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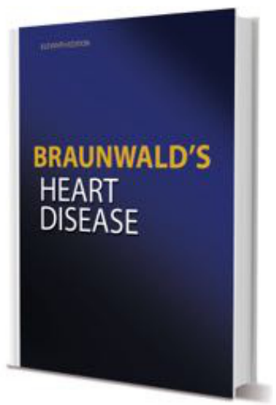

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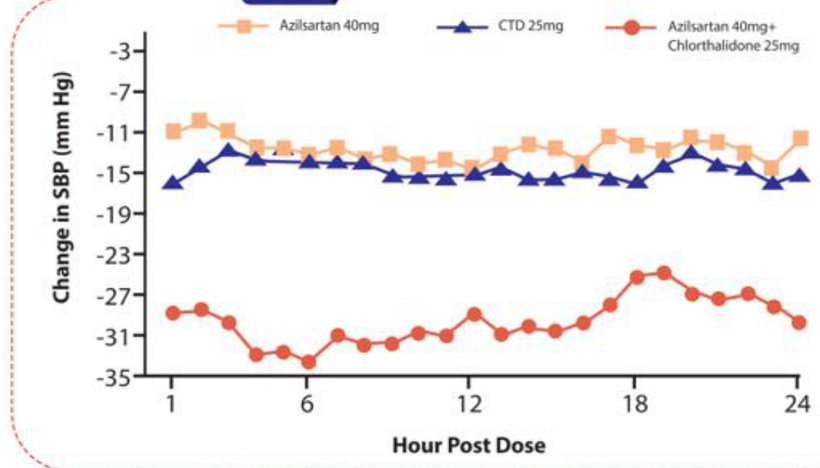

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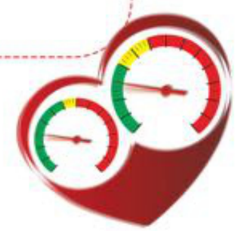

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AIMS & SCOPE

Hypertension Journal is a peer-reviewed journal which highlights epidemiology, health implications and cardiovascular risk from hypertension in India/South-Asia. Hypertension is much more common than diabetes. It is vastly under diagnosed and poorly treated in India/South-Asia. There are excellent therapeutic options to treat hypertension, but the available resources are not fully utilized by doctors therefore neglecting this disorder. The journal will hereby promote the significance of hypertension and the urgent need to bring it under control. The medical community should be educated on hypertension evaluation, diagnosis, workup and management simultaneously bringing up the literature, research, guidelines and scientific advances related to hypertension and its disorders. We are hereby starting a high-quality journal dedicated solely to hypertension and thus promoting the awareness, evaluation and effective management in India/South-Asia. Dr C Venkata S Ram is a world authority on hypertension with lifelong work (research, clinical and publications).

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Guest Editorial

Hypertension in Asia

Boon Wee Teo

Division of Nephrology, Department of Medicine, National University Hospital, and National University of Singapore

Hypertension affects a substantial number of Asians.[1] It is a disease multiplier and is associated with high rates of adverse cardiovascular events (myocardial infarction and strokes) and death. It increases the likelihood of chronic kidney disease and/or progression to end-stage kidney disease. It remains one of the easiest risk factors to control and yet is also a difficult one to target. This is because hypertension has many etiologies, which we are still constantly discovering. Nonetheless, we note that Asians may be inadequately diagnosed and treated when compared to the industrialized European or North American populations. Some of it may be attributed to socioeconomic reasons, but often cultural factors (e.g., diet) may play an important role.[2] Therefore, it is crucial that Asian countries study the determinants of hypertension in their respective populations.

There is some uncertainty on the diagnosis of hypertension based on just office blood pressure readings alone, and also, there is uncertainty on the methods of establishing the diagnosis and follow-up of hypertension. It is, therefore, important to establish the appropriate cutoffs for Asian populations through more research of the larger Asian ethnicities.[3] Besides diagnosis, even with good follow-up and access to medical care, hypertension may not be adequately controlled with current clinical practice and therapeutic drugs.[4] Perhaps, newer technologies such as retinal photography with computerized evaluation, it is possible to quantitatively assess the changes of blood vessels in hypertensive patients, particularly the adequacy of therapy.[5] Without higher fidelity assessment and follow-up, the residual risks of treated hypertension on mortality and complications cannot be completely eliminated.

The complexity managing of hypertension is not quite captured in clinical practice guidelines.[6] There is still a big gap of knowledge and inadequate practical applications to manage the very large burden of hypertension in Asia. We need more studies that improve the capture of ethnic or cultural factors affecting sodium intake and have simple and cheaper methods of assessing sodium intake.[7] Moreover, in specific Asian patient populations, we need to assess and quantify the utility of instruments helpful for managing hypertension.[8] This is because many of the devices and reference ranges were developed from patient populations in North American or European populations, and therefore, the bias and method of application are not immediately apparent in Asian patients. There is much work for hypertensionologists in Asia. Nonetheless, in this issue of the journal, we bring attention to hypertension and its association with other chronic "diseases" such as dyslipidemia and obesity. We will examine the other methods of assessing blood pressure such as retinal photography and central aortic pressure assessments and discuss some of the findings and work of Asian scientists and clinicians.

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Reviews and Clinical Debates

Contribution of Hypertension to Cerebrovascular Disease in the Asian Population

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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 (SYMPLICITY 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

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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.[3] 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.[2,4] 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.[4] 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.[5] 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.[8] 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.[9] On the other hand, another meta-analysis[10] 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.[6] 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.[11]

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.[12,13] 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.[14] 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.[15-17]

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.[18,19] 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.[20,21] 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 promotor variant of NPR3 is linked to an increased risk of early-onset ischemic stroke.[22] 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.[23]

Cytochrome P450

Cytochrome P450 family 4 subfamily F member 2 (CYP4F2) is a member of CYP450 superfamily that plays a key role in metabolism.[24] Meta-analysis study of polymorphisms of CYP4F2 gene has shown susceptibility to blood pressure.[25,26] 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.[27]

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.[28] 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.[28]

It is believed that morning hypertension may be more common and more pronounced in Asians, who may experience a morning surge of high BP.[29] This is also contributed by the decreased effect of antihypertensive drugs when the next dose is due in the morning and can often be masked 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 composite 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.[30]

Kario *et al*. have attempted to innovate home BP monitoring taking into consideration the importance of nocturnal BP and morning surges.[28] 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.[31]

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.[3]

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).[32] 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.[33]

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.[34]

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 infection, 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.[34] 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.[35] 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 CARNA study (2014) was a meta-analysis of prospective randomized controlled trials to monitor the effect of antihypertensive treatment on cardiovascular endpoints.[36] 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.[37] 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.[38] 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, $P = -1.96$ mmHg) at 6 months between the denervation group and the sham procedure group.[39]

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 4.1 ± 3.3 mmHg) and II genotype (SBP 3.0 ± 0.2 mmHg).[40] 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.

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Review Article

Blood Pressure Measurement Methodologies

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Abstract

Blood pressure (BP) is an important vital sign used to determine a patient's clinical status and is applied in numerous settings such as clinics or hospitals, ambulatory, and self-monitoring. It not only serves to help medical professionals guide treatment but also assists patients in self-monitoring of their clinical condition. Accurate measurements and user-friendly interphases are, therefore, crucial to allow for ease of interpretation and for appropriate follow-up measures once BP values are obtained. There are various methods to obtain BP measurements (intermittent, continuous, invasive, and non-invasive), each come with their own advantages and disadvantages. With the advancement of medical science, the most commonly used method to date would be the oscillatory method through automated monitoring devices and further developments are underway to improve both accuracy and accessibility of BP measurement.

Key words: Blood pressure, methodologies, pseudoaneurysm

Introduction

Blood pressure (BP), the pressure of circulating blood within the arteries, is one of the vital signs measured routinely to evaluate hemodynamics. It is expressed as systolic pressure over diastolic pressure and is measured in milliliters of mercury (mmHg) above the surrounding atmospheric pressure. Measurement allows for rapid triaging and determination of patient's clinical condition, especially pertaining to cardiovascular status and tissue perfusion.[1] As such, BP measurements should be accurate and reproducible. The standard location of BP measurement is the brachial artery. Although it is possible to obtain measurements from other parts of the body, it is important to note that BP varies considerably in different areas of the arterial circulation.[2]

Techniques of BP Measurement

BP measurement can be invasive or non-invasive. While they produce similar measurements, the invasive method measures pressure while the non-invasive method uses flow as a surrogate estimate of pressure.[3]

Invasive Arterial BP (IABP)

The gold standard of arterial pressure measurement is directly through an intra-arterial catheter.[3] It is useful for beat-to-beat measurement of BP, an alternative when non-invasive methods of BP measurement are challenging (for example, in the cases of impaired skin integrity, obesity, or anatomical limitations - such as previous lymph node excision, limb amputation, and arteriovenous fistulas), superior in accuracy at extremes of BP s or in the presence of cardiac arrhythmias and allow for frequent arterial blood gas sampling.[3] There are no absolute contraindications to IABP monitoring; however, caution must be taken to avoid placement of an intra-arterial catheter in extremities with pre-existing vascular insufficiency. Complications which usually arise from misuse of the equipment include distal ischemia from resultant thrombosis, hematoma, pseudoaneurysm, damage to surrounding structures, infection, and erroneous intra-arterial drug administration.[4] As IABP monitoring is not without risk, it is usually reserved for patients on vasoactive medications and unstable patients being managed in an intensive care setting or intraoperatively where scrupulous BP monitoring is vital to the patient.

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Non-IABP

There are several methods of NIBP measurement, all of which involve the use of a sphygmomanometer composed of a pneumatic cuff connected to a manometer for measurement. BP measurement is obtained by occlusion of a major artery with an external cuff. The cuff is inflated to a pressure higher than the BP inside the artery which collapses it. The pressure in the cuff is then slowly released allowing gradual blood flow through the artery. The pressure in the cuff when blood flow first returns through the artery is taken as an estimate of the systolic pressure, while the pressure in the cuff when the blood flow becomes continuous is taken at the diastolic pressure.[5]

The palpatory method estimates pressure through palpation of the radial pulse. The BP cuff is inflated until the radial pulse is not palpable and further inflated another 30 mmHg above that, as the BP cuff is deflated, systolic pressure is taken at the point where the radial pulse becomes palpable again. During deflation of the cuff, as the radial pulse becomes palpable again, there is also an accompanying pulsatile thrill, and the disappearance of this pulsatile thrill is taken as the diastolic pressure.[3] This method is useful in the absence of a working automatic BP monitor or a stethoscope as it only requires a sphygmomanometer. The major disadvantage of this method is that the measurement of diastolic pressure subjects to a high interobserver variability. This method is also inaccurate in severe hypotension as the radial pulse may not even be palpable then.[3,6] With the advancement of medical science, this method has largely been replaced with the auscultatory or automated BP measurement, and hence, there are very few studies validating the accuracy of this method.

The auscultatory method relies on the detection of Korotkoff sounds from inflation and deflation the BP cuff for accurate measurement of systolic and diastolic pressure. The Korotkoff sounds are detected through a transducer over the brachial artery.[7,8] The main drawbacks to this method are movement artifacts obscuring the true Korotkoff sounds.[7] The mercury sphygmomanometer has been regarded as the gold standard for office BP measurement; however, its role has diminished greatly after the widespread ban of its use due to the known toxicities of mercury.[2] Newer hybrid sphygmomanometers combining oscillatory and manual auscultatory methods have now replaced mercury devices and have also been validated by studies to be reliable alternatives.[9] Regardless, the mercury sphygmomanometer still remains as a reference and standard against any new developments or validations in BP measurement.[9]

The oscillatory method detects air volume variations or oscillatory amplitudes in the BP cuff during deflation and the maximal oscillation point corresponds to mean arterial pressure.[2,5] As the oscillations begin around systolic pressure and continue below diastolic pressure, BP is estimated through an algorithmic interpretation of the oscillatory amplitudes and the heart rate. This, therefore, allows for automated devices to be programmed for rapid and consistent BP measurements.[5,10] There is, however, no standardized method of measurement and different brands of recorders use different algorithms. Its main disadvantages are movement artifacts which will affect the bandwidth of the oscillatory signals, and variations in BP measurements depend on the type of algorithm used.[7] This method has been validated against the intra-arterial and auscultatory methods with good correlation.[11] Virtually, all automated BP devices, nowadays, employ this method for BP measurement for portability and self-measurement of BP which has greatly improved the accuracy of diagnosing hypertension, allowed for better monitoring of BP control, and most importantly increased patient's compliance with antihypertensive therapy.[12]

The ultrasound technique incorporates the use of an ultrasound probe over the brachial artery to detect Doppler phase shifts from the movement of the arterial wall during deflation of the BP cuff. Systolic pressure is recorded when a Doppler phase shift is detected and diastolic pressure is recorded at the point where there is a reduction in arterial wall motion.[2,13] Few studies have validated this method of measurement and mostly studied measurements in infants and young children with inconclusive results.[14,15]

The finger cuff method of Penaz first developed in the 1980s is a method that allows for non-invasive continuous BP monitoring by recording arterial waveform indirectly from a finger using plethysmography. The output of the plethysmography is connected to a servo system and dynamic setpoint adjuster that ensures full transmission of finger arterial BP to cuff air pressure by employing the principle of arterial unloading.[16] In essence, the diameter of a finger artery is kept constant by "clamping" it with the cuff, and this is done by dynamically applying a counter pressure to the finger artery through the cardiac cycle keeping it at a volume between collapsed and fully extended allowing internal pressure to equal external pressure, also termed unloading.[17] The plethysmogram is then analyzed and BP is determined during the short periods of steady cuff pressure. This method has since been adapted to show brachial pressures reconstructed from finger pressures. Some examples of such devices include the Finometer (Finapres Medical Systems, Amsterdam, The Netherlands) and the Nexfin (BMEYE, Amsterdam, The Netherlands). Some studies have validated the Nexfin device against non-invasive (namely, the auscultatory method) and invasive methods with good correlations to either method with adherence to the Association of the Advancement of Medical Instrumentation (AAMI) criteria.[18] Bearing in mind, however, that the other non-invasive methods and the AAMI protocol are not intended for continuous BP monitoring and hence cannot directly be applied for comparison. The major disadvantage of the method is that it cannot be used in cases with insufficient blood flow or severe vasoconstriction to the extremities as in peripheral vascular disease or patients on high doses of vasoactive drugs.[19] So far, this method has mainly been employed for research purposes.

Technical Aspects of BP Measurement from the Arm

There are significant potential sources of error or inter-operator variability with BP measurement from the upper arm. Firstly, the

cuff size in relation to the patient's arm circumference. A small cuff size will lead to overestimation of BP. As suggested by the American Heart Association (AHA), the bladder length should be 80% of the patient's arm circumference with the ideal width being 40%[20] [Table 1].

Secondly, the patient's position in relation to the BP cuff. The AHA recommends for the patient to be seated with legs uncrossed and back as well as arms supported. Ideally, the patient should be seated 5 min before measurement with all clothing covering the arm to be removed. The arm should be at the level of the heart such that the middle of the cuff corresponds to the level of the right atrium. The readings will be overestimated if the arm is too high and conversely underestimated if the arm is too low.[2,20] Thirdly, the rate of inflation and deflation of the BP cuff. Rapid inflation or over inflation can cause discomfort and erroneously overestimated BP readings as a result. Rapid deflation tends to underestimate systolic BP and overestimate diastolic BP. It is recommended again by AHA that the cuff be inflated to 30 mmHg above the point at which the radial pulse disappears and be deflated at a rate of 2–3 mmHg/s.[20,21] Lastly, the number of BP measurements taken to obtain mean BP values. At least two readings should be taken at intervals of 1 min or more. The average of the two readings represents the patient's BP. If the readings differ by >5 mmHg, an additional one or two more readings should be taken and the average of all the readings obtained is used.[2,21]

Table 1: Recommended cuff sizes by AHA[21]

Adult patients (arm circumference, cm)	Recommended cuff size (cm)
22–26	12×22
27–34	16×30
35–44	16×36
45–52	16×42

AHA: American Heart Association

Table 2: BHS grading criteria

Grade	Absolute difference between standard and test devise (%)		
	≤5 mmHg	≤10 mmHg	≤15 mmHg
A	60	85	95
B	50	75	90
C	40	65	85
D	Worse than C		

BHS: British hypertension society

Devices for BP Measurement

Devices must go through a validation process before they are recommended for use in the general population. Two protocols, AAMI and British hypertension society (BHS), have been formulated for this purpose and are used in most validation studies [Table 2]. A device is recommended for use if it fulfills the AAMI criteria for systolic as well as diastolic pressure and receives a Grade A or B under the BHS protocol for systolic and diastolic pressure. Conversely, a device is not recommended for use if it fails either AAMI criteria for systolic or diastolic pressure and receives a Grade C or D under the BHS protocol for systolic or diastolic pressure.[22] A questionable recommendation is made when the device fulfills one of the two criteria. That device should not be recommended clinical use until a confirmatory study has been performed.

Grades denote the total percentage of readings within 5 mmHg, 10 mmHg, and 15 mmHg of the mercury standard. Criteria in all three respective groups must be fulfilled before the grade is bestowed.[23]

Arm Cuff Monitors

Arm cuff is used to measure BP from the brachial artery. There are various monitors that utilize an arm cuff. The mercury sphygmomanometer measures BP using a column of mercury (liquid). This also means that the BP monitor must be placed on level ground for accuracy. The aneroid sphygmomanometer consists of a spring mechanism and a metal membrane that transduces pressure from the cuff to the needle gauge. The absence of liquid in the device permits portability and measurement on uneven or even vertical surfaces such as walls. Due to its convenience and ease of use, the most widely used automated sphygmomanometer employs oscillometry to detect pressure waves.[22]

Wrist Cuff Monitors

Wrist cuff monitors utilize automated devices (oscillometry technique) to measure BP from the radial artery. This technique was developed facilitate self-BP monitoring. However, it is subjected to several areas of inaccuracies as a result of peripheral vasoconstriction or incorrect limb placement. Although it is not yet fully established, desk support position that allows the wrist to be at heart level provides the best correlation to mercury BP measurement.[24] Further advancements such as the addition of position sensors to the wrist device which only allow BP measurements when the device is at heart level has helped to mitigate the issue of limb placement. With this development, a select few devices have since been successfully validated in research settings. Nonetheless, this technique has not been validated for use as an alternative to brachial BP measurement.[25-27]

BP Measurement in Special Populations

A validation study of BP device measurement typically includes adults from the general population who are normotensive or hypertensive. However, there are always groups of individuals who fall out of the normal population, in whom where BP measured with standard protocol devices could be inaccurate. Special populations as defined by the 2018 collaborative statement from the US AAMI, the European Society of Hypertension (ESH), and the International Organization for Standardization for a universal standard for the validation of BP measuring devices are those with theoretical and clinical evidence

of different accuracies of BP measurement on BP monitors.[23,28] A study by Stergiou *et al*. highlighted some of these individuals such as young children, pregnant women (including those with eclampsia), those with high arm circumference (>42 cm) as well as patients with arrhythmias, namely atrial fibrillation (AF). Separate validation studies are recommended for individuals in the special population after the device has gone through a successful validation in the general population.[28] As per the ESH-International Protocol, evaluation and validation studies for device suitability in special populations require an additional 35 subjects with the exception of pregnant women which requires 45 subjects after a full validation study of 85 subjects has been done in the general population.[29] If a device is only meant for special population use, a full 85 subject study must be done. Elderly individuals with end-stage renal failure or diabetes have also been considered as special populations; however, there is inadequate evidence of significant variation in their BP from the general population.[28]

BP Measurement in Children

Children have different physiological and anatomical characteristics compared to adults. They have smaller arm circumferences, significant differences between brachial and aortic BP values as well as low amplitude and consequently difficult to detect Korotkoff sounds.[30] To date, normative data on BP in children are still standardized on BP readings using a mercury sphygmomanometer.[31] Currently, it is recommended that hypertension in children be diagnosed by the auscultatory method with ambulatory BP monitoring (ABPM) being the gold standard for diagnosis. Since automated oscillatory BP monitors are widely used, nowadays, it is prudent to know if it is a reasonable alternative to the auscultatory method. Although limited studies for the oscillatory method in the pediatric population exist, they show fair correlatability between the auscultatory and oscillatory methods.[31] In addition, home BP monitoring though more accessible and practical for long-term BP monitoring has not yet been established for the diagnosis of hypertension in children.[32] Nonetheless, a noteworthy point is that day ABPM is higher than home BP, whereas there is no difference in adults.[33] This is attributed to their high level of physical activity in the daytime.

