International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR)
ISSN: 2582-7618 (Online), Volume-3 Issue-3, April 2023

Management of Hypertension: Clinical Relevance and Perspective

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Abstract: ***Hypertension, sometimes referred to as the "silent killer," is a serious and global public health issue. This review article provides an in-depth examination of the epidemiology, pathophysiology, diagnosis, complications, and therapeutic approaches related to hypertension. We investigate the prevalence of hypertension in various demographic groups, as well as the underlying mechanisms, risk factors, and effects it has on different organ systems. We also review the importance of a precise diagnosis, including methods for measuring blood pressure and established diagnostic standards. We also explore the complex field of hypertension management, which encompasses pharmaceutical interventions, lifestyle modifications, and emerging therapeutic approaches. The purpose of this thorough review is to help healthcare practitioners better understand and treat hypertension. Management of hypertension typically involves a combination of lifestyle modifications and medication. Lifestyle changes may include adopting a healthy diet (such as the DASH diet), regular exercise, maintaining a healthy weight, reducing sodium intake, limiting alcohol consumption, and managing stress. Medications, such as diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, calcium channel blockers, and others, may be prescribed depending on the individual's blood pressure levels and other medical conditions. Individuals with hypertension need to work closely with their healthcare provider to develop a personalised treatment plan. Hypertension is a significant and costly public health problem. It is a major, but modifiable, contributor to the development of cardiovascular disease. Randomized controlled trials have shown that controlling hypertension reduces the risk of stroke, coronary artery disease, congestive heart failure, end-stage renal disease, peripheral vascular disease, as well as overall mortality. The risk of developing these hypertension-related complications is continuous, starting at a blood pressure level as low as 115/75 mm Hg. Despite the inherent health risks associated with uncontrolled hypertension, elevated blood pressure remains inadequately treated in the majority of patients. This article reviews guidelines for optimal evaluation of hypertension and current therapeutic options available to combat this common yet pervasive disease.***

Keywords: Hypertension, High Blood Pressure, Epidemiology, Aetiology, Pathophysiology, Complications, Diagnosis, Management Strategies.

Manuscript received on 15 February 2023 | Revised Manuscript received on 08 March 2023 | Manuscript Accepted on 15 April 2023 | Manuscript published on 30 April 2023.

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I. INTRODUCTION

Hypertension, commonly referred to as high blood pressure, is a prevalent and significant global health issue characterised by elevated systemic arterial pressure. It is a major risk factor for various cardiovascular diseases, including coronary artery disease, stroke, heart failure, and peripheral vascular disease, contributing to significant morbidity and mortality worldwide. Hypertension affects individuals of all ages and socio-economic backgrounds and is a leading cause of premature death and disability-adjusted life years (DALYs) globally. According to the World Health Organization (WHO), hypertension is estimated to affect over one billion people worldwide, with the number expected to rise further due to population aging and increasing prevalence of risk factors such as obesity and sedentary lifestyles. The consequences of uncontrolled hypertension are far-reaching, affecting multiple organ systems including the heart, kidneys, brain, and blood vessels. Chronic hypertension leads to structural changes in the arterial walls, endothelial dysfunction, and vascular remodelling, predisposing individuals to atherosclerosis, aneurysms, and other vascular complications.

Accurate diagnosis and effective management of hypertension are crucial for preventing associated complications and improving long-term outcomes. However, hypertension often remains undiagnosed or poorly controlled, highlighting the need for enhanced awareness, screening, and comprehensive management strategies. This review aims to provide a comprehensive overview of hypertension, covering its epidemiology, pathophysiology, diagnosis, complications, and management strategies, thereby better equipping healthcare professionals to address this pervasive public health challenge [1]. Elevated resting blood pressure (BP) increases the risk of developing CVD, heart failure, stroke, and renal disease. Research indicates that this applies to individuals of various ages, races, nationalities, and genders [2]. Elevated blood pressure can be caused by a variety of factors, including physical inactivity, smoking, excessive alcohol consumption, and an imbalanced diet (high sodium, low potassium, and limited fruit and vegetable intake) [3-7]. While quitting smoking, increasing physical activity, and reducing alcohol consumption can reduce SBP and DBP, this study focuses on the role of dietary changes in preventing and managing hypertension (HTN). Consequently, the authors refer to prior reviews on how various healthy living practices can lower blood pressure [8]. The Western diet is high in sodium, saturated fats, and sugar, and has a low intake of fruits, vegetables, whole grains, and omega-3 fatty acids. This has serious

