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R E V I E W

Treatment of prehypertension: lifestyle and/or medication

Scott R Collier[1]
Michael J Landram[2]

[1]Vascular Biology and Autonomic Studies Laboratory, Appalachian State University, Boone, NC, USA; [2]Università degli Studi di Roma "Foro Italico", Rome, Italy

Abstract: Prehypertension is a warning to individuals with resting blood pressures between 120/80 mmHg and 139/89 mmHg of an insidious progression of blood pressure towards hypertensive levels ($\geq$140/90 mmHg). Prehypertension is associated with increased cardiovascular risk and end organ damage compared with individuals who are normotensive. This review primarily focuses on internal and external factors associated with the prevalence of prehypertension. Elucidating all of the factors associated with a rise in resting blood pressure and comparing the effects of medication versus lifestyle changes may aid the clinician in developing a preventive and/or treatment strategy for each individual.

Keywords: sex differences, blood pressure, lifestyle changes

Introduction

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and treatment of High Blood Pressure (JNC-7) has revised its classifications of high blood pressure (BP) to include "prehypertension" as a category that was formerly covered by both the "normal" and "borderline" groups.[1] It is well known that if prehypertension remains undetected, chronically elevated BP levels can increase the risk of developing cardiovascular disease. Longitudinal data from the Framingham Heart Study have indicated that BP values of 130–139/85–89 mmHg (now considered "prehypertensive" according to the new JNC-7 guidelines) are associated with a more than two-fold increase in relative risk of cardiovascular disease as compared with those with BP levels below 120/80 mmHg.[1] Even considering the potential increase in risk factors for cardiovascular disease, prehypertension is not a disease category. JNC-7 states that it is a designation chosen to identify individuals at high risk of developing hypertension, so that both the patient and clinician are alerted to this risk and can work to intervene and prevent or delay development of the disease. However, it is asserted that lifestyle modification should be pursued over pharmacological intervention unless a secondary disease is present (eg, type 2 diabetes mellitus or kidney disease). Additional changes that result in increased BP stem from pathological arteriolar hypertrophy.[2]

In children and adolescents, prehypertension is defined by a systolic and/or diastolic BP at the 90th percentile but less than the 95th percentile for age, gender, and height according to normative tables published in the Working Group report. Multiple longitudinal studies have established that BP levels track with age such that childhood BP levels are associated with BP levels in later life.[3] Divergent from adult treatment

Correspondence: Scott R Collier
111 Rivers Street, 051 Holmes Convocation Center, Boone, NC 28608-2071, ASU Box 32071, USA
Email colliersr@appstate.edu

Michael Landram, 111 Rivers Street, Holmes Convocation Center, Boone, NC 28608-2071, USA
Tel +1 314 504 6235
Email michaellandram@gmail.com

strategies, monitoring of adolescent prehypertension requires 6-monthly evaluations and recommendation of lifestyle changes.[4,5]

More than 95% of human hypertension cannot be explained, is due to unknown causes, and is termed "essential" or "primary" hypertension. This paper reviews both internal (ie, gender, age, and race) and external (ie, modifiable risk factors and medication) factors determining development of prehypertension and the strategies used at present to combat prehypertension (lifestyle changes and medication) for individuals of all ages.

Internal factors

Women, unlike men, show an abrupt increase in BP around the fifth decade of life, and by the sixth decade surpass men in the incidence of primary hypertension.[6] Recently, Sandberg et al have shown several gender differences related to sex chromosomes and the role that hormones play in the development of primary hypertension.[7] Studies using a four-core genotype mouse model that isolates specific sex chromosome effects from gonadal sex effects show greater elevations in BP in gonadectomized XX mice than gonadectomized XY mice.[7,8] The authors suggest that the XX sex chromosomes may have an adverse effect in the absence of sex hormones, leading to the higher prevalence of elevated BP in this population.[8] Researchers have not been able to separate the effects of sex hormones from the effects of aging on arterial pressure, mainly because sex steroid concentrations decrease in humans as they age. The search for aging mechanisms highlights the need for research within the adolescent population, especially in view of the fact that prehypertension rates are increasing in children and adolescents, with a current prevalence ranging from 3% to 5%.[4] McNiece et al[9] reported a higher prevalence of prehypertension among both Afro-American and Hispanic adolescents when compared with their white non-Hispanic counterparts, but this association has not been confirmed in other studies.[10] Although estimates of progression from prehypertension to hypertension do exist, they vary considerably (1%–7% increase per year), but it is important to note that even the low end of such estimates would yield annual increases of 119,000 adolescents (http://www.census.gov) being counted as hypertensive. This figure is startling because it has been shown that being classified as prehypertensive does not just act as a forerunner to a person becoming hypertensive, it is also associated with the presence of active disease. Some adolescents with prehypertension already demonstrate evidence of target organ damage.