BP Measurement in Pregnancy

Due to physiological changes during pregnancy, the Korotkoff sounds are more reproducible and reliable. As such, the auscultatory method is recommended for BP monitoring in this population. The oscillatory method tends to underestimate BP in this population.[28] Moreover, oscillatory signals are affected by factors such as increased peripheral vascular resistance, peripheral edema, and reduced intravascular volume which are associated with pre-eclampsia where BP is vital for diagnosis.[28] Automated oscillometric BP monitors may be used as an alternative to the auscultatory method, especially in diagnosing hypertension; however, the devices must have been successfully validated in pregnancy.[28] BP pressure during pregnancy depends on gestation, but largely BP >140/90 is considered to be abnormal and systolic BP >150 is considered a medical emergency, and treatment is necessary to prevent a subsequent stroke.[34]

BP Measurement in Patients with AF

The difficulty of BP measurement in the presence of AF stems from fluctuation in ventricular filling, stroke volume, and cardiac contractility. These directly influence beat-to-beat variability of BP and contribute to large inter- and intra-observer variability compared to patients in sinus rhythm. As such, there are no standardized guidelines for BP monitoring in AF.[35] The accuracy of the auscultatory method is largely unknown and automatic oscillatory measurement is uncertain.[36] However, studies are starting to show a good correlation of auscultatory and oscillatory methods with IABP.[37] Thus far, the best recommendation for office BP determination is still through the auscultatory method but with triplicate measurements to make up for the expected significant variations in BP. Validation studies for automated oscillatory devices when compared to auscultatory method have shown reasonable accuracy for systolic pressure but a slight overestimation of diastolic BP.

Conclusion

BP can be measured through different methods; however, with the growing demand for medical attention, it must be measured accurately and effectively to facilitate swift clinical judgment. Furthermore, patients play an important role in managing their own condition and their help with self-monitoring at home is critical to guide further medical management. As such, BP measurement should also be user-friendly and designed for independent or self-measurement. Thus far, the oscillatory method throguh an automated measurement device has allowed for this. However, we do recognize that it may not be enough in certain clinical settings, especially, when continuous BP monitoring is required. Although invasive BP monitoring provides the most accurate measurement, it is not without risk and cannot be applied in an ambulatory or outpatient setting. Development of a non-invasive continuous BP measurement method or refining of the finger cuff method of Penaz could suffice as a reasonable alternative.

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Review Article

Hypertension and Chronic Disease Burden

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Abstract

Lifestyle-related non-communicable chronic diseases are the major causes of morbidity and mortality in both developed and developing countries. The major inter-related chronic diseases that have an impact on the population include hypertension, obesity, dyslipidemia, diabetes, and metabolic syndrome. Hypertension is ranked third in terms of the global burden of disease. It is the predominant risk factor for mortality and makes cardiovascular disease the primary cause of death. While we can identify these conditions and complications, it is not so clear how we can assess the burden of these chronic diseases and their association with hypertension. Despite the development of detection methods and equipment, there are still no good markers to relate the diagnosis and control of hypertension before target organ damage occurs. Recent studies using retinal imaging suggest that it is possible to look at the microvasculature to assess disease burden as a result of hypertension. Hypertensive retinopathy is a complication of hypertension. The eye and kidney have similar structures, so there is a close relationship between retinal vessel changes and heart, cerebrovascular, and kidney diseases. Retinal vessel changes reflect the burden of hypertension on these chronic diseases. We can infer the damage of end organs and provide earlier information for the diagnosis and treatment of hypertension.

Key words: Cardiovascular disease, cerebrovascular disease, chronic kidney disease, hypertensive retinopathy

Introduction

Lifestyle-related non-communicable chronic diseases are the major causes of morbidity and mortality in both developed and developing countries. The major inter-related chronic diseases that have an impact on the population include hypertension, obesity, dyslipidemia, diabetes, and the metabolic syndrome.

These diseases are more prevalent worldwide. The estimated global age-standardized prevalence of hypertension in adults aged ≥20 years in 2010 was 31.1%.[1] 39% of adults aged ≥18 years were overweight in 2016, and 13% were obese.[2] The prevalence of dyslipidemia was 34.0% in China and 15% in America.[3,4] The total number of diabetics aged 20–79 years worldwide was 425 million in 2017, accounting for 8.8% of the total.[5] Even more intractable is that these diseases do not exist alone, they interact with one another and damage end organs together, such as the heart, brain, kidney, and eye. It leads to coronary artery disease (CAD), cerebrovascular disease (CVD), chronic kidney disease (CKD), and retinopathy and contributes to the overall chronic disease burden.[6]

Among these chronic diseases, hypertension is the biggest global health challenge due to its high prevalence and resulting target organs damage.[1] Hypertension affects >1 billion people worldwide, ranking third in terms of the global burden of disease.[7] It is the predominant risk factor for mortality in both industrialized nations and low- or middle-income countries. Hypertension is responsible for more than half of deaths from stroke, and 45% of deaths from CAD, and, alarmingly, for more than one-tenth of all global deaths.[8] Hypertension also accounts for up to one-fifth of end-stage renal disease in developing countries[9,10] and for CKD affecting 7% of the world's population.[9] Therefore, it is necessary to improve the current methods of identification, prevention, and treatment of hypertension and reduce the mortality from its complications.

While we can identify these conditions, it is not so clear how we can assess the burden of these chronic diseases (end-organ damage) and its relationship to hypertension. For example, clinical practice guidelines recommend using urine albumin-to-creatinine ratio as a means to detect target organ damage by

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hypertension but that represents a late sign of damage to the kidney.[11] Thus, to prevent injury and guide clinical treatment, we need better tools to identify the burden of hypertension on end organs. Recent studies suggest that it is possible to use retinal imaging to examine the microvasculature and assess disease burden earlier.[12-17]

Classically, hypertensive retinopathy (HR) is characterized by retinal vasculopathy in hypertensive patients.[18] Many studies indicate that many of the HR signs are commonly seen in 6–15% of non-diabetic adults aged >40 years.[19] Racial variations in the prevalence of retinopathy show that the highest rates of retinopathy are observed among Chinese (17.2%) and the lowest among White (11.9%) and Black populations (13.9%).[19] HR is the result of a combination of many factors such as age, diabetes, and vascular endothelial dysfunction. These are also common risk factors of CAD, CVD, and CKD.[20,21] The Keith-Wagener-Barker classification of HR in 1934 was defined as four grades of retinal signs: Grade 1 (narrowing), Grade 2 (arteriovenous crossings), Grade 3 (hemorrhages and exudates), and Grade 4 (papilledema). In 2004, Mitchell and Wong simplified the grading system by combining Grades 1 and 2. The three-grade classification accounts for the association between HR and cardiovascular risk.[18] However, seeing retinal signs using physician observation through the performance of fundoscopic examination are non-quantitative and limited by the skills of the attending doctor. Moreover, the fidelity of optimizing the management of hypertension through detecting residual endothelial dysfunction requires better tools.

In recent studies, retinal imaging and classification of findings using software were used in place of traditional fundus examination. Quantitative data acquisition and software analysis of retinal vessels in digital fundus photographs can be obtained by non-mydriatic fundus photography.[22-25] As an example, a high-resolution fundus camera with a collection range of 45° was used to collect digital photographs of both eyes centered on the optic disc, and quantitatively analyzed in the range of 0.5–1 disc diameter from the edge of the disc using semi-automatic software, Singapore I Vessel Assessment, version 3.0, Exploit Technologies Private Limited.[26] Based on the modified Knudtson-Parr-Hubbard formula, the diameter of the central retinal artery (central retinal arteriolar equivalent [CRAE]) and central retinal vein (central retinal venular equivalent [CRVE]) was measured. The retinal fractal dimension (Df) was measured in the range of 0.5–2 disc diameter at the edge of the optic disc.[26] In fractal geometry, a Df is a ratio providing a statistical index of complexity comparing how detail in a pattern changes with the scale at which it is measured.[27]

Risk Factors for HR

Many studies have shown that hypertensive patients have different degrees of retinopathy. This is related to age, the degree of elevated blood pressure, and duration of disease. HR is not only the result of hypertension but also closely related to other clinical events and, therefore, is an effective means of assessing the effects of hypertension on chronic disease burden. Risk factors for eye diseases include old age, smoking, hypertension, diabetes mellitus, metabolic syndrome, and obesity.[28,29] They are also the risk factors for hypertension.

Association with Obesity

In adults and children, studies have shown that obesity is a risk factor for diabetic retinopathy (DR) and retinal microvascular changes.[28,30,31] Another study shows that higher body mass index was associated with a higher incidence of diabetes but a lower incidence of DR over a 6-year period in Asian Malays and Indians.[32] Among different eye diseases, obesity has been linked with age-related cataract, glaucoma, age-related maculopathy, and DR. However, the nature and strength of these associations remain to be determined. Studies to date have not found a consistent pattern of association between obesity and risk of age-related maculopathy or DR. Thus, although obesity may be a risk factor for many ocular conditions, the present literature is inadequate to establish any convincing associations.[33]

Retinal Vessels and Dyslipidemia

Many clinical trials performed in diabetic patients demonstrate that dyslipidemia is an important factor in the development of DR.[34] In the Madrid diabetes study, higher low-density lipoprotein (LDL) cholesterol level increased the 4-year risk for DR by 8-fold in Type 2 diabetes.[35] The severity of retinopathy was positively associated with triglycerides, apolipoprotein (Apo) B, and the Apo B-to-Apo A1 ratio and negatively associated with high-density lipoprotein (HDL) cholesterol and Apo A1.[36,37] Hence, lipid-lowering medication is an adjunctive therapy for DR. Longitudinal studies in patients with Type-1 diabetes found modest impact of increased total cholesterol and HDL on the incidence of DR.[38] Changes in the circulating levels of lipids are not unlikely associated with DR progression.[39] Higher levels of total and LDL cholesterol were found to be protective of any retinopathy.[40,41]

Diabetes and the Eye

Almost all types of eye diseases can occur in patients with diabetes such as fundus bleeding, glaucoma, cataract, vitreous opacity, optic atrophy, and retinopathy. DR, which is different from HR, is characterized by microaneurysm, multiple retinal hemorrhages, microangioma, and neovascularization.[42] It is important for physicians to be aware that some retinal microvascular signs of hypertension may also be seen in other systemic and ocular conditions such as DR and radiation retinopathy.[43]

The incidence of DR increases with the progression of diabetes, it is 44.4% in 5 years and 56% in 7 years.[44] In the Wisconsin epidemiologic study of DR, 3.6% of younger-onset patients (Type 1 diabetes) and 1.6% of older-onset patients (Type 2 diabetes) were legally blind. In the younger-onset group, 86% of

blindness was attributable to DR. In the older-onset group, one-third of the cases of legal blindness were due to DR.[45] In the report of the United Kingdom prospective diabetes study, 22% of patients had developed retinopathy in 6 years. The overall prevalence was 34.6% for any DR in 22,896 individuals with diabetes.[31]

CAD

In a study on hypertensive patients, HR is an independent risk factor for predicting CAD.[15] The degree of HR is closely related to the incidence of coronary heart disease.[16] Therefore, fundus screening is recommended as a routine examination for high-risk patients.[46] In hypertensive patients,[14] the degree of progressive HR is commensurate with the degree of atherosclerosis. In patients with severe hypertension, HR is associated with the thickness of aortic plaques.[12] Therefore, HR can be used as an indicator of atherosclerosis. An Italian study of target organ damage in hypertension showed that HR progression was significantly associated with the left ventricular hypertrophy, carotid intima-media thickening, and carotid plaque formation.[47] The Df provides a measure of the microvascular status and has been associated with mortality from coronary heart disease.[48]

CKD

HR reflects the degree of kidney disease and is an important predictor of CKD.[49] In hypertension, the severity of HR is often associated with lower glomerular filtration rate.[17] Retinal arteriolar narrowing defined as a CRAE measurement of <144.0 μm is associated with CKD,[24,25] even among Whites without diabetes and hypertension.[50] There is a correlation between smaller CRAE and CKD,[25] low arteriolar/venous ratio (AVR) (AVR <1.0) and serum creatinine change in 6 years,[23] wider retinal vein (AVR <1.0), and CKD in patients with Type 1 diabetes and Type 2 diabetes.[51,52] Retinal arterial narrowing may affect kidney function through microvascular damage resulting from diabetes mellitus,[52] hypertension,[28] and inflammation.[53] In the Singapore prospective study program population, odds ratio comparing the smallest (Quartile 1) with the largest CRAE quartile (Quartile 4) to be 1.42 (95% confidence interval: 1.03, 1.96; $P_{trend} = 0.02$) for estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2, and this association was evident in the absence of diabetes and hypertension, suggesting that Df could be an independent marker of CKD.[24]

On the other hand, CKD has adverse effects on both the macrovascular and microvascular circulation. Microvascular changes in the eye can be seen in CKD patients.[12,16,54,55] eGFR <45 mL/min/1.73 m^2 was significantly associated with a 15-year risk of retinal arteriolar narrowing, suggesting that advanced stages of CKD may cause end-organ microvascular damage.[50] In addition, the presence of higher creatinine and CKD was also associated with a significant reduction in CRVE.[56,57]

However, some studies found that neither baseline CRVE was associated with CKD in either direction.[50] There is no association between CRVE and CKD.[24] Retinal venular dilation may be mediated by endothelial dysfunction[12] and increased inflammatory stress,[16,58] both of which are seen in CKD. Retinal venular dilation and CKD may have shared pathogenic mechanisms, but the evidence is inconclusive.

CVD

With antihypertensive drug treatment, there are few patients with Grade 3 HR in clinic. Most Grade 3 HR patients are younger with acute hypertension.[29] This suggests a high risk of hypertensive encephalopathy in the future.[59] HR is not only associated with acute stroke but also related to the occurrence and development of cerebral small vessel disease (SVD). Retinopathy suggests increased risk of SVD in the next 10 years.[60] Especially, the relationship with lacunar infarction is higher than that of non-lacunar infarction.[61] Among them, retinal vascular morphology induced by HR is more significant. Diffuse retinal arteriolar coarctation, arteriovenous crossover sign, and extensive venous dilatation sign were more likely to be detected in patients with acute lacunar infarction.[62] Retinal venectasia is more associated with SVD than retinal arteriostenosis and is a risk factor independent of other CVDs.[16,63] There is also a high association between the diameter of retinal artery and the risk of stroke,[22] retinal microangiopathy, and the occurrence of cerebral microbleeds.[64,65]

Effects of Blood Pressure Lowering on Retinopathy

In Type 2 diabetes patients, an intensive combined treatment targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria can reduce the risk of retinopathy progression by 55% in the follow-up period of 3.8 years. However, it is not known whether combining blood pressure lowering, glucose control and improving lipid profile can reduce the risk of retinopathy to a greater extent than either treatment alone.[66] The appropriate blood pressure control in diabetes - normotensive study showed a favorable effect, even among patients with long diabetic duration and who had a "normal" blood pressure level.[67] In contrast, in the intensive blood pressure control arm of the ACCORD study, a trend of increased risk for DR progression by 23% at 4 years was seen. The optimal target for blood pressure against retinopathy worsening might not be "the lower the better."[68] Highlighting that fact that traditional limb transduced blood pressure measurements and management may not provide the full picture, and we need to consider looking at retinal vasculature changes with interventions to optimize treatment.

Conclusions

Hypertension and the burden of chronic disease may be characterized by retinal vascular features. The use of fundoscopy to detect HR has been regarded as a part of the standard assessment of hypertension. According to the United States

joint commission on the prevention, detection, assessment, and treatment of hypertension,[69] retinopathy may be an indication of initiation of antihypertensive treatment, even in patients with primary hypertension who do not have evidence of other target organ damages. However, routine clinical application is incomplete due to practical issues of individual clinician physical examination skill, time for dilation of pupils, and interobserver variation. It may be preferable to consider using routine retinal photography coupled with computerized grading to assist the physician in making assessments of hypertension management and its impact on chronic disease burden.

We should pay more attention to the protection from late signs of injury to the heart, kidney, brain, and other target organs by controlling hypertension and assessing control through examination of the retinal vasculature. The clinical evidence suggests that fundus photography should be performed routinely in all hypertensive patients to assess the degree of retinal vascular damage and provide early clues for preventing cardiovascular events, stroke, and kidney damage.[70] It is helpful for the diagnosis and management of hypertension and to assess chronic disease burden before overt clinical signs emerge or end-organ complications arise.

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Review Article

Hypertension Trends in Asia

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Abstract

Hypertension is an often silent yet modifiable risk factor of cardiovascular morbidity and mortality. Despite increasing recognition of its adverse health impacts, global prevalence remains on the rise and hypertension control remains suboptimal. A similar trend has been observed in South-East Asia, particularly in less-affluent areas, where hypertension prevalence is rising but awareness and control rates are dismal. Contributory factors identified include accessibility of healthcare, different health-seeking behaviour, lifestyle factors such as dietary salt intake, and lack of individual recognition of potential downstream complications. Strategies employed in the fight against hypertension in South-East Asia will need to address these different needs, taking into consideration the interplay of differing socioeconomic status and education level amidst varying racial and cultural beliefs and traditions.