ramifications for the cardiovascular health of developed countries [9]. Key lifestyle patterns include an increasing consumption of foods and drinks at restaurants, ready-to-eat meals, and convenience snacks at home. Large portion sizes have led to higher intakes of sodium and energy-dense foods (kcal/g), including those with high fat content, processed carbohydrates, added sugar, sugary sweetened beverages, and inadequate intake of fruits and vegetables. As the food environment becomes increasingly obesogenic, individuals' eating habits may adjust to a low 'nutrient-dense' diet. The prevalence of CVD risk factors rapidly follows [10]. Although lifestyle choices can cause chronic high blood pressure and HTN is preventable or treatable for most people, there has been little progress in reducing its prevalence across populations. Therefore, major health organisations emphasise the importance of early detection and promotion of good lifestyle behaviours in preventing HTN. Several recent studies confirmed the importance of achieving perfect 24-h BP control. Out-of-office BP values, measured by home BP monitoring or ambulatory BP monitoring (ABPM), are superior to office BP values for predicting an individual's cardiovascular prognosis, among both hypertensive patients and community-dwelling populations.4–9 'Perfect 24-hr BP control' that would minimize the risks of organ damage and cardiovascular events that are presented by hypertension can be defined as the achievement of the following three components of out-of-office BP, as illustrated in Figure 2: 1. The average of 24-h BP levels of o130/80 mm Hg, 2. Normal circadian rhythm, that is, adequate dipping of nocturnal BP (that is, the dipper-type) and 3. Adequate BP variability (that is, morning BP surge of 45 mm Hg). .10,11 Component (1) regarding 24-h BP levels concerns the quantity of BP control, and components (2) and (3) concern the quality of BP control. The best clinical method to assess each of these BP components is ABPM.

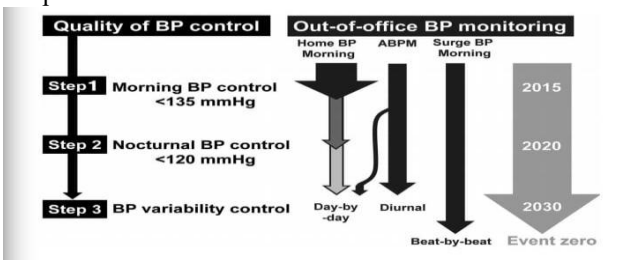
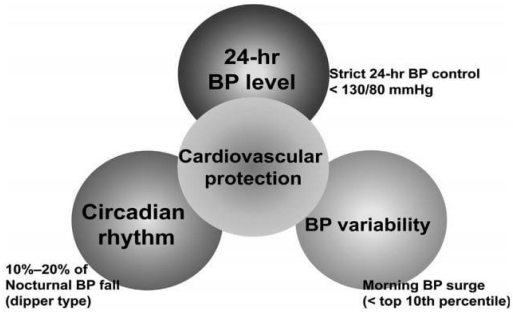


Figure 1. Perspectives on the ICT-based strategy for the 24-h management of hypertension for 'zero cardiovascular events.' Morning BP management as the first step, nocturnal BP management as the second step, and finally BP variability control within the adequate range may be a promising direction for a practical approach to the 24-h management of hypertension. This pragmatic approach would be achieved by advances in ICT and the BP monitoring device. 'Surge BP monitoring' is beat-by-beat BP monitoring in the initial experimental stage of development (Kario3).

The 24-h BP level. The 24-h BP (that is, the average of BP values over a 24-h period) is more closely associated than office BP with hypertensive organ damage and the risk of future cardiovascular events. The definition of '24-h sustained hypertension' is an average of 24-h BP values ⩾ 130/80 mm Hg. 'Daytime hypertension' is defined as an average of daytime BP values ⩾135/85 mm Hg. 'Nocturnal hypertension' is defined as an average of nocturnal BP values ⩾120/70 mm Hg. Each of these hypertension definitions is regardless of an individual's office BP data. ABPM is the gold standard for obtaining 24-h BP data without the white-coat effect, because it automatically measures BP values (that is, without the presence of healthcare personnel who would induce the white-coat impact). Systolic versus diastolic BP. Regarding systolic versus diastolic BP, it has been demonstrated that high 24-h SBP is more important as a risk of cardiovascular event occurrence, especially in the elderly,12–14. In contrast, high 24-h diastolic BP presents a greater risk of coronary events in younger adults.15 In our prospective investigation of 958 elderly hypertensive Japanese subjects, the Jichi Medical University ABPM (JMU-ABPM) Study, we observed that each 10 mm Hg increase in 24-h SBP accounted for a ~ 40% increase in the rate of cardiovascular events.

