Contribution of Hypertension to Cerebrovascular Disease in the Asian Population

Umer Khan, Chan GC, Martin Lee

Department of Nephrology, National University Hospital, Singapore

Abstract

Aim: This study aims to explore the effect of hypertension on cerebrovascular disease in the Asian population. Background: Hypertension (defined as systolic blood pressure [SBP] >140 mmHg or diastolic BP >90 mmHg) is a risk factor for cerebrovascular disease. Chronic hypertension contributes to endothelial damage and impaired autoregulation, in the long-term leading to plaque formation and increasing risk of both ischemic and hemorrhagic stroke. Review Results: In Asian populations, the proportion of hemorrhagic strokes to ischemic strokes is higher in underdeveloped areas and demonstrates a decline in longitudinal studies as areas undergo development. Asians also have a higher burden of occult small vessel disease. Hypertension, diabetes, and smoking are the main risk factors for stroke in Asian countries, exacerbated by a high-salt diet and increasing prevalence of metabolic syndrome in developed nations. Asians also have a more sustained morning surge of blood pressure, highlighting the importance of monitoring home blood pressure to guide treatment. Treatment should employ both non-pharmacological and pharmacological interventions. Targeting SBP <140 mmHg has shown to reduce the risk of stroke and other cardiovascular events, as well as occult small vessel disease, regardless of agent used. Novel treatments such as renal denervation were ineffective in reducing SBP (SYMPLECTIC trial), and work on genetic testing of polymorphisms involved in blood pressure regulation remains in its early stages. Clinical Significance: Management of hypertension should be tailored to the Asian demographic with a focus on risk factor reduction, being vigilant for subclinical stroke, as well as tight blood pressure control <140 mmHg to reduce the risk of cerebrovascular disease.

Key Words: Asian, cerebrovascular disease, hypertension, literature review, stroke

Background

Definition

Hypertension or high blood pressure (BP) is a known independent risk factor for cardiovascular diseases and continues to be a major contributor of cardiovascular mortality worldwide. The World Health Organization (WHO) reports a 40% overall prevalence of hypertension in adults over age 25 (2008), contributing to 7.5 million deaths (12.8% of all deaths) annually. While the incidence of hypertension has decreased, the overall number of hypertensive adults continues to rise due to population growth and aging.[1]

The eighth report of the Joint National Committee (JNC) classified normal blood pressure as systolic blood pressure (SBP) greater than 120 mmHg, and diastolic blood pressure (DBP) greater than 80 mmHg, while prehypertension is defined as SBP 120-139 or DBP 80–89 mmHg. Class I hypertension is SBP 140-159 mmHg or DBP 90–99 mmHg, and Class II hypertension is SBP >160 mmHg or DBP >100 mmHg. The diagnosis of hypertension can be met with either DBP or SBP meeting criteria and does not require both values to be in the reference range.[2]

Other than hyperlipidemia and diabetes mellitus, hypertension is one of the three main modifiable risk factors for stroke which is the second leading cause of death and the third leading cause of disability worldwide.[1] Hence, understanding the pathophysiology of hypertension and its contribution to...
Hypertension and Cerebrovascular disease in Asians

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Hypertension and Cerebrovascular disease is important for the treatment and prevention of strokes. Furthermore, hypertension contributes to microvascular cerebrovascular disease, leading to cognitive impairment, and a larger rate of disability and associated complications in the geriatric population.\(^6\) As the risk factors and prevalence of hypertension and cerebrovascular disease are heterogeneous, the goals of care and prevention strategies should be modified toward the intended population. In this article, we will discuss the effects of hypertension on cerebrovascular disease in the Asian population.

Pathophysiology

Less than 10% of individuals with hypertension have secondary hypertension. Most patients have primary (previously known as essential) hypertension. The pathophysiology of essential hypertension is multifactorial and attributed to sympathetic activation from the central nervous system, hormonal and electrolyte imbalances, as well as localized effects of reactive oxygen species, and inhibition of nitric oxide synthesis in blood vessels.\(^5,6\) The renin, angiotensin, and aldosterone system (RAAS) is heavily implicated in the mechanism of blood pressure, as angiotensin II causes vasoconstriction, and release of aldosterone, which, in turn, results in sodium retention and increased plasma volume. Natriuretic hormone is also involved in increasing sodium concentrations and increasing plasma volume.