Key words: Hypertension, Blood pressure, Asia, Cardiovascular

Introduction

Hypertension, often touted as a silent killer, has long been recognized as major modifiable risk factor for cardiovascular morbidity and mortality. Death from complications of hypertension including coronary artery disease and stroke was estimated to account for 9.4 million deaths worldwide every year.[1] In Asia, an estimated 1 in 3 people is affected by hypertension, slightly lower than the global average of 40%.[1] In Southeast Asia alone, hypertension has been estimated to claim 1.5 million lives each year.[2]

The clinicopathological impact of hypertension on end-organ damage and mortality may be even more pertinent in the Asian population. Not only is hypertension a leading cause of chronic kidney disease in Asia,[3] association between elevated blood pressure and hemorrhagic strokes may also be stronger in Asians.[5] Even elevated BP at pre-hypertension levels may be associated with increased cardiovascular morbidity.[4]

While hypertension control has been well-studied in the Western population, data in Asia have been scarce. The differences in sociocultural, economic, and political climate in Asia and the vast heterogeneity in race and affluence within Asia suggest that Western data and strategies may not be directly applicable to the Asian context.

This article seeks to describe trends in hypertension prevalence, control, and awareness in Asia, with a particular emphasis on Southeast Asia, and seeks to identify potential areas where strategies for BP control may be employed.

Trends in Definition of Hypertension

The definition of hypertension has traditionally been defined as a systolic BP (SBP) of 140 mmHg and above and/or a diastolic BP (DBP) of 90 mmHg and above.[1,6] However, guidelines have gradually been revised to reflect a stepwise increase in cardiovascular risk as BP increases above normal levels.[7] Since 2004, the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High BP (JNC) introduced a new classification including the term "prehypertension" for those with BPs ranging from 120 to 139 mmHg systolic and/or 80–89 mmHg diastolic.[6] In 2017, the American College of Cardiology/American Heart Association (ACC/AHA) task force lowered cutoff for hypertension to include those with BPs from 130 to 139/80 to 89 mmHg.

Guidelines on target BP differ. JNC 8 recommends for a target BP of <150/90 mmHg for those aged 60 years and

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older and <140/90 mmHg for those with age younger than 60 years or comorbidities such as diabetes or chronic kidney disease.[8] The ACC/AHA guidelines suggest for a lower BP target of <140/90 mmHg for those with no history of cardiovascular disease and atherosclerotic cardiovascular disease (ASCVD) risk of <10% and a lower target of <130/80 mmHg for those with a 10 year ASCVD risk of 10% or higher.[9]

Certain countries in Asia have adopted stricter BP targets. In Singapore, latest guidelines in 2017 recommend a target of <150/90 mmHg for those aged 80 years and older, <140/80 mmHg for those with diabetes mellitus, <130/80 mmHg for those with moderate-to-severe albuminuria, and <140/90 mmHg for other patients.[10] Guidelines in Malaysia are similar, with a target BP of <150/90 mmHg for those aged 80 years and older, <140/80 mmHg for those with diabetes, but <130/80 mmHg for those with diabetes who are young, and <140/90 mmHg for other patients.[11] BP targets in Taiwan are stricter. The Taiwan Hypertension Society recently revised its guidelines in 2017 to a lower BP target of <120 mmHg of automated office BP measurement for patients with coronary heart disease, chronic kidney disease, and elderly patients aged 75 years and above.[12]

Trends in Hypertension Prevalence

Over the years, global hypertension burden has risen from 600 million in 1980 to 1 billion in 2008[1] and has been predicted to increase to 1.56 billion by 2025.[13] This increase not only reflects population growth but also rises prevalence. Prevalence of hypertension in adults worldwide was 26.4% in the year 2000 and projected to rise to 29.2% by the year 2025.[13]

In Asia, prevalence of hypertension between the years 2008 and 2015 has been largely similar to the global average. Nationwide surveys have found prevalence to be 48.3% in Brunei,[14] 15.3% in Cambodia,[15] 33.4% in Indonesia,[16] 24.9% among men and 20% among women in Laos,[17] 35.3% in Malaysia,[18] 31% in males and 29% in females in Myanmar,[19] 23.5% in Singapore,[20] 19.1% in Thailand,[21] and 25.1% in Vietnam.[22]

Trends in hypertension prevalence have not been consistent across SEA nations. In India, the prevalence of raised BP rose from 5% in the 1960s to 12% in the 1990s, to >30% in 2008.[23] In Indonesia, the prevalence rose from 8% in the year 1995 to 32% in the year 2008 and 33.4% in the year 2015.[16,23] Similarly, in Myanmar, the Ministry of Health reported an increase in hypertension prevalence, from 18% to 31% in males, and from 16% to 29% in females during 2004–2009.[23] In Singapore, however, the prevalence of hypertension fell from 27.3% in 1998 to 24.9% in 2004 and 23.5% in 2010.[20] In Malaysia, prevalence remained largely stable at 34.6% in 2006, 33.6% in 2011, and 35.5% in 2015.[18]

The trend in the shifting of hypertension burden from higher income countries to lower income countries has also been suggested in a recent analysis. A pooled global age-standardized prevalence of raised BP found that, over the past four decades, mean BP decreased from 1975 to 2015 in high-income Western and Asia Pacific countries. Highest worldwide BP levels have shifted from high-income countries to low-income countries in South Asia and Sub-Saharan Africa.[24]

While age-standardized prevalence may have fallen in higher income Asian societies, the overall burden of hypertension is nevertheless projected to rise. Among various reasons, significant contributions include aging population, urbanization, and also potential shifts in hypertension definition.

Not only is burden of hypertension in the elderly population higher but also BP control tends to be poorer. In a study of the elderly Singaporean population aged 60 and above, nearly 3 of 4 (73.9%) were found to have hypertension.[25] The problem of expected rapid aging in Asian populations means that hypertension burden is likely to accelerate. Within the developing world, the prevalence of hypertension in rural areas is 2–3 times lower than those in urban areas in Asia.[26] A similar finding has also been described in Vietnam and Indonesia [16,22] Urbanization and adoption of western lifestyle and diet have been described as major contributors.[23]

Adoption of the new ACC/AHA definition of hypertension, which lowers cutoff of hypertension to that of BP 130/80, would lead to marked increase in hypertension prevalence worldwide. In developing countries, where a significant proportion of population resides in rural areas with limited access to health care, hypertension may often go undiagnosed. Even in event that hypertension is diagnosed, recognition of the imperative to control BP may not be a priority due to the relatively asymptomatic nature of the disease. Hypertension in Asia will continue to pose a growing problem. It is estimated that the changes in definition would label 63% of those in the United States and 55% of those in China aged 45–75 years old as having hypertension, representing an increase in prevalence of 26.8% in the US and 45.1% in China, accounting for 337 million more hypertensive patients just in these two countries alone.[27] In Cambodia, the prevalence of those with prehypertension was close to twice that of those with hypertension.[15] A change in definition would greatly increase the global hypertension burden.

Awareness of Hypertension

Awareness of prior diagnosis of hypertension also varies widely between the Southeast Asian nations. Awareness of hypertension is highest in Singapore at 73.7%,[20] followed by Thailand and Vietnam at 48.4%,[21,22] and lowest in Myanmar at 27.8%,[19] while awareness to hypertension has increased in Asian countries such as Indonesia, Malaysia, Myanmar, and Singapore levels still fall far short of awareness levels in Western nations such as the US (81%), Canada (83%), and England (65%).[28]

Treatment and Control of Hypertension

Treatment rates were generally low and varied widely across the Southeast Asian nations. In Malaysia, 83.2% of hypertensive patients were on treatment,[18] 61% in Vietnam,[22] and 42% in Thailand.[21]. In Laos,[17] <20% of hypertensive patients were on

treatment, and in Indonesia, only 11.5%.[16] BP control, defined as a SBP of <140 mmHg and DBP of <90 mmHg, was also low among these. Proportion of those with good BP control was highest in Singapore at 67.4% of all hypertensive patients and 69.1% among those patients on treatment.[20] BP control rates were lowest in Indonesia and Thailand at 14.3and 14.9%.[21] Even among those on treatment in Vietnam, only 36.3% had well-controlled BP.[22]

BP control rates, though low, have shown encouraging trends in higher income countries in Southeast Asia such as Singapore and Malaysia, which have seen increase in BP control from 49.5% in 2004 to 67.4% in 2010 and 27.5% in 2006 to 37.4% in 2015, respectively.[18,20]

However, there remains much room for improvement in BP treatment and control. Western nations in the US Canada and England have hypertension treatment rates ranging from 51 to 80% and control ranging from 27% to 66%.[28]

Factors Resulting in Poor Hypertension Control

Hypertension control in Southeast Asia, especially in developing countries, is poor. Western-based studies have cited reasons including race, lifestyle factors, and access to health care.[29,30]

The main driving factors for poor hypertension control likely vary between low- and high-income groups within Southeast Asia. In developing countries, where a significant proportion of population resides in rural areas with limited access to health care, hypertension may often go undiagnosed. Even in event that hypertension is diagnosed, recognition of the imperative to control BP may not be a priority due to the relatively asymptomatic nature of the disease.[16] In higher income countries in Southeast Asia such as Singapore and Malaysia which exhibit higher rates of awareness and control of BP, the main driving factor behind poor control likely lies in lifestyle factors and health-seeking behavior. Increasing trends in diseases of affluence such as obesity and diabetes have been identified as key risk factors. Of note, the attributable risk of hypertension begins at lower body mass index levels in Asians compared to Caucasians.[31]

Dietary salt intake, a strong risk factor for hypertension, also contributes significantly to the poor control of hypertension in Southeast Asia. Salt intake in Southeast Asia is high, ranging 10–17 g a day, which is 2–3 times as high as the recommended daily salt consumption of <5 g/day by the World Health Organization.[32] Unlike in Europe and North America where sodium intake is derived mainly from food eaten away from home,[33] majority of salt in Southeast Asia comes from tablet salt and condiments such as monosodium glutamate often used in home-cooked meals.[32,34] Various countries such as Indonesia and Thailand have adopted mandatory food labeling with mixed results due to challenges with the development of relevant alternative products and low consumer demands. In Singapore, the Health Promotion Board has been collaborating with local science expertise and industry partners in developing "healthier salt" and food with lower sodium content. However, the key to addressing the issue in dietary salt intake lies not in just implementation of single measures or solutions. In Finland and the United Kingdom, where programs have successfully achieved a significant reduction in salt consumption, factors that contributed to success identified were a combination of strong leadership and policies, technological support for food product reformulation, food nutrition labeling, promotion of consumer awareness, and monitoring of progress by frequent surveys.[32] Addressing dietary salt intake will require a concerted effort among various key stakeholders including the government, industry players, and consumers.

While information regarding adherence to antihypertensive medication in Southeast Asia is limited, available data suggest significant variability ranging 34–78%. A Vietnamese study revealed an awareness of complication risk, medication side effects, and absence of hypertension symptoms as key determinants affecting medication adherence.[35] A systematic review evaluating medication adherence factors for hypertension in developing countries cited other factors such as cost barriers, irregular follow-ups, and competing availability of traditional herbal remedies.[36] When it comes to the treatment of hypertension, a key challenge especially among the less educated is the reconciliation of the disease's asymptomatic nature and its downstream life-threatening complications. Moreover, the undertaking of educating about the importance of hypertension control in the Southeast Asian context is further complicated by differing pathogenetic models in the fields of traditional, complementary, and alternative medicine pervasive in the region.[37] Addressing patients' knowledge, attitudes, and perceptions in hypertension is likely key in improving adherence rates, and culture and context-tailored national strategies will be necessary. In terms of medication side effects deterring medication adherence, angiotensin-converting enzyme inhibitors, a common class of medication used in the treatment of hypertension, has been associated with higher incidence of a cough among Chinese populations.[38-40] It is, thus, crucial that such pharmacogenetic variations are taken into consideration and managed appropriately in the treatment of hypertensive Asians.

Conclusion

Hypertension in Asia will continue to pose a growing problem. Increasing urbanization and westernization, an aging population, and the lowering of hypertension definitions are key factors driving the increasing disease burden. In terms of disease treatment and control, while there have been encouraging trends of improving awareness, treatment rates, and control in more developed countries such as Singapore and Malaysia, the challenge to emulate nation-wide strategies critical in achieving these goals in less developed countries remains. Socioeconomic issues of stark income inequality, relatively underdeveloped medical systems, and infrastructure and cultural influences affecting diet and health-seeking behaviour will have to be addressed. Data regarding hypertension trends in Asia, especially that concern less developed countries, also remain limited. More

comprehensive and up-to-date data are necessary for a more accurate appraisal of the situation or hypertension in this region and to guide future strategies and measures in better improving the state of disease control.

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Review Article

Central Aortic Blood Pressure as an Indicator of Prognosis: An Asian Perspective

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Abstract

Brachial cuff sphygmomanometer remains the major method by which blood pressure (BP) is assessed clinically. However, this is a poor surrogate for central aortic BP. There is increasing evidence that central aortic BP can act as a marker of cardiovascular (CV) and peripheral vascular disease burden and that central pressures may be able to predict CV events and mortality. This, in turn, could have implications for the development and application of future pharmacological therapies. This review article examines the evidence surrounding the above and its controversies. It concludes that while central BP is an exciting new frontier, more research is required for central BP to become commonplace in clinical medicine.

Key words: Asian, augmentation, central blood pressure, prognosis, pulse wave velocity

Introduction

It is remarkable that despite considerable advances in technologies to assess the cardiovascular (CV) system, the technique for measuring blood pressure (BP) - through a brachial cuff sphygmomanometer - has remained unaltered for more than a century. Brachial BP remains firmly embedded in routine clinical practice in Asia and the rest of the world, and widely referenced in clinical care guidelines. There is good reason for this - the measurement of brachial BP is simple, and standardized, and therefore suited for screening of large populations, with a wide variety of devices now available for clinical use. However, it has long been recognized that brachial BP is a poor surrogate for central aortic pressure, which is invariably lower than corresponding brachial values. This concern has fuelled ongoing interest in pulse wave analysis for determining central BP and investigation into its potential superiority in CV risk prediction. The key question remains whether central BP measurement confers prognostic value beyond that provided by conventional BP. This review will discuss our current understanding of central BP and the evidence surrounding its prognostic significance with an Asian perspective.

Physiological Concepts

Concept of Systolic Pressure Amplification

Arterial pressure varies continuously throughout the cardiac cycle. Although diastolic and mean arterial pressures are relatively constant, systolic pressure may be >30 mmHg higher in the brachial artery than in the aorta.[1] This phenomenon of systolic pressure amplification arises due to an increase in arterial toward the periphery, as central arteries are highly elastic while peripheral arteries have more smooth muscle cells and are hence stiffer.[2]

Two Paradigms in Waveform Morphology

The first hypothesis of waveform morphology assumes that the arterial pressure waveform is a composite of a forward-traveling wave, generated by the left ejection fraction, and a backward-traveling reflected wave arising from mismatch in vessel stiffness.[3,4] This change in impedance generates numerous reflected "wavelets" that sum together to augment systolic pressure in central arteries. The augmentation index (AIx),

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which quantifies the extent of augmented pressure relative to central pulse pressure (PP), provides information about amplitude and timing of backward-traveling waves within the central arteries.[3,4] As augmentation pressure increases, aortic systolic BP increases, and PP amplification defined as the ratio of brachial to aortic PP decreases.[3]

The second major paradigm initially viewed the arterial system as a two-element Windkessel model (resistance and compliance), where a central reservoir fills during systole and empties during diastole.[5] Although details of this model are beyond the scope of the review, it suffices to say that the model did not consider the contribution from impedance. Subsequently, Westerhof *et al.*, in 2009, proposed adding an aortic characteristic impedance to form a three-element Windkessel model to improve the prediction of pressure and flow through the entire cardiac cycle.[6]

Variables that Affect Central Arterial Pulse Waveforms

Irrespective of the precise mechanisms underlying the observed changes in central arterial pulse waveform, systolic pressure amplification within the arterial tree is not fixed and depends on multiple variables. These include age, gender, height and heart rate, as well as systemic diseases affecting the vasculature and physiological changes (diurnal variation, menstruation, changes with exercise, etc.). For example, PP amplification is higher in men in whom aortic systolic pressure measured invasively can be up to 30 mmHg lower than that in the brachial artery.[1,7] Individuals with lower heart rates or shorter stature tend to have less PP amplification.[7]

In large population-based studies, arterial pulse waveforms have also demonstrated variation with ethnicity.[8-10] A Singapore study showed that Malay and Indian diabetic patients have higher central arterial stiffness, in the form of carotid-femoral pulse wave velocity and AIx, compared to Chinese patients.[8] These differences remained even after adjusting for glycated hemoglobin, proteinuria, and demographics. When compared to Caucasians, South Asians tend to have higher, multivariate-adjusted levels of aortic systolic BP, Aix, and novel central BP variables.[10] These differences persist after adjustment for brachial BP, suggesting that central BP can capture ethnic variations in CV risk.

Central Pressure as Marker of Disease

Coronary Artery Disease

Cross-sectional studies of Chinese diabetic patients have shown that poor diabetic control is associated with higher Aix.[11] In addition, the presence of hypertension, coronary heart disease, and ischemic stroke is independent risk factors for central BP increase.[11] In the conduit artery function evaluation (CAFE) substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), investigators found that despite comparable achievement of brachial BP, hypertensives treated with amlodipine-perindopril achieved lower central BP than the atenolol-thiazide-treated group. Importantly, central PP was significantly associated with a composite outcome of total CV events and procedures and development of renal impairment. More recently, a multicenter Japanese observational study of >3500 treated hypertensives showed that those with central systolic BP in the top three quintiles had a significantly higher incidence of morbid CV events, even after adjustment for clinical covariates and brachial diastolic BP.[12]

It remains uncertain how aggressive systolic brachial BP control should be. The action to control CV risk in diabetes trial showed no additional CV benefit in intensifying brachial systolic BP control to ≤120 mmHg.[13] Since brachial BP does not fully reflect the hemodynamic milieu in the aorta, central BP may hold the missing key in hypertension risk prediction.[13]

Left Ventricular Hypertrophy

Central BP may also be a better predictor of the left ventricular hypertrophy. In a small substudy of the pREterax in regression of arterial stiffness in a controlled double-blind (REASON) project, change in carotid PP but not brachial PP was associated with greater reduction in the left ventricular mass detected in the perindopril + indapamide arm as compared with the atenolol treatment arm.[14] Similar observations were made in a substudy of ASCOT.[15]

Vascular Disease

The strong heart study in American Indians demonstrated that compared to brachial BP, central systolic BP was more strongly related to vascular hypertrophy and extent of atherosclerosis.[16] Longitudinal observation studies have confirmed that there is a stronger relation of carotid PP than brachial PP to carotid intima-media thickness.[17] Moreover, with antihypertensive therapy, the reduction in carotid intima-media thickness relates better to the fall in central pressure.[18]

Central Pressure as Predictor of Events

CV Events

The predictive value of central pressure has been investigated in only a handful of Asian studies [Table 1]. Subjects studied included healthy community-dwelling individuals and patients with CV disease. In all these studies, there was a significant association between central systolic BP and central PP with diverse CV end points, ranging from restenosis following coronary angioplasty to CV mortality.[19-21] The strong heart study investigators observed that in over 2400 participants without overt CV disease, a central PP of >50 mmHg predicted an adverse CV outcome.[16] Other studies have also demonstrated the incremental value of central over brachial pressures.[14,22] Surprisingly, the Framingham heart study failed to show any additional value of brachial/carotid amplification and central PP.[23] However, this study was compromised by

Table 1: Association between central pressure and outcome in Asian patients

First author	Year, country	N, population	Duration of follow-up	Parameter	Outcome
Nakayama *et al.*[20]	2000, Japan	53 coronary artery disease with angioplasty	3 months	Invasive aortic pulsatility **	Pulsatility ratio is associated with restenosis. Not adjusted for brachial pressures
Lu *et al.*[21]	2001, China	87 coronary artery disease with angioplasty	6 months	Invasive aortic systolic BP and pulsatility **	Both are independently associated with restenosis.
Wang *et al.*[21]	2009, Taiwan	1272 healthy patients in the community	10 years	Carotid systolic BP and pulse pressure	All-cause mortality

**Pulsatility is the ratio of pulse pressure to mean arterial pressure

methodological issues, specifically the inappropriate use of the brachial artery rather than the radial or carotid arteries for applanation tonometry.