White-coat hypertension. Although 'white-coat hypertension' (defined as office BP 4140/90 mm Hg and normotension for 24-h BP as o130/80 mm Hg) presents a lower risk of cardiovascular events than other types of hypertensions,13,16 it may worsen to the point of becoming sustained hypertension17 and contribute to the development of diabetes,18 eventually resulting in increased cardiovascular risk. Two BP measurement methods can help exclude the white-coat effect in clinical practice: home BP monitoring and automated office BP (AOBP) monitoring, which measures a subject's BP automatically as they sit in a quiet room without the presence of medical staff. It was found that compared to standard doctor-measured office BP, AOBP values are generally lower by 5–10 mm Hg (systolic), and the AOBP values are more closely related to left ventricular hypertrophy and to the risk of cardiovascular events.19 The SPRINT protocol used AOBP measurements rather than doctor-measured office BP data. The threshold for hypertension in AOBP data is 135/85 mm Hg.



[Fig.2. Triad of Perfect 24-h Blood Pressure Control]

Masked hypertension, a subtype of hypertension. Untreated 'masked hypertension' is defined as the presence of normotensive office BP (o140/90 mm Hg) plus hypertensive 24-h BP (4130/80 mm Hg). The cardiovascular risk that accompanies untreated masked hypertension is similar to that from sustained hypertension.16,21 Masked hypertension should thus be considered a subtype of hypertension, and it should be treated. The control of 24-h SBP to 135 mm Hg is essential for reducing the risk of cardiovascular events

among medicated hypertensive patients.22 Among patients with uncontrolled 24-h SBP (⩾135 mm Hg) but well-controlled office SBP (o140 mm Hg), the incidence of cardiovascular events during a 5-year median follow-up was greater than the incidence in patients with 24-h SBP 135 mm Hg and office SBP ⩾ 160 mm Hg 22 Morning hypertension as the first target for BP control The morning is the most risky time of the day for hypertensive individuals. It is in the morning that cardiovascular events occur most frequently. The BP-lowering effect of antihypertensive medication is the weakest in the morning, just before a hypertensive patient takes a once-daily morning pill.10,23 Controlling an individual's morning BP is thus the first target for achieving perfect 24-h BP control. We first defined 'morning hypertension' as morning BP ⩾135/85 mm Hg regardless of an individual's office BP values.23,24 Morning BP appears to be more closely related to sympathetic nervous activity than the BP levels of other periods. Thus, morning BP has been effectively reduced by catheter-based renal denervation and by bedtime dosing of an alpha-blocker, doxazosin: 25,26.

The morning SBP values obtained using ABPM are calculated as follows:

- Morning BP = the average of morning BP values recorded during the first two hours after the subject arises, or the values obtained between 0700 and 0900 hours.
- Moving peak morning BP = the highest 1-h moving average of consecutive BP values recorded during the first two hours after the subject arises, or the values recorded between 0600 and 1000 hours.
- Maximum morning BP = the maximum morning BP (a single BP value) during the first three hours after the subject arises or the maximum value recorded between 0700 and 1000 hours.

The 'prewakening nocturnal BP' or 'minimal (or moving prewaking) morning BP' between 0500 and 0900 hours is used to calculate the prewakening morning BP surge. In elderly hypertensive patients, it was shown that among office and ambulatory BP values taken over 24-h periods, morning hypertension (that is, morning BP ⩾ 135/85 mm Hg) was most closely associated with cardiovascular events.24 The dependence of the various components of morning BP on sympathetic nervous activity may differ. The maximum and moving peak morning SBP were significantly reduced, but the minimum morning BP was not changed by renal denervation.

'Morning BP surge' parameters can be calculated as follows:

- Sleep-trough morning surge = the average morning BP value minus the lowest moving nocturnal BP value.
- Prewakening morning surge = the average morning BP value minus the prewakening morning BP value.

