalami, brainstem, and pons.⁶¹

The mainstay of therapy is treatment of hypertension with gradual BP lowering as per the hypertensive emergency guidelines. The offending immunosuppressant or cytotoxic agent should also be stopped if possible. This may require co-ordinated discussion with other subspecialists (e.g. nephrologist, oncologist or rheumatologist) involved in the patient's care. With removal of the inciting factor and BP control, resolution of findings on neuroimaging within days to weeks is expected. However, occasionally in severe cases, death may result from progressive cerebral oedema, from ICH, or as a complication of the underlying condition.⁶² If another immunosuppressive agent is substituted or later started, patients must be monitored closely for recurrence. Avoidance of severe hypertension, fluid overload, or progressive injury in this setting will help mitigate risk.

Haemorrhagic stroke

ICH accounts for 10-15 % of all strokes in high-income Western countries, but between 20 – 50 % of those in low- to middle-income developing countries.⁶³

Hypertensive vasculopathy is the most common aetiology of spontaneous ICH.⁶⁴

Hypertensive haemorrhages typically occur in the territory of the small penetrating arteries that branch off major intracerebral arteries as they are directly exposed to the pressure of the much larger parent vessel.

The anatomical distribution of microbleeds varies with their aetiology, with hypertensive microbleeds arising in the deep subcortical (*Figure 5*) and infratentorial regions, and CAA-related microbleeds in more superficial lobar regions of the cerebral hemispheres. In a meta-analysis of 28 studies, hypertension was twice as common in patients with deep ICH as in those with lobar ICH.⁶⁵ Hypertension has also been shown to be a risk factor for ICH in the setting of other underlying aetiologies (e.g. CAA, antithrombotic-associated ICH).⁶⁶

Patients with acute ICH should be managed in an intensive care unit or dedicated stroke unit. In the acute phase of ICH, patients may require intubation and mechanical ventilation, anticoagulation reversal, aggressive BP control, interventions for elevated intracranial pressure (ICP) and mass effect, treatment for seizures, ventriculostomy, or surgical hematoma evacuation.

Severe BP elevation may worsen ICH by representing a continued force for bleeding, causing haematoma expansion and potentially worse outcomes. A systematic review of observational studies showed that a SBP greater than 140 – 150 mmHg within 12 h of ICH was associated with a more than doubling in the risk of subsequent death or dependency.⁶⁷ Treatment is a delicate balance as increased BP may be necessary to maintain cerebral perfusion in some patients with ICH, and lowering it might cause ischaemia and worsen neurological injury.

For patients with acute ICH who present with SBP between 150 and 220 mmHg, the European guidelines suggest, based on RCTs, that acute lowering of SBP to 140 mmHg is safe and may improve functional outcome.⁶⁸ For patients with acute ICH who present with SBP >220 mmHg, aggressive reduction of BP with IV antihypertensive therapy and frequent BP monitoring is required.

Eclampsia and pre-eclampsia

Pre-eclampsia refers to the new onset of hypertension and proteinuria, or hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation (or in the postpartum) in a previously normotensive woman (*Table 3*).⁶⁹ It occurs in 3-8% of all pregnancies.⁷⁰ The pathophysiology involves abnormal trophoblast invasion of spiral arteries during placentation leading to placental ischemia and release of pro-inflammatory and anti-angiogenic placental-derived soluble factors into the maternal circulation.⁷¹

Eclampsia refers to the development of generalised tonic-clonic seizures in a woman with preeclampsia in the absence of other neurologic conditions that could account for the seizure. In the United Kingdom, recent figures show that 15.5% of direct maternal deaths were due to the hypertensive disorders of pregnancy, and more than half of these women had eclampsia.⁷²

Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on at least two occasions at least four hours apart after 20 weeks of gestation in a previously normotensive patient AND the new onset of one or more of the following*:

- Proteinuria ≥ 0.3 g in a 24-hour urine specimen or protein/creatinine ratio ≥ 0.3 (mg/mg) (30 mg/mmol) in a random urine specimen or dipstick $\geq 2+$ if a quantitative measurement is unavailable
- Platelet count $< 100,000/\mu\text{L}$
- Serum creatinine ≥ 97.2 micromol/L or doubling of the creatinine concentration in the absence of other renal disease
- Liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory
- Pulmonary oedema
- Cerebral or visual symptoms (e.g., new-onset and persistent headaches not accounted for by alternative diagnoses and not responding to usual doses of analgesics[†]; blurred vision, flashing lights or sparks, scotomata)

Table 2. American College of Obstetricians and Gynecologists (ACOG) Criteria for the diagnosis of pre-eclampsia.⁶⁹

Risk factors for pre-eclampsia include prior history, pre-gestational diabetes, chronic hypertension, systemic lupus erythematosus, antiphospholipid syndrome, BMI > 30 , CKD, multifetal pregnancy, first pregnancy, family history, prior pregnancy complications associated with placental insufficiency, advanced maternal age, and use of assisted reproductive technology.

Patients may present with persistent and/or severe headache, visual abnormalities (scotomata, photophobia, diplopia, amaurosis fugax, or rarely transient blindness), upper abdominal or epigastric pain, altered mental status, dyspnoea, retrosternal chest pain. Headache, when present, is a feature of the severe end of the disease spectrum. The pain usually has a throbbing or pounding quality. It can be quite incapacitating and refractory to treatment.

Pre-eclampsia/eclampsia may also cause stroke due to disruption of cerebral autoregulation and alterations in BBB. It is responsible for 36% of pregnancy-associated stroke.⁷³ Most strokes in this setting are haemorrhagic and preceded by severe and fluctuating BP levels.

Eclamptic seizures develop in 1 in 400 women with pre-eclampsia without severe features and 1 in 50 women with pre-eclampsia with severe features. It has variously been proposed that eclamptic convulsions result from intracerebral haemorrhage, hypertensive encephalopathy, cerebral oedema, or vasospasm. Different mechanisms may be operating in different patients, with the compounding effects of cerebral hypoxia, IV fluid and drug administration, and varying degrees of hypertension.

For women with pre-eclampsia at ≥ 37 weeks of gestation, even in the absence of features of severe disease, delivery is recommended.⁶⁹ If features of severe disease are present, then delivery at ≥ 34 weeks of gestation after maternal stabilization is indicated. When there is no evidence of serious end-organ dysfunction, an expectant approach with close monitoring is reasonable to achieve further foetal maturity. However, at any gestational age, evidence of severe hypertension, serious maternal end-organ dysfunction, or non-reassuring foetal monitoring tests are generally an indication for urgent delivery.

BP should be measured daily at home in patients being managed expectantly with pre-eclampsia without severe features and at least twice weekly in the office.

Antihypertensive therapy should be initiated if persistent SBP ≥ 150 mmHg or DBP ≥ 100 mmHg. IV labetalol or hydralazine are the recommended first-line agents for

acute therapy of severe hypertension. Magnesium sulfate is the drug of choice for the prevention of eclampsia.⁶⁹

Women with a history of pre-eclampsia have a 2- to 4-fold increased risk of cerebrovascular disease and stroke later in life⁷⁴ and thus preeclampsia has been identified as an important sex-specific risk factor for stroke by the American Heart Association/American Stroke Association guidelines. In the California Teachers Study, this excess stroke risk appeared to be reduced by long-term aspirin use.⁷⁵ The increased risk of cerebrovascular disease in women with prior pre-eclampsia is also associated with subjective cognitive complaints and increased white matter lesion burden on MRI, suggestive of a continued susceptibility to brain injury that persists after pregnancy.⁷⁶

Sleep-disordered breathing and hypertension

Sleep-disordered breathing (SDB) is an umbrella term for a constellation of sleep-related breathing disorders including obstructive sleep apnoea (OSA), central sleep apnoea (CSA), both with and without Cheyne-Stokes respiration, and sleep-related hypoventilation.