Mortality

Other than Wang *et al.*, almost no Asian studies have examined the relation of central BP and arterial stiffness to mortality [Table 1]. A meta-analysis by Vlachopoulos *et al.* of mostly European and American studies found that the age- and risk factor-adjusted pooled relative risk of all CV events was about 1.1 for every 10 mmHg increase of central systolic pressure or central PP, and 1.32 for every 10% absolute increase of central Aix.[24] They also concluded that central Aix predicted total mortality independent of brachial pressures.[24] However, of the three studies pooled for this specific analysis, two (contributing ≥50% of sample size) actually showed no significant predictive value of AIx for mortality.[24] More evidence should be accrued to show that AIx definitively impacts hard clinical outcomes such as mortality.

The meta-analysis of Vlachopoulos *et al.* also concluded that central aortic pressures had only marginal and not significant added value beyond brachial BP in predicting events. Likewise, the CAFE study reported similar predictive value of both central and peripheral PP for a composite CV and renal outcome.[25]

The main issue with existing studies is that most are underpowered to show convincingly that central pressure or PP is clinically meaningfully superior to brachial pressures in predicting events, given that both have an excellent correlation. Clearly, a definitive outcome study is required, preferably using a validated operator-independent device, suited for use in a doctor's office.

Pharmacological Reduction of Central Systolic BP

The CAFE ASCOT substudy and the REASON trial have clearly demonstrated that despite similar effects on brachial BP, antihypertensive drugs have differential effects on central BP.[26,27] The reason trial showed that while all patients had normalization of brachial BP, patients randomized to perindopril + indapamide achieved a significantly greater reduction of central BP compared to those on atenolol.[27] The CAFE substudy showed that patients randomized to amlodipine had a 4.3 mmHg lower central systolic BP compared to those on atenolol.[26] Such evidence may help to explain the excess risk associated with atenolol compared to other antihypertensives in outcome studies and provide support for the hypothesis that drugs which lower central BP most are the most effective.[28]

Since then, numerous studies have examined the influence of all classes of BP-lowering drugs including repurposed agents such as nitrates on brachial versus central pressure. However, most of these studies are small, with varying methodology of central BP measurement, follow-up duration, and study end goals. There is limited evidence that nitrates may reduce central BP more than beta-blockers and that low-dose nitrate may reduce central BP without affecting brachial BP, which may be helpful in patients with poor ejection fraction or those prone to autonomic dysfunction.[29,30] It has also been postulated that vasodilating beta-blockers may have greater capacity to reduce central systolic BP, potentially by reducing wave reflection. Nevertheless, the available data are conflicting with a recent meta-analysis concluding that differences in BP amplification between vasodilating and non-vasodilating beta-blockers are minimal after accounting for heart rate changes.[31]

Conclusion

Several issues remain unresolved. "Cutoff" values for central BP are still not well defined, unlike with brachial BP. The application of age referenced "cutoff" values for central BP may also be misleading imply that the progressive age-related phenomenon of pressure amplification is physiological, rather than pathological. Furthermore, it is crucial to determine the shape of the relationship between central hemodynamic indices and risk. In addition, a standard approach to the validation of central BP measurement devices is still lacking, and even more so, validation against an Asian cohort. Devices made by Asian companies such as BPro modified tonometry sensor© (HealthSTATS, Singapore) are promising but require more extensive evaluation.

In summary, the clinical relevance of differences between brachial and central pressure for the individual patient remains poorly answered at present. Several factors account for the current ambiguity, including the close correlation between these hemodynamic parameters, lack of a standardized approach for calibration and validation of existing methodologies for studying central aortic hemodynamics, and insufficient outcomes

evidence favoring central BP. Large studies are underway, but until more evidence is available, brachial BP will remain the point of reference for the management and prognosis of the hypertensive patient.

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Review Article

Salt and Hypertension Hypothesis - Still Relevant

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Abstract

Dietary salt intake is a common and important risk factor for hypertension. There has been a shift in the understanding of the pathogenesis of hypertension and the role that salt plays in its development - from the centrality of kidney, to the concept of salt sensitivity and more lately, hypertension as a disorder of endothelial function. There remains much heated debate and controversy about the relation between salt and hypertension, with both proponents and opponents pointing to observational, experimental, and epidemiological evidence supporting their claims. Other dietary factors such as refined sugars and potassium have also been identified as important contributory factors to hypertension, raising the question of whether the role of salt was as central as it was purported to be. While few would challenge the evidence showing the benefit of a low-salt diet in hypertensive patients, the contention is whether the same strategy of salt restriction should apply to normotensive populations to prevent hypertension, given observational data that low-salt intake may be associated with increased cardiovascular risk. With increasing prevalence of hypertension and burden of metabolic diseases worldwide, more evidence in the form of randomized controlled trials is required to determine whether a low-salt intake should be recommended as policy, which must strive to benefit majority of the population without causing harm to the minority. Until then, the salt and hypertension hypothesis is likely to remain relevant in the foreseeable future.

Key words: Controversy, endothelial function, hypertension, salt sensitivity

Introduction

The Evolving Understanding of Salt and Hypertension

Essential hypertension accounts for >90% of cases of hypertension.[1,2] The pathogenesis of essential hypertension is multifactorial, with involvement of multiple pathophysiologic factors. THESE include increased sympathetic nervous system activity, activity of the renin-angiotensin-aldosterone system, and vascular tone due to inappropriate levels of vasoconstrictors, vasodilators and alterations in adrenergic receptors; inadequate dietary intake of potassium and calcium; diabetes mellitus and insulin resistance; and altered cellular ion transport.

In addition to these, dietary sodium, or salt, intake has been found to play a key player, and the most common and important risk factor for hypertension.[3] Numerous clinical trials have shown a direct association and causal relation between salt intake and the pathogenesis of hypertension. In particular, sodium retention due to the overproduction of sodium-retaining hormones or inappropriate renal salt handling due to alterations in expression of the Kallikrein–Kinin system have been implicated as mechanisms in hypertension.[2]

In the last half a century, there has been a gradual shift in the understanding of the role of salt in hypertension. The traditional view emphasized the centrality of the kidney and its malfunction in the development of hypertension. It was proposed that hypertension was a consequence of impaired sodium and water excretion due to a failure of pressure diuresis in regulating blood volume to return arterial pressures to control values.[4,5] The hypothesis that renal salt handling plays a role in hypertension has also been supported by studies which show that genetic mutations affect blood pressure in Mendelian or monogenic forms of human hypertension and hypotension.[6-8]

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The concept of salt sensitivity developed around the same time, with observations that blood pressure responses to dietary salt intake varied among both hypertensive and normotensive individuals due to differing abilities and extents of salt excretion.[9-11] Salt sensitivity was subsequently characterized by an alteration of kidney function that necessitates higher arterial pressure to excrete a given amount of salt. While there is no universal definition of salt sensitivity, it is usually arbitrarily defined as an increase in blood pressure of 10% or greater during a high-salt diet than that during a low-salt diet. Dahl *et al.* demonstrated the concept of salt sensitivity and salt resistance by producing from the Sprague-Dawley line two strains of rats that were either susceptible or resistant to the hypertensive effects of a high-salt (8% sodium chloride) diet; salt-sensitive rats rapidly and uniformly developed hypertension and died by 12 weeks of age.[12]

In a recent scientific statement, the American Heart Association succinctly summarized salt sensitivity as not a single disease, but an entity that is superimposed on a constellation of disorders[13] - multiple inherited or acquired disorders of the endothelium, exacerbated by long-term consumption of a high-salt diet disrupt endothelial responses to high-salt intake and promote a complex syndrome of salt sensitivity.[14]

However, recent studies suggest alternative and novel paradigms of salt and hypertension. Heer *et al.* in a randomized controlled trial involving healthy males showed that instead of increasing total body water, high-salt intake increased plasma volume dependently, suggesting non-osmotic sodium storage resulting in fluid shift from the interstitial to intravascular compartments.[15] In support of this hypothesis, it has been subsequently demonstrated in rats that skin is a major site for osmotically inactive sodium storage without accompanying water retention,[16] and rats receiving a high-salt diet developed hypertonicity of the skin interstitium.[17,18]

Feng *et al.* in a recent review proposed that a central feature of hypertension may be a fine balance of endothelial homeostatic function in response of extracellular fluid volume expansion.[14] The understanding of the pathogenesis of hypertension has thus gradually shifted from kidney malfunction to endothelial dysfunction[3] and has been supported with evidence showing the role of salt in generating oxidative stress,[19-22] increasing asymmetrical dimethylarginine,[23] and transforming growth factor beta-1,[24,25] with the common pathway being their effects on a net reduction of bioavailable nitric oxide and resultant endothelium-dependent dilatation.

The Controversy - For and Against the Low-Salt Diet

Despite the understanding of the pathophysiology of hypertension above pointing clearly to salt as a key player in the pathogenesis of hypertension, there remains heated debate and controversy about the relation between salt and hypertension.[26]

Proponents of the salt-hypertension hypothesis point to overwhelming observational, experimental, and epidemiological evidence. It had been observed that hypertension was not prevalent in societies that thrived on a hunter-gatherer diet, until they became urbanized and were exposed to a high-salt diet.[27,28] A classic study is the Yi Migrant study, where the Yi population, who lived in a salt inaccessible remote mountain region of China, had a very low prevalence of hypertension in their community until they migrated and adopted salt-rich diet, after which the incidence of hypertension started to increase.[29,30]

The INTERSALT study, a worldwide epidemiology study with a sample size of more than 10,000 participants found a significant positive and independent linear relationship between 24-h sodium excretion and systolic blood pressure, concluding strongly that its results *"agree with findings from other diverse studies, including data from clinical observations, therapeutic interventions, randomized controlled trials, animal experiments, physiologic investigations, evolutionary biology research, anthropologic research, and epidemiologic studies, support the judgment that habitual high-salt intake is one of the quantitatively important, preventable mass exposures causing the unfavorable population-wide blood pressure pattern that is a major risk factor for epidemic cardiovascular disease (CVD)."*[31]

Low-salt diets, such as the Kempner's rice diet[32] and dietary approaches to stop hypertension (DASH) diet,[33] showed the benefit of a salt-restricted diet on blood pressure in hypertensive and even normotensive individuals (in the case of the DASH diet). Systematic reviews including a Cochrane review[34,35] and one conducted by the World Health Organization's nutrition policy and scientific advice unit[36] support the efficacy and beneficial effects of a very low-salt diet in a non-acutely ill, normal population.

Opponents of the salt-hypertension hypothesis dispute the benefits of salt restriction, pointing to inconsistent outcomes in observational studies.[37,38] Particular concerns and reservations include methodologies of the epidemiological studies, inadequate consideration of harmful effects of salt deprivation and lack of attention and weight attributed to studies on salt loading (as opposed to salt-deprivation), and measurement of total body sodium.[39]

Critiques of the Yi Migrant study argued that the increase in hypertension incidence coincided and was confounded by the adoption of a sedentary lifestyle and weight gain among other factors. Detractors of the INTERSALT study criticized it on the basis of its generalization that a reduced sodium intake will decrease hypertension across ethnic groups and for using epidemiological and biostatistical methods that did not adequately reduce error.[40] Statisticians Freedman and Petitti subsequently also published an article arguing that the results in INTERSALT were driven mainly by four outlying populations, and across the 48 other populations, blood pressures actually decrease with salt intake.[41]

It has also been observed that numerous populations that consume a high-salt diet that is low in refined sugar do not actually develop hypertension. These include the Kotyang inhabitants in Nepal, Kuna Indians off the coast of Panama and Buddhist farmers in Thailand.[42] An analysis of 27 populations indicated that six populations including Java, Thailand, parts

of Taiwan with an agricultural population, North India, rural Bantu, and Okayuma had an average blood pressure that was not hypertensive despite eating a high-salt diet (mean daily salt intakes ranging from 9 to 19 g of salt).[43]

DiNicolantonio *et al*. suggested that dietary salt is more of an Innocent Bystander in the phenomenon of salt and fluid overload and that added dietary sugar, fructose, in particular, is the main culprit and primary cause of hypertension.[44,45] Overconsumption of refined carbohydrates has been shown to reduce nitric oxide, possibly leading to increase peripheral vascular resistance, increase oxidative stress, activate the renin-angiotensin-aldosterone system, and cause hyperinsulinemia and insulin resistance.[46-48]

The contributory role of a diet low in potassium to the development of hypertension has been well established, with a meta-analysis by Whelton in 1997 concluding that increased potassium intake be considered as a recommendation for prevention and treatment of hypertension, especially in those who are unable to reduce their intake of sodium.[49] 20 years on, a meta-analysis by Poorolajal finds that potassium supplementation has a modest, but significant positive impact on blood pressure and may be recommended as an adjuvant antihypertensive agent for patients with essential hypertension, without significant adverse effects.[50] Data from the Third National Health and Nutrition Examination Survey indicate that a higher sodium-to-potassium ratio is associated with significantly increased risk of CVD and all-cause mortality in the general US population.[51]

Identification of these dietary factors which contribute to the development of hypertension has raised the question of whether the role of salt was as central and important as it was purported to be.

Salt - One Man's Meat, Another Man's Poison?

While few would challenge the evidence showing the benefit of a low-salt diet in hypertensive patients, the contention is whether the same strategy of salt restriction should apply to normotensive populations to prevent hypertension, given the potential harms as postulated above.

In 2003, a technical report by the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations recommended a population-wide daily salt intake of no more than 5 g. Several nations, including the United States, Canada, Finland, Ireland, and the United Kingdom, have taken steps to reduce the sodium intake of their populations.[52] The World Action on Salt and Health, a global group which aims to emulate the success of the United Kingdom salt reduction strategy, was launched in 2005 with the mission of improving the health of populations throughout the world by achieving a gradual reduction in salt intake.[53]

The Salt Intake study in Singapore comprised 800 subjects aged 18–79 years of age and was conducted as part of the National Nutrition Survey 2010. It was found that among adult Singapore residents, the estimated salt intake was 8.3 g (or 3265 mg sodium) per day, based on a mean urinary sodium excretion was 142.2 mmol/24 h. About eight in 10 Singapore residents (80.2%) exceeded the recommended dietary limit for salt. Moreover, 27.7% of the population consumed double the recommended limit.[54]

This finding has led to the introduction of the "FINEST (Functional, Innovative, Nutritious, Effective, Science-based, and Tasty) Food Programme," a multiagency collaboration between the Health Promotion Board's Centre of Excellence for Nutrition, private sector food industry Singapore Food Manufacturers Association, and knowledge institutions including the Agency for Science, Technology, and Research (A*STAR) and various polytechnics, to develop healthier salt and other functional food products.[55,56]

The effectiveness and success of this endeavor will be evaluated in the upcoming National Health Survey and National Nutrition Surveys. It will be hoped that the latest government effort taking a multipronged approach to the "War on Diabetes," which includes reducing sugar in Singaporean's diet by 25% in 2020[57] will have a synergistic effect to reduce the prevalence of hypertension further.

Several studies, including Cochrane reviews, in the early 2000s and 2010s[58-61] have observed that the magnitude of the effect of reduced sodium intake does not warrant support for a general or universal recommendation for dietary salt restriction, and may even be questionable in view of marginal benefit and suggestion of possible deleterious effects on cardiovascular outcomes.

A recent large population-based observational cohort study by Stolarz-Skrzypek *et al*. concluded that lower sodium excretion was associated with higher cardiovascular mortality,[62] leading to the extrapolation that a low-salt diet is associated with increased mortality. The main risk is attributed to the expected activation of the renin-angiotensin-aldosterone system along with increased sympathetic nervous system activity.[37] Although this study was criticized and dismissed by *The Lancet*,[63] another large population study by O'Donnell *et al*. subsequently followed shortly confirming the association between low-salt intake with increased cardiovascular risk.[64]

In 2014, the PURE study conducted also by O'Donnell *et al*. was published, showing that a J-shaped association curve exists, with both higher (>5 g/day) and lower levels (<3 g/day) of sodium excretion being associated with increased risk of CVD.[65] A subsequent meta-analysis showing that low-sodium intakes and high-sodium intakes are associated with increased mortality[66] supported this finding as well. The PREVEND cohort study also showed no association between sodium excretion and risk of coronary artery disease.[67] Most recently in 2016, O'Donnell *et al*. published a pooled analysis from four studies concluding that high-sodium intake is associated with an increased risk of cardiovascular events and death in hypertensive populations, without an association in normotensive populations, while the association of low-sodium intake with increased risk of cardiovascular events and death is observed in those with or without hypertension.[68]

Conclusion

It might be argued that the salt and hypertension hypothesis remains controversial - with strong evidence of benefit for salt restriction in hypertensives, even though it is uncertain whether salt deprivation in normotensives confers more risks than benefit. With increasing prevalence of hypertension and burden of metabolic diseases worldwide, many of which have common biochemical pathways in their pathogenesis, most nations continue to adopt a strategy of reduction in their populations' salt intakes. It would also be important to look at salt intake in the context of other dietary and environmental factors which affect blood pressure, which include but are not limited to obesity and intake of potassium and fat.[69] Nevertheless, the relevance of the salt and hypertension hypothesis is likely to remain in the foreseeable future.

Although a population-based randomized controlled trial may not be feasible to better support causality between salt intake and health outcomes, a pilot randomized controlled trial (Sodium Intake in Chronic Kidney Disease, ClinicalTrials.gov Identifier: NCT02458248) is underway to determine whether recommending a low-salt intake, compared to average/moderate intake, is associated with a slower rate of decline in kidney function in patients with chronic kidney impairment.

As in most policies, there is probably no one-size-fits-all approach, especially in the salt and hypertension debate given the effect of sodium on multiple physiological systems and processes. The sweet spot would be crafting an approach which benefits the majority of the population without causing harm to the minority.

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Review Article

The Dual Disease Burden of Hypertension and Diabetes

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Abstract

Hypertension and diabetes are among the most common non-communicable diseases worldwide with a global prevalence of 22% and 9%, respectively. In Singapore, the prevalence of both diseases is higher at 23.5% and 11.3%, respectively, and similar trends are evident in much of Asia. There is an even higher prevalence of hypertension among diabetics, likely contributed to by inappropriate activation of the renin–angiotensin–aldosterone system (RAAS), altered sodium transport, a complex interaction of hyperinsulinemia and insulin resistance with obesity, RAAS, arterial baroreceptor reflex impairment, leading to an activated sympathetic nervous system, and the coexistence of kidney damage accelerated by hypertension. While angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers remain the mainstay of treatment for the comorbidities of hypertension and diabetes, various guidelines are inconsistent with blood pressure thresholds and treatment goals. Shared lifestyle factors in the etiology of hypertension and diabetes do provide further opportunities for non-pharmacologic intervention. Taken together, strategies that incorporate early diagnosis of diabetes and hypertension and its complications, disease self-management and education, and optimal medical and lifestyle management will reduce the burden of complications from these dual conditions.