Left ventricular hypertrophy is the most widely recognized abnormality attributed to high BP in children.[4] Earlier supervised, play-based exercise interventions seem necessary to prevent prehypertension and start more children on a healthy active lifestyle, in the hope that they will maintain this into adulthood. Increased participation in physical education at school is normally considered to be the start of this, but a recent study has found that supervised play-based physical activity during the summer break has a beneficial effect on the metabolic profile and cardiovascular end points.[11,12]

In terms of ethnic variables, the NHANES (National Health and Nutrition Examination Survey) III found no difference in the prevalence of prehypertension between non-Hispanic whites, non-Hispanic blacks, Mexican Americans, and others,[13] whereas the more recent REGARDS (REasons for Geographic And Racial Differences in Stroke) study in 2011 found that the prevalence of prehypertension was higher in Afro-Americans than in whites (62.9% versus 54.1, respectively).[14,15] Further, the NHANES III report stated that men were more likely to have prehypertension than women (40% versus 2%) and prehypertension was higher in individuals with overweight/obesity. The REGARDS study also reported a higher prevalence of prehypertension in obese individuals and those with heavy alcohol consumption.[15] However, these results are misleading in view of the gender differences that exist, ie, women demonstrate the greatest prevalence of prehypertension and increased rates of cardiovascular disease with advancing age. Gender differences may be related to higher heart rates and earlier reflected pulse waves leading to higher BP and pulse pressures in women, and these changes may be linked to gender differences in the extent of perturbation of the renin-angiotensin-aldosterone system (RAAS).[7]

Medication

A seminal study reported in 2006 examined the effectiveness of prescribing an angiotensin II blocker in patients with prehypertension.[16] The results of this study support the idea that essential hypertension can be prevented or delayed, showing a 26% reduction in the number of subjects prescribed this treatment presenting with hypertension compared with those given placebo.[16] In 2008, the authors resubmitted their findings to conform to contemporary BP measurement protocols (two consecutive elevated measurements instead of three) and found outcomes similar to those in the previous study. Regardless of the algorithm used to determine hypertension, both methods agree that treatment of prehypertensive BP can markedly reduce or completely avoid the

development of essential hypertension.[17] It should be noted that more than two thirds of individuals with hypertension cannot adequately control their BP with one medication and require two or more antihypertensive agents from different drug classes for effective control.[1]

Physicians are generally in agreement that antihypertensive treatment begins with lifestyle modification, but if the BP goal is not achieved, thiazide-type diuretics should be used as initial therapy for most patients, either alone or in combination with one of the other classes, ie, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, or calcium channel blockers. Several randomized, controlled trials have shown that this treatment regimen will reduce one or more hypertensive complications.

The RAAS have been implicated in the development of hypertension. Activation of the RAAS system leads to endothelial dysfunction and inflammation by promoting release of angiotensin I, which induces vascular injury via several mechanisms, including vasoconstriction, cell growth, oxidative stress, and inflammation (inducing release of cytokines and proinflammatory transcription factors).[18] These mechanisms contribute to a prothrombotic state, plaque buildup, and instability, ultimately leading to plaque rupture. Currently, widespread use of angiotensin-converting enzyme inhibitors are administered to millions of patients, to great effect. In addition to this, it is now thought that these agents promote upstream blockade of overformation of renin and/or its precursors, preprorenin and prorenin. This change in thinking has come from the discovery of the renin receptor, that stimulates the formation of angiotensin II, which is able to bind prorenin equally as well. Angiotensin II inhibitors have been shown to be as effective as diuretics.[19] It is well known that the sympathetic nervous system strongly influences the RAAS, which is activated by many common comorbidities, including type 2 diabetes, hyperinsulinemia, excess weight, and a diet rich in carbohydrates and fats. Interestingly, two large clinical trials[20,21] have shown that angiotensin-converting enzyme inhibitors decrease the risk of developing type 2 diabetes in patients with hypertension and/or vascular disease. Drug type and time of dosage determines the time course of BP suppression.[22] Overall, pharmacological intervention in prehypertensives has yielded mixed results, with some researchers showing benefits[23] while others have not.[24] It seems that the existence of comorbidities determines whether a prehypertensive patient is likely to respond to pharmacological intervention.[25] However, it has been shown that both young (<65 years) and older (>65 years) patients may achieve some benefit from a course of antihypertensive

pharmacologic intervention, although the absolute change and cost-effectiveness may be greater in older patients, who often present with more pronounced risk factors.[23]