Chronic hypertension contributes to chronic endothelial damage, which results in a prothrombotic, procoagulant, and proinflammatory state, leading to atherosclerosis. The most common areas of atherosclerotic plaque formation include the bifurcation of the common carotid artery, the origin of the middle cerebral artery, the origin and distal portion of the vertebral artery, and middle basilar artery.\(^5\) In patients with hypertension, the brain’s autoregulation thresholds are adjusted to higher mean arterial pressures. Therefore, symptoms of cerebral ischemia occur at higher values of mean arterial pressures in hypertensive patients.

Hypertension also leads to changes in arteriolar structure, including fibrinoid necrosis, medial degeneration, and microaneurysm formation, which makes vessels more susceptible to rupture and causing hemorrhagic stroke. Saccular aneurysms, which cause subarachnoid hemorrhage, occur due to degenerative and inflammatory changes, leading to thinning of the media, atherosclerosis, and presence of medial and elastic defects in the aneurysmal wall. Other contributing factors include the lack of elastin and surrounding supporting tissue in the subarachnoid hemorrhage which makes these vessels more likely to form aneurysms. Congenital defects in the arterial media and genetic disorders, leading to abnormal collagen deposition, are also thought to be associated with familiar intracranial aneurysms. Finally, acute rise in blood pressure, such as with cocaine, amphetamine, and other sympathomimetic drugs, as well as post-endarterectomy patients, is associated with increased risk of intracranial hemorrhage even in otherwise normal arterioles who have not been exposed to chronic high blood pressure.\(^4\)

Unlike cardiovascular disease, which is almost always due to large vessel atherosclerosis, strokes can be ischemic (80%) or hemorrhagic (20%) and be subdivided further based on etiology. Ischemic strokes can be due to large vessel or small vessel disease, cardioembolic, vessel dissection, or lacunar strokes.\(^6\) Knowing the incidence of different types of strokes is important in primary prevention as well as the management of stroke patients, to allow targeted risk factor modification.

Results

Risk Factors

Risk factors for stroke include obesity, sedentary lifestyle, tobacco use, high-sodium diet, excessive alcohol use, stress, sleep apnea, hyperlipidemia, and diabetes.\(^6\) Age, family history (genetic predisposition), and race are considered non-modifiable risk factors. Hypertension is a risk factor for both classifications of stroke but has a more direct role in hemorrhagic strokes.\(^7\)

Asian countries tend to have higher mortality and morbidity from stroke than coronary artery disease, and the opposite is true in Western countries. This has previously been attributed to dietary differences, as Asian diet tends to be higher in salt, but lower in fat content compared to Western diet intake.\(^6\) Age-adjusted mortality from stroke itself is also generally higher in Asia than in Western countries, with the exception of Japan and Singapore. Mortality in South Korea and China is decreasing in urban areas but remains stable in rural areas.\(^6\)

The ratio of hemorrhagic stroke-to-ischemic stroke in East Asian countries is 2:1–3:1 while in Western countries is 5:1–10:1.\(^6\) Lacunar stroke tends to be the most common type of ischemic stroke in Asian countries, while in Western countries, large vessel and thromboembolic strokes are more common. However, decrease in smoking rates has contributed to a decrease in lacunar strokes in Japan from 1961 to 2000.\(^6\)

Socioeconomic status is associated with different epidemiological characteristics of stroke, including higher rate of hemorrhagic stroke, higher fatality rate, and younger onset. This becomes a factor in Asian populations as many countries have recently undergone significant development over the past 10–20 years. Zhao et al. conducted a 20-year observational study of a Chinese population as the region underwent significant development. The age-standardized incidence rate of hemorrhagic stroke declined by 1.7% (CI −2.7, −1.2) annually, and even more significantly so by 3.2% (−4.4, −1.9) in the second decade. Conversely, the rate of ischemic stroke increased by 8.7% (CI 4.3, 8.9) annually. The mean age of onset increased by 2.7 in men and 3.6 years in women.\(^7\)

The Asia Pacific Cohort Studies Collaboration, which included >650,000 participants from China, Hong Kong, Taiwan, Japan, South Korea, Singapore, Thailand, New Zealand, and Australia, showed that diabetes, hypertension, and smoking are the main medical risk factors for stroke. The
population attributable fraction of hypertension and smoking for cerebrovascular disease is 60% and 30%, respectively. These studies showed that the relationship between blood pressure and stroke was more prominent in Asian countries than Australia and New Zealand. The relationship between total cholesterol and stroke in Asian populations is not entirely clear, and some studies have shown that total cholesterol was not significantly associated as a risk factor for total stroke. On the other hand, another meta-analysis showed that cholesterol-lowering therapy with statins can prevent total stroke without increasing rate of hemorrhagic stroke.