Key words: Cardiovascular disease, diabetic kidney disease, renin–angiotensin–aldosterone system, vascular complication

Introduction

Hypertension and diabetes are common chronic diseases and contribute to significant morbidity and mortality worldwide. Hypertension is estimated to have caused 10.7 million deaths globally in 2015.[1] If left uncontrolled, hypertension causes stroke, ischemic heart disease, cardiac failure, atrial fibrillation and flutter, dementia and cognitive impairment, chronic kidney disease (CKD), and end-stage renal failure (ESRF). Diabetes is also a well-recognized cause of premature death and disability, increasing the risk of cardiovascular disease, kidney failure, blindness, and lower-limb amputation. Diabetes was considered directly responsible for 1.5 million deaths in 2015.[1] Its impact is expected to increase in the future as in recent decades, the prevalence of diabetes has been increasing globally and has been particularly accelerated in low- and middle-income countries. Further, hypertension and diabetes are among the most common non-communicable diseases across developed to developing countries, from Europe to Asia and to Africa, and from the elderly to the young. Driven by economic development, nutrition transition, and increasingly sedentary lifestyles, we face a threat from the dual disease burden of both hypertension and diabetes globally.

As in much of the developed world, non-communicable diseases are the leading cause of death in Singapore, with diseases of the heart and hypertensive diseases; cerebrovascular diseases (e.g., stroke); kidney (CKD) and disorders of the urinary system; and diabetes representing 2nd, 4th, 5th, and 6th leading causes of death in 2016.[2] Diabetes has an additive impact on mortality by contributing to 1 of 2 heart attacks, 2 in 3 cases of kidney failure, and 2 of 5 strokes in Singapore.[3]

Apart from the association of hypertension and diabetes with mortality through complications as listed above, both these conditions contribute significantly to disability-adjusted life years (DALY), a measure of a combination of years of life lost due to premature mortality, and from years lived with disability (any short-term or long-term health loss). In Singapore, a total of 399,675 life years were lost due to all mortality and ill-health in 2010. Diabetes

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alone accounted for 10% of DALY.[4] In addition, hypertension and diabetes contribute to the large proportion of outpatient public sector primary care with hyperlipidemia (16.4%), hypertensive disease (15.7%), and diabetes mellitus (DM) (9.8%) representing the top three conditions contributing to polyclinic attendances. Finally, these diseases also impose a severe economic burden in the country in terms of lost productivity and unsustainable medical costs.[5] Diabetes alone cost Singapore >$1 billion in 2010, and this cost has been predicted to soar to beyond $2.5 billion by 2050.[6]

In this review article, we examine the dual burden of hypertension and diabetes from an Asian perspective with particular reference to Singapore, a Southeast Asian country with a multiracial society, and a population of 5.61 million. Singapore is known for its transition from third world to first world in a single generation. Given the multi-ethnic population in Singapore, the data have relevance for other Asian countries likewise transitioning in their socioeconomic development.

Prevalence of Hypertension and Diabetes in Singapore and Asia

The global prevalence of raised blood pressure (defined as systolic and/or diastolic blood pressure (DBP) ≥140/90 mmHg) in adults aged 18 years and above was around 22% in 2014. The global prevalence of diabetes (defined as a fasting plasma glucose value >7.0 mmol/L [126 mg/dl] or being on medication for raised blood glucose) was estimated to be 9% in 2014.[7] Of note, the prevalence of diabetes has increased exponentially throughout the world, with that among adults over 18 years of age increasing from 4.7% in 1980 to 8.5% in 2014.[7] In Asia, the prevalence of hypertension and diabetes from Singapore, Malaysia, Japan, and Thailand is summarized and compared in Table 1.

As noted [Table 1], in Singapore, the prevalence of hypertension and diabetes was both higher than the global average at 23.5% and 11.3%, respectively.[8] Trends over the years [Table 2] demonstrate that although the prevalence of hypertension remains steady, that of diabetes has increased significantly, and is likely still underestimated considering inclusion of only residents aged 18–69 years in the survey.

Prevalence of Hypertension among Diabetics

Hypertension and diabetes are intertwined conditions, and the prevalence of hypertension among diabetics is consistently higher than that in the general population. In the United States, among adults aged 18 years or older with diagnosed diabetes, 73.6% (95% confidence interval [CI], 69.9%–77.1%) had systolic blood pressure (SBP) of 140 mm Hg or higher or DBP of 90 mm Hg or higher, or were on prescription medications for high blood pressure.[15] In Korea, the prevalence of hypertension in adults with diagnosed diabetes was 55.5%, based on the Fourth Korea National Health and Nutrition Examination Survey; as compared with the general population, the prevalence of hypertension among adults with diagnosed diabetes was higher in all age groups in both genders.[16] In Japan, one study showed that approximately 50% of diabetic patients had hypertension.[17] In Thailand, approximately half the diabetics (49.0%, 95% CI 45.6-52.5) had hypertension and 14.4% (95% CI 13.0-16.0) of hypertensives had diabetes.[18] In Singapore, 86.4% of patients self-reported to have diabetes had hypertension according to one study.[19] In an enterprise-wide diabetes study in Singapore at the National Healthcare Group, one of two public health-care clusters in Singapore spanning across three acute hospitals, nine primary care polyclinics, and national specialty centers serving 2.2 million population, among diabetics under primary care, only 1.5% was considered "diabetes only," 5.1% was "diabetes and hypertension only," and 77.7% was "diabetes with hypertension and dyslipidemia." In other words, 82.8% of diabetics in primary care had hypertension and 79.7% of diabetics under specialists care had hypertension.[20] This high prevalence of hypertension among diabetics, hence, portends a dual risk of end organ damage with its attendant morbidity and mortality.

Pathophysiology of Hypertension in Diabetes and their Relationship to End Organ Damage

Several pathophysiological mechanisms likely contribute to the development of hypertension in diabetes.[21,22] The renin–angiotensin–aldosterone system (RAAS) may be activated leading to hypertension directly mediated by Angiotensin II. In addition, a complex interaction between obesity, hyperinsulinemia, and insulin resistance, impairment in arterial baroreceptor control

Table 1: Prevalence of hypertension and diabetes in four Asian Countries

Disease	Singapore	Malaysia	Japan	Thailand
Hypertension (global 22%)	2010 23.5% for age 18–69 years [≥140/90][8]	2011 43.5% for ages >30 years [≥140/90][9]	2010 (Male/Female) 20.0%/5.6% for age 30–39 years 29.9%/12.6% for age 40–49 years 63.2%/38.4% for age 50–59 years 65.6%/62.3% for age 60–69 years [≥140/90][10]	2009 21.4% for age ≥1 year [Diagnosed by a physician][11]
Diabetes (global 8.5%)	2010 11.3% for age 18–69 years[8] [2-h plasma glucose during an oral glucose tolerance test ≥11.1 mmol/L]	2011 15.1% for age >18 years [Diagnosed in the clinic][12]	2007 (Male/Female) For≥age 20 years 15.3%/7.3% for HbA1c ≥6.1%; 14.0%/15.9% for 5.6%≤HbA1c<6.1%[13]	2014 9.9% for age ≥20 years [Diagnosis by a physician][14]

Table 2: Prevalence of hypertension and diabetes from 1992 to 2010 in Singapore

Prevalence	Hypertension (%)	Diabetes (%)
1992	22.2	8.6
1998	27.3	9
2004	24.9	8.2
2010	23.5	11.3

and an activated RAAS may enhance sympathetic nervous activity and lead to increased peripheral vascular resistance and hypertension.[22] Renal sodium handling differs in diabetes due to upregulation of sodium transporters in the kidneys thereby upregulating RAAS.[21] Moreover, insulin stimulates obesity through fat accumulation, and this leads to obesity-induced hypertension in association with diabetes.[23] Chronic low-grade inflammation and oxidative stress in the adipose tissue lead to increased production of angiotensinogen and angiotensin II with consequent tissue RAAS activation. Angiotensin II exerts many of its detrimental effects through activation of the angiotensin II type 1 receptor, resulting in multiple intracellular events, including the production of reactive oxygen species, reduced insulin metabolic signaling, and proliferative and inflammatory vascular responses, all of which cause endothelial dysfunction, insulin resistance, and hypertension.[24]

The superimposition of hypertension on diabetes further aggravates microvascular and macrovascular complications through additive mechanisms that include arteriolar and capillary damage resulting subsequently in end organ damage.[25] The pathophysiology of the microvascular disease involves a combination of direct glucose-mediated endothelial damage, oxidative stress due to superoxide overproduction, and the production of sorbitol and advanced glycation end-products.[26] In combination with hypertension, these metabolic injuries cause altered blood flow and change in endothelial permeability, extravascular protein deposition, and coagulation resulting in organ dysfunction.[27] These microvascular complications are best exemplified in diabetic kidney disease (DKD), in which initial local renal damage mediated by metabolic effects from uncontrolled hyperglycemia, compounded by hemodynamic effects from an activated RAAS and impaired afferent arteriolar autoregulation contribute to renal damage. Over time, this local renal damage results in decreased glomerular filtration rate (GFR) and albuminuria. As GFR is reduced, there is further impairment in sodium excretion resulting in increased extracellular volume. In addition, oxidative stress is increased in kidney disease, leading to further endothelial cell dysfunction and vasoconstriction. Systemic RAAS is not appropriately suppressed despite the increased extracellular volume. Angiotensin II increases vasoconstriction through increases in oxidative stress through induction of NADPH oxidase and directly through binding to vascular smooth muscle cells.[28]

These pathophysiologic interactions of hypertension and diabetes underpin the clinical link between hypertension and diabetes in relation to outcomes, especially with regard to renal and cardiovascular damage. In the UK Prospective Diabetes Study, blood pressure control ameliorated cardiovascular complications in patients with type 2 diabetes: Each 10 mmHg decrease in mean SBP was associated with 12% reduction in the risk for any complication related to diabetes, 15% reduction in deaths related to diabetes, and 11% reduction in myocardial infarction.[29] There was also a 13% reduction in microvascular complications with improved blood pressure control in this study; other studies have demonstrated similar benefits with blood pressure control and progression of DKD[30] and retinopathy.[31] The pathophysiologic link between hypertension and diabetes for macrovascular disease includes possibly direct effects of glucose, activation of protein kinase C, endothelial dysfunction from oxidative stress, activation of athero-inflammatory cytokines, and epigenetic changes in vascular endothelial cells.[32] In relation to these macrovascular complications, patients with hypertension and concomitant diabetes, compared to non-hypertensive diabetics were found to have higher rates of cardiovascular death, myocardial infarction, angina pectoris, amputation, and stroke, and independent of other risk factors.[33]

As suggested above, the interaction of hypertension and diabetes is particularly relevant to the development of kidney damage. Globally, diabetes and hypertension are the leading causes of CKD.[34] In Singapore, the crude prevalence of CKD has been reported to be 15.6%,[35] with older age, diabetes, hypertension, and dyslipidemia significantly associated with risk for CKD. Age-standardized prevalence may have better-permitted comparisons between this prevalence in comparison to countries with high incidence of end-stage renal failure (ESRF)[36] in Asia such as Korea,[37] Japan,[38] and Taiwan.[39] From a study done in a primary care cluster in Singapore, the overall prevalence of DKD, which was defined as microalbuminuria (UACR 30–299 mg/g), macroalbuminuria (≥300 mg/g), or renal impairment (estimated glomerular filtration rate eGFR <60 mL/min per 1.73m2), was high at 52.5%. DKD prevalence within ethnic subpopulations was different: 52.2% of Chinese, 60.4% of Malays, and 45.3% of Indians had DKD, respectively. Malays had a 1.42-fold higher DKD prevalence, while Indians had a 0.86-fold lower prevalence.[35] Notably, this high incidence of DKD in primary care translates to a high incidence of ESRF due to diabetes in Singapore. From data from the Singapore Renal Registry, in 2016, among patients initiated on dialysis (including hemodialysis and peritoneal dialysis) 66.6% of ESRF was due to diabetes, this percentage having been increasing steadily from 45.9% in 1999 to 61.8% in 2009.

The high burden of CKD and ESRF due to diabetes is also reflected across the region. In a study from Asian-Pacific region, DKD was the most common cause of ESRF in 9 of the 12 countries surveyed.[40] Indeed, in international comparisons from the USRDS, 5 Asian countries (Singapore, Malaysia, Hong Kong, Korea, and Taiwan) feature among the top 10 countries with the highest incidence of ESRF due to diabetes in the world.[41] It has been suggested that Asian diabetics exhibit a higher risk

for renal complications than their non-Asian counterparts even after accounting for socioeconomic status. In an international survey, 55% of Asian and 40% of white patients with type 2 diabetes had increased albuminuria. Chinese individuals with impaired glucose tolerance were found to have a high prevalence of albuminuria, with 2-h plasma glucose level as an independent predictor. In observational studies as well as clinical trials, Asian patients with diabetes were more likely to develop ESRF than their white counterparts.[42]

In terms of macrovascular complications, cardiovascular disease, a major target organ damage from hypertension and diabetes, is the leading cause of non-communicable disease deaths and responsible for 17.5 million deaths, or 46.2% of the non-communicable disease deaths globally.[7] In Singapore, ischemic heart disease caused 17.0% of deaths, in 2016, and was the 3rd leading cause of hospitalization (3.1% discharges) in 2015.[43] For diabetics under primary care in 2008, cardiovascular complications were reported among 17.8%.[20] From the Singapore Myocardial Infarction Registry, 2016, among these patients with more advanced cardiovascular disease, 75.0% had hypertension, and 50.2% had diabetes.[44] Females were more likely to have hypertension (85.6% in females vs. 68.6% in males) or diabetes (59.3% in females vs. 45.8% in males) compared to males. Chinese patients had the highest proportions of hypertensives (75.3% in Chinese vs. 72.6% in Malay vs. 72.7% in Indian), while Indians had the highest proportions of diabetics (76.3% in Indian vs. 66.4% in Chinese vs. 73.0% in Malay).[45] As with DKD, the burden of cardiovascular disease has been steadily increasing in Singapore with the age-standardized incidence rate of acute myocardial infarction increasing from 208.9 per 100,000 population in 2007 to 220.8 per 100,000 population in 2016. In a retrospective cohort study involving 34,460 patients in Singapore to identify the prognosis of heart failure (HF) with the effect of multimorbidity focusing on type 2 DM (T2DM) and CKD, the cohort of "T2DM+CKD+HF" had a 56% higher risk of all-cause mortality (HR: 1.56, 95% CI 1.48–1.63) and a 44% higher risk of cardiovascular disease-specific mortality (HR: 1.44, 95% CI 1.32–1.56) compared with patients diagnosed with HF only.[46]

Other comorbidities also contribute to the end organ damage from hypertension and diabetes. Both the aging population and obesity play a role for the coexistence of hypertension and diabetes. Singapore has a high prevalence of hypertension among the elderly population as defined by age 60 years and above,[19] indicating that more than two-thirds of elderly populations will require antihypertensive treatment. For the elderly >75 years, the prevalence of hypertension was even higher at 83.7% in this study. Another developed country, Korea, showed similar data, with 68.7% of the population above the age of 65 having hypertension.[47]

Obesity is also strongly associated with hypertension and may be partly explained by the associated increased renal sodium reabsorption and blood volume expansion.[48] A 5% increase in body weight (equivalent to a gain of 4 kg in an average man or 3 kg in a woman) was closely correlated with a 20–30% increased odds of being hypertensive on 4-year follow-up.[49] Worldwide, the prevalence of obesity has nearly doubled for the past 30 years. In 2014, 11% of men and 15% of women aged 18 years and older were obese. More than 42 million children under the age of 5 years were overweight in 2013.[7] In Singapore, among those with body mass index (BMI) of 23.0–27.4 kg m^2, the prevalence of hypertension was 76.3%, and among those with BMI of >27.5 kg m^2, hypertension prevalence was even higher at 87.6%.[19] However, obesity not only affects the elderly but also affects young people and adolescents. In Asian and especially Southeast Asian populations, a "metabolically obese" phenotype (i.e., normal body weight with increased abdominal adiposity) has been described. Peoples of South Asian descent appear to be more prone to abdominal obesity and low muscle mass with increased insulin resistance. The increased risk of gestational diabetes, combined with exposure to poor nutrition in utero and overnutrition in later life in some populations, may contribute to the increasing diabetes epidemic through "diabetes begetting diabetes" in Asia.[42]

Apart from the burden of end organ damage and its associated morbidity and mortality, costs of health-care become additive with increasing burden of disease. A Canadian study showed that the unadjusted annual incremental direct all-cause health-care costs associated with CKD among cohorts with (a) diabetes only, (b) hypertension only, and (c) both diabetes and hypertension were USD11,814, USD8,412, and USD10,625, respectively.[50] These data highlight the need to mitigate the effects of hypertension to reduce the burden of disease.

Management of Hypertension in Diabetes to Ameliorate Risk of Progression of End Organ Damage

Apart from an agreement on the need to control blood pressure to mitigate the risks of high blood pressure on end organ damage, the various guidelines are inconsistent with blood pressure thresholds and treatment goals for control of hypertension in the diabetic patient [Table 3].