II. CLINICAL MANAGEMENT OF ELEVATED BLOOD PRESSURE

The AHA and ACC updated their guidelines for preventing, detecting, evaluating, and managing hypertension, reclassifying resting blood pressure levels. ("Normal": <120mm Hg SBP and <80mm Hg DBP; "Elevated: 120-129mm Hg SBP and <80mm Hg DBP; "Hypertension Stage 1", 130-139mm Hg SBP or 80-89mm Hg DBP; "Hypertension Stage 2", 140mm Hg SBP or 90mm Hg DBP). An extensive literature analysis revealed roughly double the risk, prompting this upgrade.

Individuals with an SBP/DBP of 130-139/85-89mmHg had a higher risk of having CHD and stroke compared to those with a normotensive SBP/DBP (<120/80mmHg) [11]. Clinicians should prioritise lifestyle changes, particularly dietary modifications, to prevent and manage high blood pressure, regardless of pharmacological treatment. Overexposure to fad diets that promise quick weight loss is a typical obstacle to physician endorsement and patient adoption of recommended diets.

There is insufficient scientific evidence to support long-term behavior change through these improvements. Health groups, including the National Heart, Lung, and Blood Institute, the American Heart Association, and the American College of Cardiology, advocate for evidence-based diets for patients. This review will present the expected BP-lowering effects of rigorously validated dietary treatments, rather than refuting popular fad diets.

III. BLOOD PRESSURE-LOWERING EFFECTS OF THE DIETARY APPROACHES TO STOP HYPERTENSION DIET

Recent dietary recommendations for preventing and managing hypertension (HTN) have emphasised the importance of empirical evidence from food consumption. The relationship between food and blood pressure varies depending on the overall dietary pattern. The Dietary Guidelines for Americans [11] and the AHA/ACC/The Obesity Society [12] support a greater emphasis on dietary patterns to assess the nutritional density and quality of a population's "realistic" eating habits [13]. The Dietary Approaches to Stop Hypertension (DASH) diet has been endorsed by health organisations such as the National Heart, Lung, and Blood Institute (NHLBI), the Dietary Guidelines for Americans, and the United States (US) guidelines for treating high blood pressure. Its development was influenced by early observational studies highlighting the relationship between low prevalence rates of HTN and CVD in individuals with eating behaviours that avoid consuming animal products, are low in saturated fat, high in polyunsaturated fat, and low in cholesterol [14]. Adopting a vegetarian diet and limiting red meat consumption has been demonstrated to reduce blood pressure in normotensive and hypertensive individuals [15,16]. The DASH diet focuses on plant-based foods, whole grains, and low-fat dairy products. Compliance with the diet has been demonstrated.

Reduced SBP in HTN by 11 and 3 mmHg in normotensive patients [17,18], comparable to early pharmacologic treatments for HTN [2]. The study randomized adults with SBP <160mmHg and DBP between 80 and 95mmHg to an 8-week control diet (low in fruits, vegetables, and dairy products, with an average fat content similar to the American diet), a diet rich in fruits and vegetables, or a combination diet rich in fruits, vegetables, and dairy products. low-fat dairy products, with reduced saturated and total fat [17]. The combination diet

reduced SBP and DBP by 5.5 and 3.0mmHg, respectively, while the fruits and vegetables diet decreased SBP and DBP by 2.8 and 1.1mmHg, respectively. Participants with HTN (140, 90, or both) at baseline showed a 11.4 and 5.5mmHg decrease in SBP and DBP following the combination diet, compared to the control diet. Individuals without HTN (<140 and 90mmHg) experienced a 3.5 and 2.1mmHg drop in SBP and DBP after the combination diet compared to the control diet. A meta-analysis of the DASH diet (or modified DASH-style dietary patterns) on CVD risk factors found significant decreases in SBP and DBP of 5.2 and 2.6mmHg, respectively, contributing to a 13% reduction in the 10-year Framingham risk score for CVD [19]. Many trials have found that decreasing blood pressure with the DASH diet is adequate under investigator-controlled conditions, such as providing meals and regular dietary counselling. The practicality of obtaining and maintaining BP reductions only through dietary advice is uncertain [20]. Adhering to low-fat diets can be challenging for individuals who have previously followed a Western diet [21]. To address issues, the DASH diet has been modified to allow for different macronutrient compositions. A recent study by Chiu et al [22]. Performed a three-period, 3-week, randomised crossover study in participants with an SBP. The modified DASH diet replaced non-fat and low-fat dairy products with full-fat options and reduced carbohydrate intake by 12%. Both variations of the DASH diet resulted in similar declines in blood pressure. The study found no significant variations in SBP (~4mmHg) or DBP (3mmHg) levels when compared to the control diet. The small sample size and short intervention duration limit the ability to make conclusive recommendations on the modified DASH diet, despite favourable results. Adoption of a DASH-style diet with flexible food choices has been advocated for sociocultural feasibility [23], indicating its applicability to diverse cultures. Changing an individual's diet to a DASH-like pattern can improve long-term adherence and reap similar health advantages as the traditional DASH diet in both non-HTN and HTN patients.