Intermediate factors
Obesity

Many causal factors for elevated BP have been identified, including excess body weight, excess sodium intake, reduced physical activity, inadequate intake of fruit, vegetables, and potassium, and excess alcohol intake. JNC-7 reports that the prevalence of these factors is high. At least 122 million Americans are overweight or obese. Being classified as either overweight or obese is a major worldwide risk factor for prehypertension and hypertension (Guo et al, 2011).[26] Average sodium intake is nearly twice what is recommended for men and elevated for women, and much of this comes from processed foods. Females consume an amount of sodium which is elevated beyond the daily recommendation, while males consume over twice that amount. Less than 20% of Americans engage in regular physical activity and less than 25% consume the recommended amount of fruit and vegetables.

Leptin

Plasma leptin concentration correlates positively with adiposity,[27] and hyperleptinemia is an independent risk factor for coronary artery disease[28] and a strong predictor of myocardial infarction.[29] Additionally, leptin has been implicated in the formation of inflammatory cytokines and calcification of vascular smooth muscle cells.[30] Leptin receptors are known to be expressed in coronary arteries, and hyperleptinemia causes significant endothelial dysfunction.[31] One study reported marked increases in body weight (66.2 kg ± 12.6 to 69.4 kg ± 13.5) over the course of 4 weeks, noting a concomitant increase in leptin release during the night.[32]

External factors

The increasing incidence of hypertension and cardiovascular disease has been related to changes in lifestyle and dietary patterns[33] which could be sodium-related, given that communities that do not consume large amounts of sodium do not see the same age-associated rise in BP. Under an unnatural overload of dietary sodium, the kidneys switched their handling from retention to excretion. This increase in sodium results in extracellular volume expansion, increased cardiac output, and subsequently increased peripheral resistance. Chronic BP elevation may result in end organ damage. In the kidneys, the loss of glomeruli and renal arterioles may exacerbate natriuresis and further elevate BP due to dysregulation of

the RAAS. However, several factors play a role in sodium sensitivity, including race and ethnicity, making BP control difficult to achieve with pharmacological intervention. Further, with approximately 17% (or 12.5 million) of children and adolescents aged 2–19 years now being obese, it is well recognized that earlier onset of drug therapy will not attenuate the increasing incidence of hypertension if obesity and inactive lifestyles continue to increase.[34] Also, as our population ages, vascular hypertrophy resulting from advancing atherosclerosis may diminish responsiveness to antihypertensive medications.[35]

At the forefront of BP research is the need to develop studies aimed at elucidating the time point at which human arterial health is compromised, and to develop meaningful studies that lead to prevention of prehypertension and avoidance of progression to the need for pharmacological intervention. Also, the development of studies to replace pharmacological therapy in those on current treatment given that lifestyle modification can be used as a prevention/treatment for several other factors contributing to prehypertension. Daily living can impact on BP to a great extent, so there is a need for reliable and repeatable measurements.[36] Compounding this issue is the fact that many physicians fail to follow best testing measures when taking BP, resulting in variable and often high estimates. This may lead to the start of patienthood if pharmacologic action is prescribed which has shown to increase job absenteeism, leading to economic impact in insurance costs for the company and increased healthcare costs.[37]

Lifestyle habits

Most individuals with prehypertension have one or more concomitant conditions associated with increased cardiovascular risk. The NHANES II and the NHANES II Mortality Study showed that 90% of individuals with prehypertension have at least one other cardiovascular risk factor.[38] These risk factors include the dyslipidemias, an early family history of cardiovascular disease, cigarette smoking, abdominal obesity, hyperinsulinemia and insulin resistance, impaired fasting glucose, a prothrombic state, endothelial dysfunction, and impaired vascular distensibility.

As previously stated, modest consumption of alcohol, ie, <30 g of ethanol a day or approximately two "drinks" daily for men and one containing <15 g of ethanol for women, is not generally associated with increases in BP. Ingestion of larger quantities of alcohol has a dose-related effect on BP, both in hypertensive and normotensive subjects.[39] Tobacco use, specifically cigarette smoking, increases BP and is an independent risk factor for cardiovascular disease.