Nevertheless, there is general agreement on the preferred treatment of hypertension among diabetics. Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) remain the mainstay of treatment for the comorbidity of hypertension and diabetes. The Heart Outcomes Prevention Evaluation study showed that ACE inhibition in type 2 diabetes reduced the risk of vascular complications.[29] American Diabetes Association suggested that an ACEi or ARB, at the maximum tolerated dose indicated for blood pressure treatment, was the recommended first-line treatment for hypertension in diabetics with urine albumin-to-creatinine ratio ≥300 mg/g creatinine or 30–299 mg/g creatinine; if one class was not tolerated and the other should be substituted.[56] In the 2017 ACC/AHA guideline, ACEi or ARB was recommended for anti-hypertensive therapy among stable ischemic heart disease, HF with preserved ejection fraction, CKD, diabetes, and for prevention of atrial fibrillation.[53] The JNC8 recommended that in the general non-black population, including those with

Table 3: Summary of guidelines for blood pressure control in diabetes

Guidelines	BP thresholds (in mmHg)		BP targets (in mmHg)	
	General Population	Patients with DM and/ or CKD	General Population	Patients with DM and/ or CKD
Singapore MOH 2017[51]	Younger than 80 years old: ≥140/90	DM ≥ 140/80	Younger than 80 years old: <140/90	DM <140/80
	80 years old and above: ≥150/90	CKD ≥ 130/80	80 years old and above: <150/90	CKD <130/80
ESC 2013[52]	≥140/90	DM:SBP≥140 and DBP≥85	<140/90	DM: SBP<140 and DBP<85
		CKD: SBP≥140		CKD: SBP<140; <130 with severe proteinuria
ACC/AHA 2017[53]	≥130/80	DM and CKD: ≥130/80	<130/80	DM and CKD: <130/80
JNC8 2014[54]	<60 years old: ≥140/90	DM and CKD: ≥140/90	<60 years old: <140/90	DM and CKD: <140/90
	≥60 years old: ≥150/90		≥60 years old: <150/90	
KDIGO[55]	-	-	-	Normal to mild albuminuria: ≤140/90 Moderate to severe albuminuria ≤130/80

DM: Diabetes mellitus, CKD: Chronic kidney disease, MOH: Ministry of Heath, ACC/AHA: American Colleague of Cardiology/American Heart Association, ECS: European Society of Cardiology, JCN 8: Eighth Joint National Committee, Ministry of Health (MOH) Singapore. Hypertension: MOH Clinical Practice Guidelines, 2017, KDIGO: Kidney Disease: Improving Global Outcomes guideline 2012

diabetes, initial anti-hypertensive treatment should include a thiazide-type diuretic, calcium channel blocker, ACEi, or ARB; in the population aged 18 years or older with CKD and hypertension, initial (or add-on) anti-hypertensive treatment should include an ACEi or ARB to improve kidney outcomes. This was to apply to all CKD patients with hypertension regardless of race or diabetes status.[54] In Singapore's hypertension guideline, ACEi or ARB was recommended for HF, previous myocardial infarction, atrial fibrillation prevention, peripheral artery disease, diabetes (with or without albuminuria), and CKD.[56]

The shared lifestyle factors in the etiology of hypertension and diabetes provide an opportunity for additional non-pharmacologic intervention. Indeed, as patients with diabetes are at risk for developing hypertension and its complications, lifestyle management may help prevent or delay a diagnosis of hypertension with the need for pharmacologic therapy.[56] Lifestyle intervention consists of (1) weight loss if overweight or obese; (2) a dietary approaches to stop hypertension -style dietary pattern including reduced sodium and increased potassium intake; increased fruit and vegetable consumption; and (3) increased physical activity (moderately intense physical activity, such as 30–45 min of brisk walking most days of the week).[56] Insufficient physical activity has been shown to contribute to 3.2 million deaths and 69.3 million DALYs each year. Adults who are insufficiently physically active have a higher risk of all-cause mortality compared with those who do at least 150 min of moderate-intensity physical activity per week, or equivalent, as recommended by the World Health Organization (WHO). Globally, in 2010, 23% of adults aged 18 years and over were insufficiently physically active. Women were less active than men, and older people were less active than younger people.[7] Lifestyle intervention is remarkably effective in the primary prevention of diabetes and hypertension and is also pertinent to the prevention of downstream macrovascular complications of the two disorders. Studies have shown that an environment supporting health-promoting behaviors is more likely to enable individuals to adopt and sustain healthy lifestyles by making healthy living more accessible, natural, and effortless.[57]

As a global target, the WHO has advocated for a 25% relative reduction in overall mortality from cardiovascular diseases, a 10% relative reduction in the prevalence of insufficient physical activity, a 25% relative reduction in the prevalence of raised blood pressure, or to contain the prevalence of raised blood pressure, according to national circumstances, and to halt the rise in diabetes and obesity.[7] A recent study has shown that elevated SBP, even as defined by SBP at least 110–115 mm Hg, is a leading global health risk. The estimated annual death rate and DALYs associated with elevated SBP increased significantly over the years.[58] While this study may not translate into clinical practice guidelines for BP threshold, it nevertheless strengthens the case to lower the risk for cardiovascular diseases in those with SBP of 140 mm Hg or higher.[59]

In summary, there is much to be done to reduce the global burden of disease due to hypertension and diabetes. Increasing awareness of the risks of diabetes and hypertension among the young and middle-aged will be of benefit to prevent these dual conditions. Control of hypertension and diabetes, once diagnosed, by all effective means available, including improving uptake of healthy diets, minimizing weight gain or promoting weight loss in overweight and obese individuals, and promoting, uptake, and adherence to drugs as well as management of related complications will mitigate the adverse effects of these dual conditions and reduce end organ damage due to their macrovascular and microvascular complications.

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Review Article

The Dual Burden of Hypertension and Hyperlipidemia

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Abstract

Hypertension and hyperlipidemia are chronic diseases with high socioeconomic burdens. They contribute significantly to mortality and morbidity amongst populations. Globally, hypertension is estimated to cause 7.1 million deaths and hypercholesterolemia contributes to 4.4 million deaths. They share common pathophysiological pathways and the combination of hypertension and hyperlidpidemia predisposes individuals to higher risk of cardiovascular events. Despite this knowledge, we are far from attaining the target treatment goals and these dismal results are sobering in the face of cardiovascular morbidity and mortality.

Key words: Hypertension, Hyperlipidemia, Cardiovascular, Mortality

Introduction

Hypertension and hyperlipidemia are rapidly becoming chronic diseases with high health care and socioeconomic burdens. Globally, hypertension is estimated to cause 7.1 million deaths and hypercholesterolemia contributes to 4.4 million deaths.[1] The prevalence of hypertension and hyperlipidemia in Singapore is 23.5% and 17.4%, respectively.[2] Data from the Framingham Heart Study[3] have shown that increases in blood pressure double the risk of cardiovascular events. Hyperlipidemia has also been found to be an important risk factor in the development of cardiovascular disease in the same study. The combination of these risk factors results in a multiplicative effect on endothelial dysfunction, leading to accelerated atherosclerosis and resultant cardiovascular disease.[4] Cardiovascular disease accounted for 17.9 million deaths worldwide in 2016.[5] Understanding the dual burden of hypertension and hyperlipidemia on cardiovascular health is especially pertinent as cardiovascular disease (including deaths from ischemic heart disease, cerebrovascular disease, hypertensive, and other cardiac diseases) as a whole accounted for 30.1% of all deaths in Singapore in 2017.[6]

Combined Cardiovascular Risk With Hypertension And Hyperlipidemia

Hyperlipidemia is more commonly present in hypertensive than in normotensive patients.[7] Both hypertension and hyperlipidemia share common complex pathophysiology with environmental and genetic influences. Allayee *et al.* previously conducted a genome-wide scan in 18 Dutch families with familial combined hyperlipidemia and found evidence that support the presence of multiple genetic factors that affect both blood pressure and plasma lipid parameters.[8] Sprecher *et al.* observed that lipoprotein lipase mutations were associated with elevated triglyceride levels and higher blood pressures.[9] Insulin resistance contributes to the development of both hypertension and hyperlipidemia[10] through various mechanisms. Activation of the sympathetic nervous system, renal sodium retention, altered transmembrane cation transport, growth-promoting effects of vascular smooth muscle cells, and vascular hyperreactivity have been reported as contributory mechanisms. Physiological studies purport that insulin predisposes to hypertension by the stimulation of renal sodium absorption and the sympathetic nervous system. Both of these, in turn, result in higher blood pressures.[11]

Endothelial dysfunction also plays an important role in the pathogenesis of both hypertension and hyperlipidemia. The vascular endothelium functions to regulate vascular tone. It synthesizes and releases several vasoactive substances, including nitric oxide, which is a potent vasodilator. Hypertensive patients have impaired vascular endothelial vasodilatation. Lectin-like ox-low-density lipoprotein (LDL) receptor 1 (LOX-1) is the oxidative form of LDL. The upregulation of LOX-1 in patients with hyperlipidemia results in

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the generation of reactive oxygen species and decreases nitric oxide release from endothelial cells. This leads to reduced vasodilatation, increased vascular tones, and increased peripheral vascular resistance which contribute to higher blood pressures.

Due to the common pathogenetic pathways, patients with hyperlipidemia are more often found to be hypertensive. The clustering of hypertension and hyperlipidemia has been shown to increase cardiovascular disease risk. In a study performed by the French, published in European Heart Journal in April 2012, patients with the highest systolic blood pressure (SBP) and highest cholesterol levels were found to have the highest cardiovascular disease mortality as well as coronary heart disease mortality.[7] The combination of hypertension and hyperlipidemia is also associated with increased health-care cost burden.[12] Cardiovascular risk assessment is, hence, of utmost importance and the various tools available consider the additive effects of hypertension and hyperlipidemia. For example, the European systemic coronary risk evaluation (SCORE), risk assessment tool predicts the 10-year risk of fatal cardiovascular disease [Figure 1]. It takes into account an individual's gender, age, smoking status, blood pressure, and cholesterol levels. For the same level of SBP, the higher the total cholesterol level, the higher the risk score for every defined age groups. In the same manner, a higher SBP will add to the overall cardiovascular risk of a given total cholesterol level at a defined age group. Cardiovascular risk assessment based on the Framingham heart study also similarly takes into consideration the individual's blood pressure and cholesterol levels.

Effect of The Treatment of Hypertension on Lipid Levels

Reduction of cardiovascular risk requires appropriate management of both blood pressure and lipid levels. Medications used for the treatment of hypertension and hyperlipidemia can provide independent and additive reductions in cardiovascular risk. However, some medications used in the treatment of hypertension can affect the lipid profile in an unfavorable manner.

The use of diuretics, especially thiazides in the treatment of hypertension, has been found to have dose-dependent deleterious effects on total cholesterol, LDL cholesterol, and triglyceride levels.[13] In the antihypertensive and lipid-lowering treatment to prevent heart attack trial, patients on chlorthalidone had higher serum cholesterol levels than the lisinopril group at 2 years and 4 years of follow-up. Similar results were seen when compared with patients taking amlodipine - total cholesterol levels were higher in chlorthalidone group at 2 years.[14] Beta-blockers with cardioselectivity and intrinsic sympathomimetic activity decreased total cholesterol and LDL cholesterol levels and increased high-density lipoprotein (HDL) cholesterol.[15] Alpha-blockers decreased total and LDL cholesterol levels and increased HDL cholesterol levels. Of the antihypertensive medications, this class provides the greatest lipid-lowering benefit.[13] Angiotensin-converting enzyme inhibitors are especially useful in the diabetic population where they have been found to be associated with reductions in total cholesterol.[13,15] In the RENAAL study, losartan resulted in a statistically greater fall in total and LDL cholesterol levels compared to placebo.[16]

Effects of Lipid-Lowering Therapy on Hypertension

Similarly, lipid-lowering medications were also found to have beneficial effects on blood pressure control. In a randomized, double-blind, placebo-controlled trial - the UCSD statin study, participants were randomized to take either 20 mg simvastatin, 40 mg pravastatin, or placebo for 6 months. The study found that statins modestly but significantly reduced blood pressure relative to placebo, by 2.2 mmHg for SBP and 2.4 mmHg for diastolic blood pressure.[17]

LDL has been shown to upregulate angiotensin 2 Type 1 receptor (AT1) in animal studies and cell cultures, resulting in elevated blood pressures in hypercholesterolemic patients.[18]

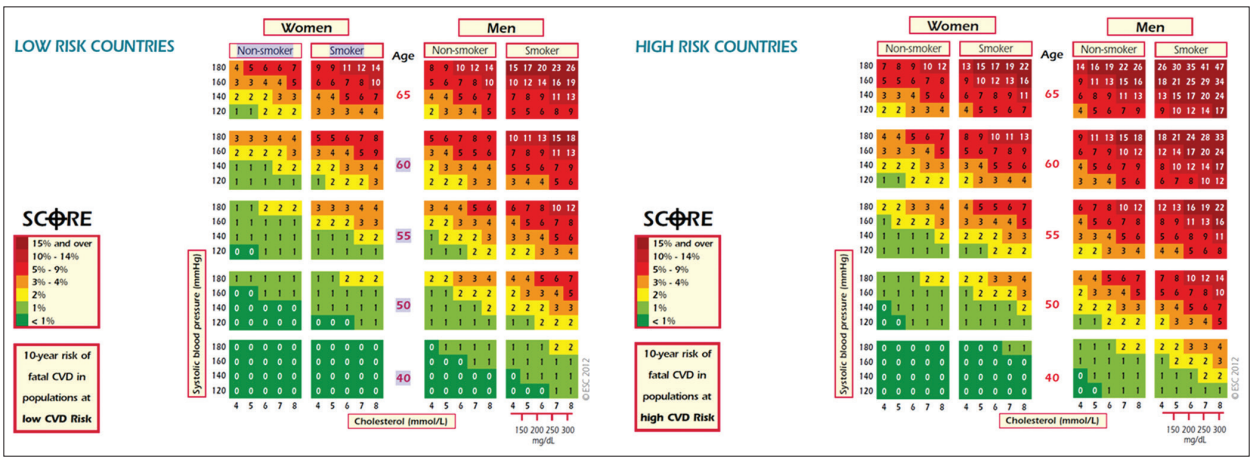

Figure 1: Adapted from European society of cardiology

Nickenig *et al.* studied the effects of cholesterol-lowering therapy on AT1 receptor overexpression and found that statins reversed the elevated blood pressure response to angiotensin 2 and downregulated AT1 receptor density.[19] This is in concordance with the findings that statins improve blood pressure control in the UCSD study mentioned earlier.

The Anglo-Scandinavian cardiac outcomes trial-lipid-lowering arm (ASCOT)[20] trial went further to study the effects of lipid-lowering therapy in hypertensive patients who were not traditionally deemed dyslipidemic. The study was stopped prematurely as participants who were receiving atorvastatin compared to placebo had highly significant reduction in the primary endpoint of cardiovascular events compared with placebo. They were also observed to have a significant reduction in the incidence of stroke.

ASCOT legacy study results recently published in 2018 revealed sustained long-term benefits of improved cardiovascular outcomes in patients treated with both antihypertensive and lipid-lowering therapy. These patients were followed up for a median of 15.7 years,[21] demonstrating long-term cardiovascular benefits up to >10 years.

Treatment Targets

Hypertension

The 2018 European Society of Cardiology/European Society of Hypertension guidelines recommend that the first target for all patients on pharmacotherapy for hypertension would be <140/90 mmHg. If such a target is well tolerated, treated blood pressure should be targeted to 130/80 mmHg or lower in most patients. In elderly patients (>65 years old), SBP should be targeted to between 130 and 140 mmHg and diastolic blood pressure to <80 mmHg. In diabetics receiving pharmacotherapy for hypertension, office SBP should be targeted to ≤130 mmHg and diastolic blood pressure <80 mmHg. In older patients with diabetes, an SBP target range of 130–140 mmHg is acceptable.[22]

The 2017 American Heart Association (AHA) guidelines suggested a blood pressure goal of <130/80 mmHg in majority of patients. The threshold blood pressure is slightly higher in individuals with no clinical cardiovascular disease and a 10-year atherosclerotic cardiovascular disease risk of <10% and patients on antihypertensive therapy for secondary stroke prevention. These individuals have a blood pressure threshold of ≤140/90 mmHg. In other individuals, blood pressure threshold is set at ≤130/80 mmHg.[23]

The Eighth Joint National Committee (JNC 8) guidelines[24] recommend a blood pressure target of <150/90 mmHg in patients 60 years or older without diabetes or chronic kidney disease. Patients with diabetes and hypertension should be treated to a target of <140/80 mmHg. In patients aged 18-50 years with no major comorbidities and in patients 60 years or older with diabetes, chronic kidney disease or both, the target blood pressure is <140/90 mmHg. It is important to note that the recommendations for JNC 8 were published early in 2014. The final draft of the guidelines was circulated in January 2013 for external peer review and various comments were incorporated in the second half of 2013.

Studies have been performed to study the effects of intensive blood pressure lowering therapy (SBP <120 mmHg) versus patients treated to standard targets (SBP <140 mmHg). The SPRINT study,[25] which studied hypertensive patients without diabetes, showed that relative risk of death from cardiovascular causes was lower in the intensive treatment group compared to the standard treatment group. However, patients in the intensive treatment group also encountered higher incidence of adverse events such as acute kidney injury. The result from systolic blood pressure intervention trial (SPRINT) was published in November 2015, 2 years after JNC 8 was finalized.

The ACCORD study,[26] which studied hypertensive patients with Type 2 diabetes, revealed that targeting an SBP of <120 mmHg in compared to <140 mmHg did not reduce the rate of the prespecified combined cardiovascular events. Lowering blood pressure to <120 mmHg did reduce the incidence of stroke by 40%. Similar to the SPRINT study, it also reported higher incidence of serious adverse events in the intensive blood pressure lowering arm.

In Singapore, the Ministry of Health Singapore (MOH) hypertension clinical practice guidelines (CPG) recommend a target blood pressure of <140/90 mmHg in patients under 80 years and <150/90 mmHg in patients aged 80 years or older. In addition, in patients with moderate-to-severe albuminuria, the target blood pressure advised is <130/80 mmHg. Patients with diabetes mellitus should be treated to a blood pressure target of <140/80 mmHg.[27] The final draft of the guidelines was finalized before the SPRINT result being published.

Hyperlipidemia

A meta-analysis conducted by the Cholesterol Treatment Trialists' Collaboration[28] in 2010 revealed a reduction in all-cause mortality of 10% per 1.0 mmol/L (38 mg/dL) LDL cholesterol reduction. This was primarily due to significant reductions in deaths related to coronary heart disease and other cardiac causes.

The 2017 American Association of Clinical Endocrinologists medical guidelines[29] for the management of dyslipidemia recommend personalized treatment targets for dyslipidemia according to patients' level of risk. This is determined by the presence of atherosclerotic cardiovascular risk factors as well as 10-year cardiovascular risk estimated by various tools such as the Framingham Risk Assessment tool.

For low-risk individuals with no risk factors, the recommended target LDL cholesterol level is <130 mg/dL. For individuals with moderate or high risk, an LDL cholesterol level target of <100 mg/dL is recommended. Treatment target goals for patients at very high and extreme risk are <70 mg/dL and <55 mg/dL, respectively. The guidelines recommend a triglyceride goal of <150 mg/dL and total cholesterol targets <200 mg/dL.

The American College of Cardiology (ACC) and AHA deliberated and proposed a cholesterol treatment guidelines that are quite distinctly different for the fact that it no longer advocates a "treat to target" strategy that has been the mainstay of most cholesterol treatment guidelines but instead recommends to match the intensity of the statin therapy according to the overall cardiovascular risks of the patient. The greater the risk category, the stronger the intensity of statin to be used for treatment in a given patient.[30]

The Singapore MOH CPG 2016[31] for dyslipidemia recommends similar LDL cholesterol target levels. It recommends target LDL cholesterol levels of <80 mg/dL for very high-risk individuals and <100 mg/dL for high-risk patients. Recommended LDL cholesterol target for moderate risk is <130 mg/dL, or <100 mg/dL if benefits of more intensive therapy are deemed to outweigh risks. Similarly, for low-risk patients, recommended target LDL cholesterol level is <160 mg/dL or <130 mg/dL if deemed beneficial.

Impact on Clinical Practice

As physicians, attention to patients' cardiovascular health is extremely important, regardless of setting of practice. Screening of individuals for hypertension and hyperlipidemia should be routinely performed as mitigation of these risk factors has been proven to improve outcomes and reduce incidence of cardiovascular disease. The dual burden of hypertension and hyperlipidemia predisposes an individual to higher risks of accelerated atherosclerosis and subsequent cardiovascular disease. This highlights the importance of assessing each patient's cardiovascular risk and individualizing each patient's target lipid and blood pressure targets based on their comorbidities and risk profiles. Cardiovascular risk assessment can be rapidly and easily performed with the aid of a variety of tools.