IV. REDUCED SODIUM INTAKE

The average American consumes approximately 3,400 mg of salt per day, exceeding the clinically recommended limit of 2,400 mg [2, 4, 6]. Excessive sodium intake has been linked to an increased risk of stroke (risk ratio 1.24, 95% CI 1.08-1.43), as well as higher mortality risk from stroke (1.63, 95% CI 1.27-2.10) and CHD (1.32, 95% CI 1.13-1.53). High sodium intake may impact cardiovascular health through changes in renal function, fluid volume, fluid-regulatory hormones, vascular function, cardiac function, and the autonomic nervous system [24-28]. However, the exact mechanisms are unknown. Reducing daily salt intake has been shown to effectively reduce hypertension in older, African American, and sodium-sensitive groups [29]. The positive results of the DASH diet intervention on blood pressure led to changes, including a reduction in sodium intake [30]. Sacks et al. studied the impact of three salt intake levels (high 3600mg/day, middle 2300mg/day, and low 1200mg/day) combined with a control diet (average US diet) or regular DASH diet on blood pressure in HTN and normotensive patients. Over 30 days, both the control and DASH diets showed dose-dependent decreases in blood pressure, regardless of sodium intake levels [31]. Participants in the interventions were grouped based on their pre-intervention resting blood pressure levels (<130, 130-139, 140-149, and> 150 mmHg). Lowering sodium consumption from 3600mg/day to 1200mg/day resulted in significant average SBP differences of ~3.2, ~8.56, ~8.99, and ~7.04mmHg across all SBP categories in the control diet. While following the DASH diet, there was no significant trend in mean SBP differences (~4.5, ~4.2, ~4.7, and ~10.6 mmHg) between high and low sodium consumption (P = 0.66). The low-sodium DASH diet demonstrated substantial mean differences compared to the high-sodium control diet across categories (5.3, 7.5, 9.7, and 20.8 mmHg, respectively). Both sodium reduction and the DASH diet have been shown to lower blood pressure, making them effective for preventing and managing hypertension. High-risk groups, including those with heart failure, diabetes, kidney disease, and CVD, should not reduce their sodium intake to 1500mg/day or less, since this has been linked to adverse CVD outcomes [6]. Reducing sodium intake has been difficult for the general population to maintain over time [32,33]. Reducing sodium consumption by at least 1000mg/day has been shown to lower blood pressure effectively [4].

V. POTASSIUM SUPPLEMENTATION

Maintaining electrolyte balance is essential for optimal cardiovascular function and health. Potassium regulates blood pressure by dilating the peripheral vasculature and promoting urinary sodium excretion, thereby helping to maintain normal sodium levels in the circulation [34]. Elevated blood pressure can be caused by both high sodium and low potassium levels. Modifying either component alone can reduce blood pressure [34]. A Western diet high in salt and low in vegetables and fruits can lead to a high sodium-potassium ratio, which has been linked to higher blood pressure levels [35-37]. Increased consumption of fruits and vegetables has been linked to higher urinary potassium levels and lower resting SBP/DBP in healthy individuals (4.4/2.5mmHg in HTN and 1.8/1.0mmHg in non-HTN) [38].

Sodium and potassium have independent effects on blood pressure, but their complicated inverse interactions also affect its biological regulation. Increased potassium consumption has been shown to reduce blood pressure more effectively in those with high sodium intake compared to those with low sodium intake [39]. The most significant impact is seen when sodium intake exceeds 4 g/day [36]. Low salt intake reduces blood pressure when potassium levels are low, and vice versa. There is limited evidence to support the idea that combining a low-sodium and high-potassium diet can improve blood pressure control [29]. While some research suggests that increasing potassium consumption can lower blood pressure, there is inadequate evidence to make recommendations [48].