Hypertension continues to be more prevalent in East Asia than South Asia, and relationship between salt consumption and blood pressure has been reported in Japan, China, and Korea. Japan has observed substantial decrease in salt intake, now 13 g/day, with a concomitant reduction in stroke mortality as well. The rate of smoking in Asian men is down trending but still remains high at 40–60% compared to Western countries. It remains a strong contributor to the development of stroke. Interestingly, migrant studies have shown that Japanese people who have migrated to the West have higher rates of coronary artery disease, type 2 diabetes mellitus, and atherosclerosis, but a reduced risk of stroke. This points to the importance of lifestyle and modifiable factors contributing to disease burden in cerebrovascular disease, rather than genetic factors.

**Prehypertension**

Prehypertension is defined as SBP of 120–139 mmHg or DBP of 80–90 mmHg. While the effects of hypertension as a risk factor for cerebrovascular disease are well recognized, the effects of prehypertension are not so clear. A cohort of 4422 patients in China underwent ultrasound of carotid arteries as well as a transcranial Doppler to identify evidence of cerebrovascular disease. In this study, patients with prehypertension had an odds ratio of 1.60 (P = 0.003) and hypertension had an odds ratio of 2.12 (P < 0.001) of association with asymptomatic intracranial artery stenosis. This association was stronger in men (P < 0.001) than women (P = 0.06). However, neither prehypertension nor hypertension was significantly associated with the presence of asymptomatic extracranial arterial stenosis. This study supports the findings of early development of small vessel disease even with mild increment in blood pressure in the Asian population and the need for aggressive blood pressure control.

**Genetics of Hypertension**

Various studies have investigated the consequence of signaling pathways on blood pressure. These signaling pathways include vasoconstriction, vasodilation, sympathetic nerve-adrenergic receptor system (genes contributing to regulate renal salt level), and RAAS.

Determining which of these signaling pathways contributes to essential hypertension as primary variations or secondary responses have been complicated. Therefore, the study of monogenic forms of essential hypertension has proven that variants of genes involved in renal salt handling originally derive the genetic basis of hypertension. Activation of these pathways results in arterial remodeling and increased vascular tone, thereby increasing blood pressure. Once vascular tone is increased chronically, it is impossible to resume normality, although current antihypertensive drugs are used to temporarily reverse the vascular tone to normal. Therapy targeting on irreversible vascular remodeling could potentially assist in decreasing the morbidity and mortality in coronary heart disease, stroke, and kidney failure caused by hypertension. The current focus on the genetics of hypertension is targeted toward the hormonal components implicated in blood pressure control, namely the RAAS and natriuretic peptide (NP) pathways.

**RAAS System**

The gene encoding angiotensinogen from renin-angiotensin system-related genes along with angiotensin I-converting enzyme (ACE) gene is among the candidate genes associated with essential hypertension. A molecular variant of the ACT gene, M235T has been shown to have a significant involvement in essential hypertension, thereby making it a potential risk factor and hereditary marker for essential hypertension. M235T genotype was linked to a significant increase in angiotensinogen levels in Asian population.

**NP Receptor (NPR)**

The NP family comprises atrial NP (ANP), B-type NP (BNP), and C-type NP along with three NPR-A, NPR-B, and NPR-C. This family plays a significant part in the development and diagnosis of a variety of cardiovascular diseases including hypertension and heart failure. NPs have shown to increase vasodilation, natriuresis, and endothelial permeability, in addition to suppressing the RAAS system. Increase in circulating ANP/BNP levels can lead to decrease in blood pressure. NPR-C, encoded by NPR3, is a scavenger receptor that helps in clearing NP. Allelic variants of NPR3 have been linked to hypertension. Therefore, deactivation of NPR3 can potentially reduce both ANP clearance and blood pressure. A promoter variant of NPR3 is linked to an increased risk of early-onset ischemic stroke. In 2011, the Asian Genetic Epidemiology Network BP group identified genetic variants of NPR3 inducing blood pressure among East Asian population. Kato et al. identified novel genome-wide associations between high blood pressure and NPR3 variants that affected SBP, DBP, stroke, and coronary artery disease.