There are many well-established modifiable cardiovascular risk factors and as each contributes to the combined risk, they should be considered as a whole. Most available tools incorporate combinations of multiple risk factors in the determination of an individual's absolute cardiovascular risk. These include the QRISK, QRISK 2, the World Health Organization score, and the ACC/AHA 2013 Pooled Cohort risk equations. The SCORE and Framingham risk assessment tools were previously discussed.[32] Educating patients on their cardiovascular risk allow physicians to work in tandem to prevent the development of cardiovascular disease and avoid adverse cardiovascular outcomes. The personalization of treatment goals helps physicians tailor treatment for optimal results while at the same time reducing unwanted adverse effects of treatment. Modification of these risk factors known to be a major contributory factor toward cardiovascular disease and death can help to reduce morbidity and mortality.

Despite the compelling evidence that pushes us toward modifying these risk factors, it seems that we are still far behind our intended targets. In a study conducted to assess the burden of hypercholesterolemia in Singapore, the authors found that in patients who were assessed to be at high risk of coronary heart disease by the National Cholesterol Education Program Adult Treatment Panel III risk determinants and Framingham risk score, only 39.6% of them were on lipid-lowering therapy. In those receiving lipid-lowering therapy, less than half met the group-specific LDL-C treatment goal.[33] The return on expenditure achieved for lipid therapy-Asia study also showed that attainment of target goal of LDL-C is poor among the Asian population.[34] This is in spite of the well-known fact that hyperlipidemia is a major risk factor for cardiovascular disease.

On the hypertension front, a study performed by the Japanese revealed that only 52% of diabetic patients achieved the blood pressure target of <130/80 mmHg.[35] Similar rates of optimal blood pressure control were reflected in the National Health and Nutrition Examination Survey 2015–2016, where only 48.3% of patients were attaining recommended blood pressure goals.[36]

These dismal results bring to our attention the need for more action. Various reasons have been cited in the above studies for the suboptimal control of blood pressure and lipid targets. These include obesity, smoking, lower education levels, and patients with greater number of cardiovascular risk factors. More studies are needed to elucidate the link between these risk factors and poor control of hypertension and hyperlipidemia.

Conclusion

The combination of hypertension and hyperlipidemia translates into a higher risk of cardiovascular disease and higher health-care costs. Considering the prevalence and rising rates of hypertension and hyperlipidemia, these costs will contribute to a large portion of the health-care budget. Medications used in the treatment of either of these cardiovascular risk factors have unique effects on the other. The additive effect on cardiovascular disease and the effect of pharmacological therapy must be taken into consideration in the management of both conditions. The suboptimal attainment of treatment goals is sobering in the face of cardiovascular morbidity and mortality. Greater vigilance should be called upon in the management of these established risk factors.

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Review Article

Obstructive Sleep Apnea and Cardiovascular Disease - An Asian Perspective

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Abstract

Obstructive Sleep Apnea (OSA) is a chronic condition in which there is repetitive partial or complete collapse of pharynx during sleep. OSA is the most common sleep-related breathing disorder, and is increasingly being recognized as an important risk factor in cardiovascular diseases. OSA is prevalent in Asian populations despite lower prevalence of obesity as compared to Caucasian counterparts, suggesting possible differences in pathophysiology. There is increasing evidence that the effect of OSA on cardiovascular diseases is significant in the Asian population and is associated with poorer outcomes. In this review article, we look at OSA particularly in the Asian context, as well as examine the correlation between OSA and cardiovascular disease.

Keywords: Asians, cardiovascular disease, OSA, arrhythmias, heart failure, CPAP

Introduction

Obstructive sleep apnea (OSA) is a chronic condition in which there is repetitive partial or complete collapse of pharynx during sleep. OSA is the most common sleep-related breathing disorder and is increasingly being recognized as an important risk factor in cardiovascular diseases.[1] In this review article, we look at OSA, particularly in the Asian context, as well as the correlation between OSA and cardiovascular disease.

OSA is defined by having five or more predominantly obstructive respiratory events per hour of sleep, together with symptoms such as sleepiness, waking up with breath holding, snoring, or having comorbidities of medical or psychiatric disorders (hypertension, coronary artery disease, stroke, congestive cardiac failure, atrial fibrillation [AF], Type 2 diabetes mellitus, cognitive dysfunction, or mood disorder).[2] Alternatively, a frequency of 15 or more predominantly obstructive respiratory events per hour of sleep, even in the absence of associated symptoms or comorbidities, also satisfies the criteria of OSA.[2] Obstructive respiratory events can be demonstrated on polysomnography or derived from out-of-center sleep testing. The number of apneas and hypopneas on sleep studies is quantified as the apnea-hypopnea index (AHI).

Prevalence of OSA

Epidemiological studies from the United States show that of those now aged between 30 and 70 years, approximately 13% of men and 6% of women have OSA with an AHI ≥15 events per hour demonstrated on formal polysomnography.[3]

The prevalence of OSA in Asian adults is less clear. A systemic review of the literature states that OSA prevalence in Asia ranged from 3.7% to 97.3%.[4] This large range in prevalence varies with how investigators define OSA. In this systemic review, 732 articles on OSA prevalence in Asia were identified, of which 24 were eligible for in-depth review. Of these 24 articles, 10 studies used various sleep questionnaires to evaluate prevalence, and 14 used instrumental sleep monitoring and/or full polysomnography assessment. The systemic review has acknowledged that since the studies were of different methodological quality, tested different populations and many countries lack any epidemiologic data, it is particularly difficult to extrapolate the data to the global OSA prevalence in Asia. Based on its results, the estimated prevalence of OSA is around 7% in Hong Kong and 13.74% for OSA in India.[4] The rates are similar to Caucasian counterparts despite the general impression that Asians are less obese. Asians can develop OSA at lower body mass index (BMI).[5] More

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severe OSA is found in Asians when compared to Caucasians of similar BMI.[6] Asians have a greater body fat content at similar BMI compared to Caucasians.[7] Parapharyngeal fat deposition can result in a reduction in caliber and a change in shape of the upper airway promoting collapsibility.[8]

Craniofacial shape has been recognized as an important contributor to OSA risk. Skeletal features implicated are maxillary-mandibular shape, inferior hyoid position, and small cranial base. Soft tissue features implicated are the size of the tongue, soft palate, tonsils, pharyngeal walls, and parapharyngeal fat pads. Studies suggest that skeletal restriction such as shorter cranial base, difference in length, and positioning of maxilla and mandible predicts OSA in Asians. An inferiorly positioned hyoid and an extended craniocervical angle are also risk factors.[9]

Male gender, older age, a higher BMI and waist-to-hip ratio, greater neck circumference, arterial hypertension, smoking, snoring, and a higher Epworth sleepiness scale score were related to OSA in Asians.[4] Interestingly, a population-based study found that the risks of OSA may be different between different ethnic groups within the Asian population.[10]

The Singapore Health Study 2012 was a national cross-sectional study in a multiethnic population. Of those sampled, 30.5% had AHI ≥15 events per hour and 91.0% were previously undiagnosed.[11] The most common symptoms of OSA are snoring and excessive daytime sleepiness. However, these symptoms may be regarded as common by patients depending on cultural context and they may not seek medical attention for it.

Pathophysiology of OSA

OSA includes repetitive hypopneas, cyclical apneas, excessive hypoventilation, or a combination of these induced through pharyngeal collapse to the point of ventilatory constraint. During sleep, it is a physiological phenomenon to have reduced tonic activation of upper airway dilator musculature, leading to increased airway compliance and an enhanced collapsibility. However, OSA patients have more susceptible and collapsible airways.

Pathogenesis of OSA is thought to be a complex interaction of unfavorable pharyngeal anatomical compromise, upper airway dilator muscle dysfunction, reduced end-expiratory lung volume, and upper airway edema.[12,13] There are multiple upper airway dilator muscles, the largest being the genioglossus. These muscles receive input from the respiratory pattern generating neurons, chemoreceptors, and negative pressure receptors in the airway.[13] Patients with highly compromised upper airways tend to develop complete obstruction, leading to apnea. Accumulation of arterial carbon dioxide during apnea will trigger ventilator efforts and transient cortical arousal.[14]

Cardiovascular Consequences of OSA

There are several mechanisms in OSA that contributes to the pathogenesis of a range of cardiovascular consequences. When the airway is occluded, there is a sudden increase in negative intrathoracic pressure, which, in turn, increases the left ventricular transmural pressure and wall stress, increases cardiac afterload, resulting in myocardial oxygen supply-demand mismatch. To avoid asphyxia, there is arousal from sleep, which raises sympathetic activity during sleep, causing a surge in heart rate and blood pressure (BP).[15] This hemodynamic impact has been described to be equivalent to minute by minute bolus administration of a pressor agent throughout the night, continuing over several years.[16] In addition, there is evidence that longstanding OSA causes oxidative stress, triggers a pro-inflammatory state and endothelial dysfunction and insulin resistance,[1,17,18] which stiffens conduit arteries, and accelerates atherosclerosis.[15]

Hypertension

OSA and hypertension frequently coexist. This is hypothesized by the heightened sympathetic activity and inflammatory state in OSA. Clinical observations show that 24 h urinary catecholamine excretion is increased in individuals with sleep-disordered breathing.[19] OSA is now recognized as the most common secondary cause of hypertension.[20] Recent meta-analysis suggests that OSA confers a significant association with both essential and resistant hypertension, even after controlling for potential confounding factors. A dose effect is demonstrated, whereby the risk of hypertension is proportionate to the number of apneic episodes.[21] Caucasians with OSA seem to suffer more from uncontrolled hypertension, with a pooled odds ratio (OR) of the causal association of 4.406, as compared to Asians with pooled OR of 2.460.[21]

Ischemic Heart Disease

A recent systematic literature review analyzed three prospective works that followed 5067 patients, of which 53.5% had different degrees of untreated OSA diagnosed by polysomnography. All the studies found an association between OSA and fatal and non-fatal cardiovascular outcomes.[22] In Singapore, up to 66% of patients who were admitted with acute myocardial infarction were found to have previously undiagnosed OSA.[23] This may be mediated by the association between OSA and multiple vascular risk factors, pro-inflammatory state with endothelial dysfunction, as well as dyslipidemia. Although a clear causal relationship of OSA and dyslipidemia is yet to be demonstrated, there is increasing evidence that chronic intermittent hypoxia that occurs in OSA is possibly the root cause of the dyslipidemia through the generation of stearoyl-coenzyme A desaturase-1 and reactive oxygen species, peroxidation of lipids, and sympathetic system dysfunction.[24] Meta-regression analysis pooling data from 18,116 patients showed significantly greater levels of plasma low-density lipoproteins, total cholesterol, and triglycerides in those with OSA, while high-density lipoprotein cholesterol concentrations were lower.[25] A prospective Singaporean study examined atheroma volumes in patients with angiographically proven coronary artery disease and found that moderate-to-

severe OSA was independently associated with a larger total atheroma volume in the target coronary artery.[26]

In a meta-analysis of studies done in Asian and Caucasian cohorts including patients who underwent percutaneous coronary intervention (PCI), there is increased risk of major cardiovascular event (MACE), including all-cause or cardiovascular death, myocardial infarction, stroke, repeat revascularization, or heart failure (HF).[27] One of the studies in this meta-analysis was from Singapore, which showed that patients who underwent PCI for ST-elevation myocardial infarction have a lower event-free survival at 18 months if they have severe OSA.[28]

Heart Failure

Sleep-related breathing disorders, including obstructive and central sleep apnea, often coexist with HF. This is postulated to be due to a bidirectional relationship between sleep apnea and HF. Confluence of intermittent hypoxia, elevated sympathetic activity, and reduced intrathoracic pressure promotes HF development. Rostral shift of fluid into peripharyngeal structures in HF also worsens OSA.[15] Epidemiology reported prevalence's of 37–53% of chronic HF patients to have OSA.[29,30] In the sleep health heart study (SHHS), risk-adjusted prevalence of HF with baseline OSA and an AHI ≥11 increased 2.38-fold relative to those without OSA.[31] In patients with HF, OSA confers an increased risk of death independently known risk factors.[32] There are limited data in Asia that looks at the prevalence and association of HF with OSA.

Arrhythmias

OSA is involved in multiple arrhythmogenic mechanisms. Apnea and hypoxia predispose to vagally mediated bradycardic responses and atria-ventricular blocks during sleep.[15] There are also exaggerated intrathoracic pressure oscillations which distend the atria and cause increased cardiac wall stress.[33] Several cross-sectional and case–control studies found significantly increased the prevalence of AF and other arrhythmias in OSA patients, with up to 4-fold higher odds between OSA and AF.[34,35] In a large arrhythmia-free clinical cohort with suspected OSA, nocturnal hypoxemia was independently associated with increased hazard of incident hospitalized AF by 77%.[36] Patients with untreated OSA have a higher risk of the recurrence of AF after successful cardioversion compared to treated OSA patients and those without OSA.[37] Most studies on the relationship of cardiac arrhythmias and OSA were predominantly done in the Western population. The first large study in Southeast Asia that explored the relationship between OSA and cardiac arrhythmias showed increased the prevalence of cardiac arrhythmias among Asian patients with OSA as opposed to those who had primary snoring.[38] However, the prevalence of arrhythmias in OSA patients in this Asian study (8% of OSA patients) is far lower than that of Western counterparts (up to 49% of OSA patients).[39,40] Postulated mechanisms for this include ethnic variations in atrial size, atrial electrophysiological parameters, and cardiac calcium ion channels.[41] Further, Asian studies should be conducted to ascertain if ethnicity affects arrhythmogenesis in OSA patients.

Cerebrovascular Disease

Large prospective cohort studies suggest that OSA increases the risk for stroke, after adjusting for confounding risk factors including hypertension.[42-45] The risk of ischemic stroke is reported to increase by 6% with every unit increase in baseline AHI from 5 to 25.[42] A study of patients with acute stroke demonstrated that obstructive apnea persisted despite neurologic recovery, suggesting that the OSA may have predated the development of stroke.[46] Among those who survive stroke, OSA is associated significantly with a lower cognitive and functional status.[47] Data from Taiwan report sleep apnea as a risk factor for stroke, with women at a higher risk than men, and younger women at higher risk than older women.[45] This is contrary to findings of the meta-analysis that suggests males with OSA are at significantly higher risk than women to develop stroke.[48]

Continuous Positive Airway Pressure Therapy (CPAP) Treatment and its Impact on Cardiovascular Outcomes

CPAP is known as the first line and mainstay therapy for adults with OSA. The CPAP machine generates a positive pharyngeal transmural pressure so that the intraluminal pressure exceeds the surrounding pressure, hence, preventing upper airway collapse. With evidence to suggest causal relationship between OSA and cardiovascular disease, there is a need to review if CPAP therapy can reduce cardiovascular morbidity and mortality.

With regard to hypertension, a meta-analysis of randomized controlled trials showed that CPAP reduces systolic BP (SBP), diastolic BP (DBP), and nocturnal BP in patients with OSA.[49] Mean net change in SBP for those treated with CPAP compared with control was −2.46 mmHg (95% confidence interval (CI): −4.31–−0.62); mean net change in DBP was −1.83 mmHg (95% CI: −3.05–−0.61); and mean net change in mean arterial pressure was −2.22 mmHg (95% CI: −4.38–−0.05). Similar improvements in BP were seen in OSA patients who had resistant hypertension. After CPAP, 24 h ambulatory SBP and DBP were −4.78 mmHg (95% CI: −7.95–−1.61) and −2.95 mmHg (95% CI: −5.37–−0.53), respectively. CPAP was also associated with reduction in nocturnal DBP (−1.53 mmHg, 95% CI, −3.07–0).[50]

When looking at cardiovascular events as a whole, there are multiple observational studies to suggest that CPAP may reduce the risk of fatal and non-fatal cardiovascular events and CPAP in OSA patients.[51-54] The sleep apnea cardiovascular endpoints (SAVE) study is a randomized multicenter trial which recruited patients with cardiovascular disease and moderate-to-severe OSA from China and Western countries.[55] Patients were randomized to CPAP versus usual care. Primary endpoint was a composite of

death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, HF, or transient ischemic attack. Patients using CPAP reported less daytime sleepiness and improved quality of life as expected. However, it did not show to have statistically significant benefit on primary composite endpoints, despite reducing AHI from 29 to 3.7 events per hour per night. A concern was that on average, patients assigned to the CPAP arm used it for about 3.3 h instead of ideal 4 h or more, and there is a possibility that increased adherence may improve treatment benefit. When a subgroup analysis was performed for patients who were adherent to CPAP therapy, it showed a lower risk of stroke in patients who were adherent. Despite that, the CPAP adherence achieved in the SAVE trial is likely to reflect "real world" clinical experience where CPAP is used 3–3.5 h per night on average.[55]

A meta-analysis of 10 randomized trials of patients with OSA, compared with no treatment or sham, also showed that CPAP did not result in a reduction in the risk of MACEs (acute coronary events, stroke, or vascular death) or all-cause death.[56] Plausible reasons for these findings include non-adherence to therapy and short follow-up duration of most trials giving insufficient time for CPAP to have affected vascular outcomes.[56] Poor adherence was common to all large clinical trials with cardiovascular end points.[15]

Barriers to CPAP Therapy

Non-adherence to CPAP is a major issue limiting its benefits.[51,55] Adherence is defined as using CPAP >4 h per night on >70% of nights, as this is the minimum duration required to experience reduction in daytime somnolence and neurocognitive function. There is a high rate of CPAP rejection in Singaporean patients with OSA.[57] The overall non-adherence rate in studies done in a time frame of 20 years was 34.1% with no improvement over the years.[58] Cost of therapy, discomfort with mask and difficulty breathing through the nose, insomnia, and other psychosocial factors are associated with non-adherence.[59] Individualized strategies to improve adherence rates should be employed.[59]

Other Treatments

Alternative treatments for OSA include oral appliances and surgical therapy. Oral appliances work by increasing the dimensions of the upper airway, hence, reducing its collapsibility, and maintaining patency. Patients consider them to be a more acceptable treatment modality compared to CPAP,[60] as they are quiet, portable and do not require a power source.[61] A large randomized trial comparing CPAP and oral appliances demonstrated CPAP to be superior in terms of AHI reduction, but self-reported compliance with oral appliance treatment was higher.[62] There are data to suggest that oral appliances can reduce awake mean SBP and DBPs, with the peak effect (approximately 3 mmHg) noted during the late sleeping period and early morning.[63] However, there are currently no randomized trials comparing cardiovascular morbidity between CPAP and oral appliance treatment,[62,64] and comparative efficacy data with long-term follow-up for cardiovascular endpoints are lacking.[62]

Upper airway surgery as the treatment for OSA is generally considered for patients who have failed CPAP or oral appliances therapy and appears to be most effective in those with a surgically correctable lesion obstructing the upper airway.[65] Surgical outcomes depend on the pattern of upper airway obstruction.[66] Surgical treatment seems to improve outcomes such as snoring and daytime sleepiness in patients appropriately selected, but there is limited evidence on improving cardiovascular outcomes.[67] Higher level evidence with outcome measures that evaluate treatment effectiveness will be necessary to advance the field; however, it is acknowledged that there are methodological challenges, particularly in the field of surgery.[12,67]

Conclusion

OSA is prevalent in Asian populations despite the lower prevalence of obesity as compared to Caucasian counterparts. There is increasing evidence that the effect of OSA on cardiovascular diseases is significant in the Asian population and is associated with poorer outcomes. Most studies investigating the impact of CPAP and alternative OSA treatment options are from the Western population. Further, research on OSA treatment and its impact on cardiovascular outcomes, particularly in the Asian context, is essential. Given that, craniofacial features play a key role in Asian OSA, there could be a larger role for surgical treatment as well.