VI. MEDITERRANEAN DIET

Mediterranean diets are known to promote heart health and reduce the risk of CVD. Individuals may easily identify foods associated with this diet, which typically includes fruits, vegetables, bread, potatoes, beans, nuts, cheese, yoghurt, fish, and lean poultry. Olive oil is the primary source of fat, with a limited intake of red meat and a moderate approach to food and wine consumption. These properties are like the DASH diet, with interventions resulting in BP drops comparable to the traditional DASH diet [2, 22]. A meta-analysis of six investigations with an average follow-up of two years found moderate decreases in both SBP and DBP (<2mmHg) [40]. Although the results were not outstanding, the Mediterranean diet outperformed low-fat diets in terms of blood pressure alterations and other cardiovascular disease risk factors. The studies were not stratified by BP category, which may have resulted in more significant declines in those with greater resting BP.

VII. WEIGHT LOSS

Obesity has become an epidemic in Westernized countries and is linked to high blood pressure. Weight loss has a dose-response relationship with blood pressure, with each kilogram loss resulting in a one mmHg reduction in SBP [49, 50]. Numerous randomized controlled trials have investigated the impact of weight loss on blood pressure by caloric restriction, increased physical activity, or a combination of the two. A meta-analysis of available data indicates a 4.44 mmHg decrease in blood pressure, regardless of the method used for weight loss. Losing 5 kg can lead to lower SBP and DBP of 3.57 mmHg. Losing more than 5 kg of weight can lead to lower SBP and DBP levels (SBP ~6.63 mmHg and DBP ~5.12 mmHg, respectively) compared to losing less than 5 kg (SBP ~2.70 mmHg and DBP ~2.01 mmHg) [41]. Improving the quality of foods consumed, particularly for attaining and maintaining weight loss, is especially important, considering the substantial impacts of decreased blood pressure, even without weight loss [14,17].

VIII. PRACTICAL CONSIDERATIONS

Physicians may struggle to effectively communicate the need for dietary alterations and provide techniques for adhering to specific regimens due to patients' difficulty initiating and maintaining lifestyle changes. Building a multidisciplinary team with specialists from various disciplines is crucial for implementing healthy lifestyle interventions [7]. Several Western eating patterns have been linked to poor cardiovascular health. Many diets have been designed and sold, but lack scientific basis for their efficacy. Experts must provide evidence-based recommendations for particular dietary alterations to achieve desired outcomes. Integrating certified dietitians into clinical settings to offer nutritional recommendations and evaluate the success of BP-lowering therapies has been effective [42, 43]. Using dietitians can be especially beneficial when delivering care in low-income regions or for those with poor socioeconomic status. These traits are associated with limited access to supermarkets, proximity to fast-food restaurants, and financial hurdles that limit the availability of DASH diet-friendly options. Individuals may be less likely to follow the DASH diet compared to those with greater geographic and economic accessibility [44]. Technology is increasingly being used to encourage healthy lifestyle changes and foster transdisciplinary ties within organizations. Digital lifestyle programs, such as the DASH diet, can overcome hurdles to implementing BP-lowering dietary interventions, which were previously limited to paper forms and in-person consultations [45]. Digital initiatives offering coaching and tools for nutritional interventions can significantly enhance health outcomes. A recent study recruited 50 participants to investigate the efficacy of a 24-week mobile HTN prevention program based on the DASH diet. The program included in-app human coaching, biweekly phone calls, food logging, blood pressure tracking, and access to instructional content [46].

Completing the training resulted in a significant drop in both SBP (~ eight mmHg) and DBP (~4 mmHg) for 40 of 50 participants. Digital methods for nutritional behaviour change are becoming increasingly realistic as smartphone penetration increases across demographics [47]. However, further study is needed and lengthier interventions are necessary.

IX. PERSPECTIVES

BP variability is a crucial parameter in anticipation medicine, designed to combat cardiovascular disease. Particularly in high-risk patients with the SHATS, repeated and exaggerated BP variability triggered by some conditions may result in organ damage, and a single massive dynamic BP surge generated by the synergistic resonance of various BP surges at different time phases may trigger a cardiovascular event. In the future, a paradigm shift in the individualised management of cardiovascular disease could be achieved by the development of a BP monitoring device with an ICT-based real-time feedback system. Artificial intelligence-based anticipation medicine is another promising approach to achieving the goal of personalised medicine with zero cardiovascular events.