**Cytochrome P450**

Cytochrome P450 family 4 subfamily F member 2 (CYP4F2) is a member of CYP450 superfamily that plays a key role in metabolism. Meta-analysis study of polymorphisms of CYP4F2 gene has shown susceptibility to blood pressure. CYP4F2 polymorphisms have also shown to decrease the risk of hypertension among male patients in Asian population, thereby making it a potential biomarker for patients with essential hypertension.
**Discussion**

**Clinical Considerations**

Studies have also shown that masked hypertension (normal BP in clinic, but high BP at home) and sustained hypertension are associated with higher risk of cardiovascular events. Hence, there is increasing emphasis placed on home and ambulatory BP monitoring and evidence to support that ambulatory and home BP demonstrate a prognostic relationship with major cardiovascular diseases. A study of 2400 patients demonstrated a significant association between home SBP, ambulatory SBP (24 h, night-time, and daytime), and silent cerebrovascular disease on MRI brain as well as carotid atherosclerotic disease on ultrasound. However, there was no association between casual and clinic SBP and silent cerebrovascular disease and atherosclerotic disease. The ambulatory night-time SBP was more strongly associated than daytime or home SBP. It is believed that morning hypertension may be more common and more pronounced in Asians, who may experience a morning surge of high BP. This is also contributed by the decreased effect of antihypertensive drugs when the next dose is due in the morning and can often be missed or missed by clinic readings for this reason. The morning surge is associated with inflammatory biomarkers and risk of stroke. The HONEST trial demonstrated a 2.5 times increased risk of cardiovascular disease, including stroke, in patients with morning home BP >145 mmHg even with office BP <130 mmHg, compared to patients with home BP >125 mmHg and office BP <130 mmHg over a 2-year monitoring period.

Kario et al. have attempted to innovate home BP monitoring taking into consideration the importance of nocturnal BP and morning surges. One such modification was triggered nocturnal BP monitoring, which measured BP based on oxygen saturations as well as at the lowest basal heart rate, to capture blood pressures triggered by stress such as hypoxia in patients with obstructive sleep apnea (OSA), as well as resting blood pressure. This would allow physicians to determine contributing factors to nocturnal hypertension and tailor specific medications or management plans based on the underlying etiology of hypertension. The trigger BP system could also be used to monitor the efficacy of continuous positive airway pressure treatment and serve to detect the presence of OSA, as apneic and desaturation episode can vary on a night-to-night basis. OSA is associated with a sustained morning surge of blood pressure, as well as increased intracranial pressure and decreased autoregulation, thereby promoting ischemia. It also causes higher fibrinogen levels and increased blood viscosity in the morning, as well long-term atherosclerosis from oxidative stress due to hypoxia, all of which contribute to increased stroke risk.

In an analysis of small vessel disease in the general elderly Asian population, Hilal et al. compared microvascular cerebral disease on neuroimaging with cognition testing. Of 1797 patients, 36.6% had white matter hypodensities, 24.6% had lacunes, and 26.9% had microhemorrhages. Hypertension, hyperlipidemia, and diabetes were significantly more common in Singapore compared to Hong Kong and Korea. In terms of the prevalence of small vessel disease, lacunes were highest in Hong Kong, while the prevalence of cerebral microbleeds and white matter hypodensities was highest in Singapore. Cognitive impairment was also more common in Singapore compared to Hong Kong and Korea. There was an independent association between burden of small vessel disease and MMSE and MOCA scores. Age and hypertension were identified as the major risk factors for small vessel disease.

**Treatment**

As discussed earlier, the current guidelines by the JNC for hypertension suggest targeting SBP <140 mmHg. These guidelines are supported by the Systolic Hypertension in the Elderly Program study showed that the reduction of SBP to 140 mmHg significantly reduces the 5-year incidence of total stroke (5.2/100 for active treatment and 0.2/100 for placebo). Similarly, in patients with established lacunar stroke, the SPS3 randomized trial showed non-significant rate reductions for stroke (Hazard ratio 0.81) in patients with reduced SBP of <130 mmHg, demonstrating that reducing blood pressure >140 mmHg is important for both primary and secondary prevention of stroke.