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Review Article

Contribution of Hypertension to Chronic Kidney Disease

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Abstract

Hypertension is one of the most prevalent chronic diseases worldwide and is a major risk factor for a decline in kidney function in patients with diabetic and non-diabetic kidney diseases. Conversely, patients with chronic kidney disease (CKD) inevitably develop hypertension during the course of the disease. Hypertension causes loss of autoregulation of afferent arterioles which leads to transmission of high systemic blood pressure to the glomeruli resulting in glomerular ischemia and subsequently glomerulosclerosis. Achieving optimal blood pressure control remains an integral component in the care of managing patients with CKD and is relevant at all stages of the disease irrespective of the underlying etiology. Blood pressure targets should be individualized based on age, comorbidities, and presence of proteinuria. Lifestyle changes notably sodium restriction should be implemented in all patients in addition to the antihypertensive therapy. Blockers of the renin-angiotensin-aldosterone system should be the agents of choice in the treatment of hypertension in CKD because of their antiproteinuric and renoprotective effect.

Key words: Hypertension, chronic kidney disease, proteinuria, blood pressure monitoring, nephrosclerosis, cardiovascular diseases

Introduction

The incidence of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) is on a rise worldwide.[1] The prevalence of CKD varies across countries in Asia but tends to be higher in rural areas.[2] In the COBRA-BPS trial, the overall prevalence of CKD was found to be highest in Sri Lanka (58.3%), followed by Bangladesh (36.4%) and Pakistan (16.9%).[2] One of the independent factors that was associated with the higher odds of developing CKD in this study included uncontrolled hypertension. A cross-sectional survey in China revealed that 71.2% of prevalent hypertensive patients have CKD and demonstrated the relationship between poor blood pressure control and worsening stages of CKD.[3] It is well established that hypertension is intimately associated with worsening kidney function in both diabetic and non-diabetic nephropathies.

Clinical Epidemiology of Hypertensive Kidney Disease

Estimating the true prevalence of CKD and eventually ESKD attributable to hypertension alone is difficult. First, the rate of progression of CKD secondary to hypertensive kidney disease is slow and decades-long of follow-up is required to appreciate the temporal evolution of kidney function.[4] Individuals with clinically presumed hypertensive kidney disease are rarely subjected to a kidney biopsy.[5] The 2017 US Renal Data System (USRDS) Annual Data Report alluded that the clinical judgment used by nephrologists on establishing the etiology of ESKD could be quite variable; only a small proportion of patients listed to have ESKD secondary to hypertensive nephrosclerosis on financing administrative forms fulfilled the clinical criteria established by Schlessinger and the ASSK trial investigators for hypertensive kidney disease.[6] The criteria require clinical evidence of end-organ damage from hypertension on cardiac imaging, urine protein studies, history of uncontrolled blood pressure preceding kidney dysfunction, and absence of immune-mediated diseases or diabetes mellitus. In yet another study, <½ of patients clinically diagnosed with hypertensive nephrosclerosis were found to have histological evidence of nephrosclerosis on their kidney biopsies.[7] Nephrosclerosis is also a non-specific finding on kidney biopsies which can be caused by pathologies other

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than hypertension.[4] Moreover, these older patients often have concomitant diabetes mellitus contributing to cardiovascular diseases, and etiology of ESKD is multifactorial.[8] Hypertension is cited as the third most common etiology of ESKD locally, after diabetes mellitus and glomerulonephritis.[9]

Regardless of adjudication bias in kidney disease causation, the connection between blood pressure control and the risk of worsening nephropathy has been demonstrated in multiple studies. In a 15-year follow-up study of approximately 12,000 hypertensive individuals at Multiple Veteran Affairs centers in the USA, the odds for CKD were incremental from 2.8 for pre-treatment systolic blood pressure (SBP) of 166–180 mmHg and 7.6 for pre-treatment SBP of >180 mmHg[10] compared to a pre-treatment SBP of >140 mmHg. Importantly, a decrease in SBP by >2 mmHg after treatment was associated with a marked relative risk reduction (RR) in developing ESKD (RR of 0.65 for a decrease in SBP level 2–15 mmHg, RR 0.56 for a decrease of 15–20 mmHg, and 0.39 for a decrease >20 mmHg); findings consistent with that from the multiple risk factor intervention trial involving 12,000 patients which was conducted a year later.[11] Despite individuals with baseline CKD being excluded from the trial, the investigators found that elevation of either systolic or diastolic blood pressure one standard deviation above the range in the lowest group was associated with a 1.7-fold increased risk of developing ESKD.

Pathophysiology of Nephropathy Contributed by Hypertension

The pathogenic determinants of hypertensive kidney damage include systemic blood pressure "load," the degree to which it is transmitted to the renal microvasculature, and the local tissue susceptibility to any given degree of barotrauma.[12]

Systemic BP Load and its Transmission to Renal Microvasculature

Chronic hypertension contributes to loss of afferent arteriolar autoregulation with subsequent transmission of high systemic blood pressure to the glomeruli. Under normal conditions, renal blood flow varies minimally within a broad range of systemic mean arterial pressure (MAP) (80–160 mmHg).[13] Increase in blood pressure within this range leads to proportionate autoregulatory vasoconstriction of the preglomerular vasculature, thereby maintaining the renal blood flow and glomerular hydrostatic pressure relatively constant. This serves as a protective adaptation in chronic hypertension, and hence, in a vast majority of patients with hypertension, the glomerular capillaries are still protected from barotrauma and significant proteinuria is not seen.[14,15] In contrast, when blood pressure exceeds a critical threshold as in the case of malignant hypertension, there is acute vascular injury which compromises the autoregulatory response of glomerular vasculature, further amplifying the degree of kidney damage.[16,17] Proteinuria, hematuria, and rapid loss of kidney function ensue.[15]

Kidney damage can also occur with blunting of the autoregulatory mechanism of glomerular vasculature. This leads to enhanced transmission of elevated systemic pressures to the renal microvasculature.[12] Significant preglomerular vasodilatation, as observed after a unilateral nephrectomy or in early type 1 diabetes, results in a greater fractional transmission of the ambient systemic pressures.[18] If the renal autoregulation is intact, only a modest increase in the vulnerability to hypertensive injury is expected and a benign course of nephropathy follows.[18] However, if renal autoregulation is additionally impaired, the susceptibility to hypertensive injury is markedly enhanced with a greatly reduced BP threshold for damage primarily, leading to accelerated glomerulosclerosis.[14,19] This phenomenon is seen in the rat 5/6 ablation model which mimics the progressive kidney failure after loss of renal mass in humans.[20] Brenner *et al.* used this model to formulate the concept of glomerular hyperfiltration injury which is caused by increase in the glomerular capillary plasma flow rate and mean capillary hydraulic pressure, secondary to the adaptive reduction in pre- and post-glomerular arteriolar resistances.[15]

Genetic Determinants of Tissue Susceptibility

The theory on the genetic variants of APOL1 being strongly associated with kidney disease including hypertension-attributed CKD has received much emphasis recently.[21] In African-Americans, the rate of CKD progression to ESKD secondary to hypertensive nephrosclerosis, focal segmental glomerulosclerosis (FSGS), and HIV-associated nephropathy (HIVAN) is higher compared to European-Americans.[22] This can be attributable to the two protein-changing alleles of the APOL1 gene, namely the APOL1 G1 allele and APOL1 G2 allele. APOL1 high-risk genotypes are defined as two risk alleles in any combination (homozygous G1/G1, homozygous G2/G2, or compound heterozygous G1/G2).[23] More than 50% of African-Americans carry at least one risk allele.[23] High-risk genotypes were found in African-Americans with FSGS and HIVAN (72%) and hypertension-associated ESKD (44%) compared to 12–14% in healthy controls.[23] Compared to individuals carrying APOL1 low-risk genotypes (0 or 1 risk allele), the odds ratio for these diseases in carriers of high-risk genotypes is 17 for FSGS, 29 for HIVAN, and seven for hypertensive nephrosclerosis.[24] The APOL1 protein is expressed within the glomerular podocytes and arteriolar endothelial cells in normal kidney and within glomerular arterioles and interlobular arteries in FSGS and HIVAN.[25] It has been speculated that APOL1 expression in the arterial wall could have a biologic role in the pathogenesis of hypertensive kidney disease by altering cellular physiology promoting arteriosclerosis as it is a lipid-binding protein.[21]

Blood Pressure Control and Progression of CKD

The kidneys play a key role in long-term blood pressure regulation. In his seminal experiments using isolated perfused kidneys, Guyton demonstrated that an acute rise in blood

pressure results in a brisk increase in renal sodium excretion and subsequent loss of extracellular fluid and overall blood pressure reduction.[26] Due to a decrease in the number of viable nephrons and abnormal kidney tubular function in CKD, sodium excretion is affected, and hence, the usual diuretic response seen in pressure natriuresis is blunted. This leads to worsening hypertension in CKD and observation of increasing prevalence of salt-sensitive hypertension as kidney function declines. Salt sensitivity is an inability of the kidney to respond appropriately to high sodium load and often results in uncontrolled hypertension.[27] It is observed more frequently in the elderly, patients with progressive CKD, certain genetic abnormalities, and African-Americans.[28]

The second key player in CKD-related hypertension is the increased activity of the renin-angiotensin-aldosterone system (RAAS).[29] The kidneys secrete renin in response to decreased renal perfusion, leading to an increase in angiotensin-2 which causes a host of vascular responses including direct vasoconstriction, aldosterone secretion, and increase in sympathetic activity. In polycystic kidney disease, the compression of renal vasculature by enlarging cysts causes the activation of the RAAS system resulting in hypertension.[30] Treatment of such cases with bilateral nephrectomy or inhibitors of RAAS has been shown to result in control of blood pressure, suggesting failing kidneys as the source of excess renin.[31]

Other factors proposed to explain increased vascular resistance in CKD include the increased production of endothelin and endogenous digitalis-like substance, reduced generation of vasodilators such as nitric oxide and kinins, and imbalance between the vasodilator and vasoconstrictor prostaglandins.[29] Lastly, medications used commonly in CKD, in particular, erythropoiesis-stimulating agents have been associated with the long-term side effect of hypertension, possibly the result of increased hematocrit and blood viscosity. There has also been some evidence that it is in part due to vascular production of thromboxane, a vasoconstricting prostaglandin.[29] Normal physiology allows nitric oxide vasodilation to offset prostaglandin-induced hypertension.[29] However, this response is impaired in CKD.

Management of Hypertension in CKD

General Rules

The latest guideline from the Joint National Commission VIII on management of hypertension recommends a blood pressure goal of <140/90 mmHg for patients with CKD aged between 18 and 60 years.[32,33] However, it is questionable as to whether this target is applicable to all patients with CKD.[27] The safety of intensive blood pressure lowering in CKD patients older than 70 years, who have been largely excluded from clinical trials examining the benefit of blood pressure control, is not yet established.[27] The systolic hypertension in the elderly program has shown that the treatment of systolic hypertension to a mean target of 143 mmHg as achieved in the active treatment group, reduced morbidity and mortality. However, this trial excluded patients with renal dysfunction. It has been recognized that target SBPs are harder to attain in older participants in whom widening of pulse pressure may occur when diastolic blood pressure levels are lowered in the course of treatment.[34] Since patients with CKD tend to be older and have more cardiovascular risk factors, it is advisable to individualize treatment in patients according to their age and comorbidities.

SPRINT trial investigated the effect of two different SBP treatment goals (target SBP <120 mmHg in the intervention arm vs. <140 mmHg in controls). The primary outcome was a composite of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, or death from cardiovascular causes.[35] There was a significant improvement in the primary composite outcome with more aggressive blood pressure control. However, this was at the expense of a higher incidence of acute kidney injury with electrolyte abnormalities, syncope, and bradycardia. In a subgroup analysis of patients with CKD, there was no significant difference in incident albuminuria or the rate of CKD progression between the two groups. Several limitations of the SPRINT trial have been identified. Patients of East Asian ethnicity contributed to only a minority of study subjects (<2%). This limits the applicability of trial results to the Asia-Pacific region. The baseline blood pressure for the participants in both the intensive treatment and standard treatment groups was approximately 139/78 mmHg. The blood pressure in the trial was also measured using the automatic oscillometric method which is usually lower than the auscultatory SBP measurement by 5–10 mmHg. Hence, a target of an SBP of <120 mmHg was easily attained.

Non-pharmacologic (lifestyle changes) and combined pharmacologic treatments are both necessary to achieve the target blood pressure.[36] Sodium restriction is an important adjunct to all medication regimens for CKD patients with hypertension. In a randomized trial involving patients with CKD Stages 3–4 and poorly controlled hypertension, a low-sodium diet (100 mmol/day that translates to 2.4 g sodium per day or 6 g of salt per day) was associated with substantial reductions in BP (decrease in SBP by 9.7 mmHg and diastolic BP by 3.9 mmHg), the need for antihypertensive medications, and extracellular volume.[37] The magnitude of change was more pronounced compared to patients without CKD, suggesting that patients with CKD are particularly salt sensitive. The KDOQI guideline on hypertension in patients with CKD in 2004 recommends limiting sodium intake to 2.4 g/day (i.e., 6 g of salt) in patients not on dialysis.[33] This recommendation is a notable dietary restriction, as a no-added-salt diet already contains roughly 4 g sodium which exceeds the amount that a patient with CKD can excrete irrespective of diuretic administration. Sodium intake is reduced in a low-protein diet as a consequence of the selection of low-sodium foods, which results in a better-controlled BP; however, this has to be balanced against the risk of malnutrition in CKD patients.

Blockers of the RAAS system are preferred for their antiproteinuric effect as a result of decreasing systemic and intraglomerular pressure. Dual blockade with ACE inhibitors

(ACEI) and angiotensin receptor blockers (ARB) reduces the proteinuria to a greater degree than either class alone but has not been proven to preserve renal function or improve cardiovascular outcome.[38] Of note is the increased risk of syncope, hyperkalemia and acute kidney injury observed in the 2008 Ongoing Telmisartan Alone and in Combination with Rampiril Global Endpoint Trial (ONTARGET).[39] In a meta-analysis that included 11 randomized clinical trials in adult CKD patients, the addition of non-selective aldosterone antagonists together with ACEi or ARB significantly reduced proteinuria, but this did not translate into a longitudinal improvement in kidney function and there was a significantly higher risk of hyperkalemia.[40]

Diuretic therapy combined with RAAS blockade is preferred in CKD with manifest edema.[36] Thiazide diuretics may lose their effectiveness with advanced CKD and can be replaced by loop diuretics in the latter. The primary site of action for thiazides is the Na+/Cl- cotransporter in the distal convoluted tubule of the nephron, which is responsible for only 5% of total filtered sodium reabsorption. With impaired glomerular filtration and reduced filtration of sodium, it is presumed that distal diuretic therapy alone becomes insufficient. Potassium-sparing diuretics including aldosterone receptor antagonists such as spironolactone and eplerenone typically maintain their therapeutic effectiveness in the more advanced stages of CKD because their effect does not require tubular entry and, hence, independent of glomerular filtration and tubular secretion.[36] However, they should be used with caution due to hyperkalemic risk in advanced CKD.

CKD with Proteinuria

The KDIGO 2012 guidelines recommend a target blood pressure of <130/80 mmHg for patients with albuminuria.[34] In *post hoc* and subgroup analyses of the modification of diet in renal disease (MDRD) and The African-American Study of Kidney Disease and Hypertension (AASK) studies, a target MAP of 92 mmHg was associated with a slower decline in kidney function in patients with proteinuria of >0.3–1 g/day.[35,36] The Steno-2 study showed a reduced risk of cardiovascular disease with a blood pressure target of 130/80 mmHg compared to 135/85 mmHg in patients with Type 2 diabetes and microalbuminuria.[37]

Most clinical trials have established the renoprotective impact of ACE inhibitors and angiotensin receptor blockade in the management of patients with proteinuria, especially in diabetic kidney disease. Treatment with captopril was shown to retarded the progression of microalbuminuria to overt proteinuria and of overt nephropathy to ESKD in patients with Type 1 diabetes mellitus.[41,42] Irbesartan and losartan have been demonstrated to reduce the risk of progression of kidney disease in patients with type 2 diabetes mellitus.[43,44] The Irbesartan in Diabetic Nephropathy Trial assessed the renoprotective effects of adding irbesartan, amlodipine, or placebo to standard blood pressure-lowering regimen in type 2 diabetics with proteinuria. The primary composite end point was a doubling of the baseline serum creatinine concentration, the development of end-stage renal disease, or death from any cause. Treatment with irbesartan was associated with a significantly lower risk of primary composite end point, despite comparable blood pressure attainment in all arms.

CKD without Proteinuria

The benefit of tighter blood pressure control (<140/90 mmHg) and the use of RAAS blockade in non-proteinuric nephropathy are not well established.[27] The AASK trial was a randomized trial comparing the effects of two levels of blood pressure control and three antihypertensive drug classes on the kidney function decline in hypertension.[45] The average blood pressure achieved in the low blood pressure group and usual blood pressure group was 128/78 mmHg and 141/85, respectively. Ramipril appeared to be more effective than amlodipine or metoprolol in decreasing the composite secondary outcome of worsening kidney function. The trial also showed that in patients with negligible proteinuria, a usual blood pressure goal had a more favourable effect toward the change in eGFR from baseline compared with a lower blood pressure goal. This is consistent with the findings from the MDRD study that largely involved non-diabetic patients and compared the effect of intensive (MAP 92 mmHg) versus usual blood pressure (MAP of 107 mmHg) control in eGFR decline.[46] There was no difference seen between these two groups. In summary, current available evidence is inconclusive with regard to the benefit of aggressive BP lowering in the treatment of non-proteinuric kidney disease.

Conclusion

Hypertension can be both a cause and consequence of CKD. Understanding the factors that are involved in the pathogenesis of hypertension-induced renal damage forms the platform for targeted therapy to retard the progression of kidney disease. Blood pressure goals and treatment therapy should be individualized with respect to the age group of patients, severity of proteinuria, and presence of cardiovascular comorbidities. The benefits of RAAS blockade agents in CKD with overt proteinuria have been widely demonstrated. These agents should be the treatment of choice for hypertension in patients with proteinuric kidney disease, with caution exercised in cases of more advanced CKD due to competing risks of hyperkalemia and acute kidney injury.

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