Typical symptoms of OSA including excessive daytime sleepiness, frequent awakening during sleep, snoring, reduced concentration and impaired memory. Risk factors include increasing age, male gender, obesity, craniofacial and upper airway soft tissue abnormalities, and certain medical conditions (pregnancy, heart or renal failure, prior Stroke/TIA, hypothyroidism).⁷⁷

Approximately 50% of OSA patients in turn have hypertension.⁷⁸ OSA was associated with a 2.2 fold increased risk of incident ischaemic stroke in a meta-analysis of 5 studies (8435 participants).⁷⁹ In addition to hypertension, proposed mechanisms for cardiovascular risk include sympathetic activation, metabolic dysregulation, left atrial enlargement, endothelial dysfunction, systemic inflammation, and hypercoagulability. Treatment with CPAP therapy in OSA patients is associated with a lower risk of hypertension, stroke and cardiac events.⁸⁰

SDB can also occur in patients post-stroke irrespective of type and is typically obstructive in nature. In a meta-analysis of studies inclusive of 2,343 ischaemic or haemorrhagic stroke and TIA patients, the frequency of SDB with AHI > 5 was 72% and with AHI > 20 was 38%.⁸¹ Only 7% of the SDB was primarily central apnoea. Patients with unknown aetiology of stroke had a higher percentage of SDB than other aetiologies. According to the ASA/AHA guidelines, a sleep study should therefore be considered for patients with an ischaemic stroke or TIA on the basis of the very high prevalence of sleep apnoea in this population.⁸² Although it is likely that patients are still under-investigated for SDH post-stroke, there is at least an increasing awareness that it is associated with worse outcomes including increase risk of recurrence,⁸³ and worse functional and cognitive function at 90 days poststroke.⁸⁴

Conclusions

Neurologists frequently bear witness to the consequences of untreated and uncontrolled hypertension, not only in the form of acute stroke but also in memory or

sleep clinics, and more rarely, in the emergency department with the encephalopathic patient. Early diagnosis of hypertension with regular monitoring and treatment is essential to promote and sustain brain health.

Key points:

- The brain may play an important role in the genesis and maintenance of hypertension.
- Clinical manifestations of hypertension-related SVD include stroke, depression, gait disturbance, cognitive decline, and dementia.
- The strongest evidence that elevated BP is a risk factor for dementia and cognitive decline comes from observational studies with midlife measures of BP and late-life measures of the cognitive performance.
- Hypertensive emergencies often have a neurological presentation including encephalopathy, ischaemic or haemorrhagic stroke, and preeclampsia/eclampsia.
- Hypertensive disorders of pregnancy are associated with increased long-term stroke risk, cognitive complaints and white matter disease.
- Hypertension is common in OSA, which is in turn associated with incident stroke risk and is an under-recognised condition in patients post-stroke.

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Figure legends

Figure 1: Short-term neural regulation of blood pressure

Figure 2: Cerebral autoregulation curve: in patients with chronic systemic hypertension, this range is “right-shifted”, or in other words, the normal range of MAP in which CBF remains constant due to cerebral autoregulation is higher. Both the lower and upper limits are shifted.

Figure 3: MRI brain of patient with severe SVD showing (A) Area of restricted diffusion in the right parietal lobe, (B) Periventricular and deep subcortical white matter lesions, and (C) Multiple basal ganglia microbleeds.

Figure 4: An MRI brain of a poorly controlled hypertensive patient showing (A) Area of restricted diffusion in the left parietal and temporal lobes, (B) Hyperintense T2 signal change, and (C) Severe left ICA stenosis.

Figure 5: A classic example of a hypertensive haemorrhage centred on the left basal ganglia, extending into the left lateral ventricle, with modest dilatation of the ventricles in keeping with early hydrocephalus.

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