The SBP intervention trial (SPRINT) was an open-label trial which compared aggressive treatment of SBP (target <120 mmHg) with standard treatment to a target of <140 mmHg, in a total of 9361 participants. The study terminated early after a median follow-up of 3.26 years. The mean SBP was 121.4 mmHg in the intensive group and 136.2 mmHg in the standard group. There was significant reduction of primary outcome (composite first occurrence of myocardial infarction, stroke, heart failure, or death from cardiovascular events). However, there was no statistically significant reduction in stroke (Hazard ratio 0.62, P = 0.50), demonstrated in the study. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial had similar BP targets, but the differences in cardiovascular mortality in the intensive treatment and standard treatment group were not statistically significant. However, the ACCORD trial included diabetic patients exclusively while in SPRINT diabetic patients were excluded from the study. In summary, these studies show that aggressive treatment of hypertension to targets of SBP <120 mmHg does not show a significant benefit in reducing the risk of stroke and that other risk factors such as diabetes also play a significant role in the overall risk of stroke.

In Asian patients, the CARNAS study (2014) was a meta-analysis of prospective randomized controlled trials to monitor the effect of antihypertensive treatment on cardiovascular endpoints. It showed significant benefit with a BP target of <140/80 mmHg in Asian patients with hypertension, with a 30% reduced risk in stroke events and 39.5% reduced risk in composite cardiovascular events. There was no difference for any outcome between renin-angiotensin blockers and calcium channel blockers, thus highlighting the importance of blood pressure control as primary determinant of cardiovascular health rather than choice of agent.
Non-pharmacological Treatment

As discussed earlier, Asians have higher incidence of stroke than that of myocardial infarction, which is the opposite of the Western population.\(^6\) Diet high in salt is common in many parts of Asia, and hypertension in Asians tends to be more sensitive to salt. Furthermore, diabetes and metabolic syndrome are becoming more prevalent in Asian countries, and the WHO predicts the number of diabetics in Asia to double by 2030.\(^6\) Hence, non-pharmacological methods of treating hypertension such as patient education, dietary advice, and regular exercise should continue to complement pharmacological therapy.

Choice of Agents

With regard to choice of antihypertensive agent, a meta-analysis by Tran et al. showed that calcium channel blockers were not superior to ACE inhibitors in the Asian population.\(^7\) The Singapore National Guidelines for hypertension are consistent with most treatment guidelines, with initiation of treatment with ACE inhibitor or calcium channel blocker, and adding a second agent of either beta-blocker or diuretic to achieve target goals of blood pressure treatment.\(^8\) Physicians should also tailor each patient’s antihypertensives appropriately according to their comorbidities, drug tolerance, and threshold of compliance.

Novel Treatments

The RAAS system is thought to play a pivotal role in hypertension, and renal denervation may be a promising treatment for refractory hypertension. The SYMPLICITY trial was a single-blind trial with 535 patients with resistant hypertension (on at least three agents) to undergo renal denervation. There was no statistical difference found in SBP (difference of −2.39 mmHg, \(P = 0.26\) for a superiority margin of 5 mmHg) and ambulatory blood pressure (difference of −1.96 mmHg, \(P = 0.002\)) at 6 months between the denervation group and the sham procedure group.\(^9\)

The Global SYMPLICITY Registry - Korea trial compared renal denervation in Korean patients with Caucasian patients and found comparable results in SBP control over 6-month period (−20.9 ± 21.4 mmHg, \(P = 0.998\)), after adjusting for lower body mass index and lower baseline clinic blood pressure. The 12-month SBP reduction was larger than in the Caucasian group (−20.1 ± 23.9 mmHg, \(P = 0.002\)). However, overall, the SYMPLICITY study did not show significant blood pressure reduction by renal denervation in patients with resistant hypertension.

Gene therapy may be an alternative approach to the treatment for refractory hypertension and individualizing treatment for populations and individuals. A study of 72 male Malay participants was followed up for 24 weeks with either lisinopril or enalapril and had genotyping of the ACE gene. There was a statistically significant reduction in SBP for patients carrying the DD genotype (SBP 18.5 ± 8.1 mmHg) rather than ID genotype (SBP 21.1 ± 3.3 mmHg) and II genotype (SBP 30.0 ± 2.0 mmHg).\(^10\) Experimental studies on genes for the RAAS, beta1 adrenergic receptor, endothelin, NP, cy-P450 hydroxylase, growth factors, and many others have not reached the clinical stage yet.

Conclusion Clinical Significance

Hypertension continues to have a significant burden and contribution to cerebrovascular disease. Due to the large burden of hemorrhagic stroke in underdeveloped areas and progressive microvascular disease in the Asian population, hypertensive patients should ideally have early and aggressive treatment. Clinicians should also be aware of physiological differences such as a prolonged morning surge of blood pressure, the importance of home blood pressure monitoring, and tailor treatment regimens to individual patients where appropriate.

References

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