X. MATERIAL AND METHODS

A. Primary Screening

i. Determination of Ld50 Values:

The primary screening of all compounds began with the determination of the approximate lethal dose to 50% of animals (LD50) and the effect of the test compound on Blood pressure (BP) of anaesthetized normotensive dogs and cats.

To determine the LD50 values, albino mice (20-50g) of either sex (Haffkine inbred strain) were used. As a rule, all experiments began at 0930 hours, to minimise any possible vitiation of the results due to changes in the circadian rhythm (Reinberg and Halberg, 1971) and room temperature. The ambient temperature ranged from 28 °C to 30 °C. The compounds were injected intraperitoneally (IP) as a suspension in 1% aqueous gum acacia (vehicle) if they were not water-soluble. The test doses varied from 10 to 800 mg/kg. The LD50 values were calculated from the percentage mortality produced by each dose of the compound at the end of

24 hours (Litchfield and Wilcoxon, 1949; Trwin, 1962; Dhawna, 1976). Each group consisted of 4 mice, and the control group received the vehicle. The onset, peak, duration, characteristics and intensity of the drug action were closely observed and recorded at regular intervals. The results are expressed by computing the data obtained in semiquantitative and more or less arbitrary scoring signs like alertness, stupor, spatial orientation, struggle response, excitation and/or depression of central nervous system, change in motor activity and muscle co-ordination, posture, muscle tone, pinna, corneal and scratching reflexes, etc. were observed and recorded. Urination, defecation, and other observable signs of autonomic activity, as well as behavioural changes, were also observed. Observations were made three times before and regularly up to four hours after the administration of the test compounds, with the final observation made at the end of 24 hours.

B. Effect on blood pressure

All the compounds were studied for their effect on mean arterial blood pressure (BP) in anesthetised normotensive mongrel dogs and cats. Dogs were anaesthetized with pentobarbital sodium (35 mg/kg) injected intravenously (IV) into the saphenous vein, and anaesthesia was maintained with 5 mg/kg of pentobarbital injected through the cannulated femoral vein. In cats, the same dose of pentobarbitone was administered intraperitoneally to induce anaesthesia. The trachea was cannulated to provide a patent airway. A three-arterial glass cannula was inserted into one of the common carotid arteries, and the BP was recorded on kymograph (palmar) using a mercury manometer. Femoral vein was cannulated for injecting the drugs, vehicle and/or saline. The experiments began after the preparation got stabilised. Before the administration of all the test compounds, the change in the arterial BP produced by bilateral carotid occlusion (CO, for 30 seconds), as well as to the injections of epinephrine (1-3/ug/kg), norepinephrine (1-3/ug/kg), isoprenaline (1-3/ug/kg), acetylcholine (1-3/ug/kg) histamine (1-3/ug/kg) and serotonin (5-HT, 1-3/ug/kg) were recorded. All test compounds were administered intravenously at a slow rate in a dose of 5 mg/kg, except for clonidine (3-20 µg/kg) and PSP 211 (-10 mg/kg). Generally, doses of up to 5 mg/kg were chosen for the test compounds. However, if this dose proved fatal to the animal, lower doses were selected for investigation. Responses for CO and agonists mentioned were repeated periodically up to 240 minutes, after the test compound was administered.

The results of the primary screening indicated that, out of all the compounds studied, only PSP 211 showed a promising hypotensive effect. Hence, this compound was selected for detailed investigation due to its potential antihypertensive properties and to study its mode of action.

XI. DISCUSSION

RAS is involved in the development of essential hypertension, which is an inflammatory condition that not only influences the cardiovascular system but also dysregulates glucose control and kidney disease and can also influence gut microbiota and the functionality of the gut (Kuba et al., 2013; Yang et al., 2015; Zhu et al., 2016). We examined the effects that three classes of antihypertensive drugs may have on SHR gut function after 16 weeks of treatment. In the first experiment, SHRs were treated with the ACE inhibitor enalapril and the direct-acting smooth muscle arteriole relaxant hydralazine, resulting in no significant differences in gut contractility in response to all agents tested ex vivo compared with untreated SHR controls. In human patients undergoing hypertension treatment, complications to the gut due to ACE inhibitors are uncommon. However, they have been reported to induce intestinal angioedema, which may lead to unnecessary invasive procedures, such as exploratory laparotomy (Weingärtner et al., 2009). To our knowledge, contraindications for gut motility have not been reported. Indeed, in animal models such as the mouse, enalaprilat has been shown to reduce the severity of dextran sulphate sodium–induced colitis and decrease tumour necrosis factor-α levels and epithelial cell apoptosis (Spencer et al., 2007). In contrast, enalapril was shown to attenuate the upregulation of IκBα phosphorylation and reduce the severity of colitis, as assessed by histologic examination (Lee et al., 2014). In this study, we utilised hydralazine, a non-nucleoside DNA methyltransferase inhibitor and a potent arterial vasodilator (Knowles et al., 2004), which is approved for the treatment of severe hypertension and heart failure (Graça et al., 2014). Hydralazine is not routinely used as a primary drug for treating human hypertension because it elicits a reflex sympathetic stimulation of the heart (the baroreceptor reflex). The sympathetic stimulation may increase heart rate and cardiac output and, in patients with coronary artery disease, may cause angina pectoris or myocardial infarction. However, in animal models, this class of drug can inhibit gastric emptying in rats and gastrointestinal propulsion in mice (Chiba et al., 1981). Nevertheless, this dysmotility was not evident in ex vivo intestinal contractility in hydralazine-treated SHRs used in this study. Losartan is an orally active, nonpeptide AT1 receptor antagonist which provides a more specific and complete blockade of the actions of angiotensin II than renin or ACE inhibitors (Simpson and McClellan, 2000) and is effective in controlling BP and long-term renal damage in hypertensive patients. Although it has been reported that a specific ARB, Olmesartan, may interfere with gut immune homeostasis, is known to cause rare cases of sprue-like enteropathy in predisposed individuals, and is associated with an increased risk of hospitalization for intestinal malabsorption and celiac disease (Sciolom et al., 2015; Basson et al., 2016), losartan has been reported to be well tolerated alone and in combination, with only limited reports of gastrointestinal side effects, such as constipation (Weber, 1997; Gokhale et al., 2002), and generally no association with increased risk of cancer for ARBs (Bhaskaran et al., 2012). In our study with SHRs, losartan treatment led to increased receptor-independent, depolarisation-driven ileal contractility, which was not evident in the colon. There was also an increase in ileal contractility after losartan treatment, like the effect observed with the muscarinic agonist carbachol, with no significant change in sensitivity. (EC50) and no effects noted in the colon. The electrical-stimulated colon also demonstrated no difference in response to

losartan treatment. Although the proteinoid response is depressed in SHRs (Patten et al., 2004, 2005), there was also no change in ileal or colonic response to the proteinoid PGE2. However, losartan treatment led to a significant suppression of both ileal and colonic response to angiotensin II. For the ileum, there was a concomitant decrease in sensitivity to angiotensin II. The colon showed decreased sensitivity to angiotensin II. The changes in contractility due to losartan treatment could not be explained by changes in either ileal or colonic tissue density or muscle mass, which were not significantly different from those of no-treatment SHR controls. It remains to be determined whether other ARBs currently used in clinical settings have similar effects.

XII. CONCLUSION

Dietary measures, such as the DASH diet and sodium reduction, can effectively prevent and control HTN. Research suggests that diets with meals or frequent dietary advice are more helpful for older adults and those with HTN. Clinicians should use multidisciplinary techniques to help patients establish balanced dietary patterns, given the difficulty associated with changing their eating habits.

DECLARATION STATEMENT

After aggregating input from all authors, I must verify the accuracy of the following information as the article's author.

- **Conflicts of Interest/ Competing Interests:** Based on my understanding, this article has no conflicts of interest.
- **Funding Support:** This article has not been funded by any organizations or agencies. This independence ensures that the research is conducted with objectivity and without any external influence.
- **Ethical Approval and Consent to Participate:** The content of this article does not necessitate ethical approval or consent to participate with supporting documentation.
- **Data Access Statement and Material Availability:** The adequate resources of this article are publicly accessible.
- **Author's Contributions:** The authorship of this article is contributed equally to all participating individuals.

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