Although conflicting data have been reported, a 2011 meta-analysis indicated that alcohol and tobacco intake were related to development of hypertension (Gao et al, 2011). In addition to BP changes, cigarette smoking and second-hand exposure to cigarette smoke increase all-cause mortality in both males and females by about 1%.[40]

It is well known that poor cardiorespiratory fitness is a strong and independent predictor of cardiovascular disease and all-cause mortality, and higher activity levels equate to higher cardiorespiratory fitness, which is also correlated with lower resting BP, making exercise an antihypertensive lifestyle modification. In fact, meta-analyses of exercise-based cardiac rehabilitation studies have shown reductions in mortality of up to 32%, and exercise alone has been associated with a 30% reduction in cardiac risk, making it similar to statin and antihypertensive interventions.[41–44]

It was proposed by Green that exercise provides cardioprotection by protecting the vascular wall and that increased transient bouts of sheer stress confer a "vascular conditioning" effect.[45] Increases in endothelial nitric oxide synthase levels lead to increased bioavailability of nitric oxide, a powerful vasodilator that reduces BP by decreasing vessel resistance. Repeated bouts of exercise lead to a resetting of the baroreflex to lower operating pressures which, in turn, lowers resting BP. With its ability to achieve a mean reduction of 3 mmHg in both systolic and diastolic BP, either mode of exercise serves a form of treatment for the prehypertensive subject, and also improves the autonomic, renin-angiotensin-aldosterone, and skeletal muscle systems, without any side effects.

A large number of studies have been performed to examine the effects of aerobic and/or resistance exercise on BP in hypertensive, prehypertensive, and normotensive groups, and a recent review has examined the relevant findings.[46] Independent of weight loss, exercise has been shown to decrease BP.[47,48] However, studies using conventional measurements show more agreement, whereas those utilizing ambulatory BP monitoring have yielded more conflicting results. In a meta-analysis of 54 randomized controlled studies including intervention and control groups which differed only in aerobic exercise, aerobic exercise was associated with a statistically significant reduction in BP of 3.8/2.6 mmHg. This change was seen in both normotensive and hypertensive patients.[49]

Another meta-analysis examining resistance exercise showed a $3 \pm 3/3 \pm 2$ mmHg decrease in BP in studies lasting at least 4 weeks.[50] However, resistance exercise has been shown to increase arterial stiffness, which discredits its use as an antihypertensive exercise, and the American

Heart Association states that resistance exercise should only be undertaken if complementing a good aerobic-based exercise program. In direct comparison with aerobic exercise programs, recent studies have shown that resistance exercise yields comparable hemodynamic results with slight increases in resting heart rates.[51] Also, gender differences exist, such that only men have been shown to develop increased arterial stiffness,[47] leaving resistance exercise an excellent choice for prehypertensive women, with the additional benefits of prevention or amelioration of osteoporosis as a result of weight-bearing exercise.

Weight loss has been shown to be the most effective lifestyle strategy for prevention of hypertension,[52] and addition of antihypertensive medication has been shown to have an effect on BP reduction that is additive to that achieved by weight loss alone.[53] However, it has been shown that the type of medication prescribed may decrease the ability of the patient to lose weight.[52] A substudy of the DASH (Dietary Approaches to Stop Hypertension) trial also showed that by reducing sodium intake to less than 100 mmol in your daily diet, in addition to dietary changes provided greater benefit than either approach alone.[54] The JNC-7 also found that two or more intervention treatments worked better than any individual strategy used alone to reduce BP.

For overall risk reduction it is advised that a patient stop smoking, and a myriad of other methods are also available to reduce BP. Dietary intervention is the most effective of the lifestyle measures for reducing high BP. Adhering to the DASH diet, which is high in fruit, vegetables, and low-fat dairy products, can reduce BP by 8–14 mmHg. Further, reduction in sodium intake and body weight can reduce BP by 2–8 mmHg and 5–20 mmHg, respectively. Moderating alcohol intake to the recommended levels of no more than one or two drinks per day for women and men, respectively, can lower BP by 2–4 mmHg. Additional lifestyle factors, such as physical activity, have a large impact on BP, being able to reduce systolic BP by 4–9 mmHg. However, outside of controlled clinical trials, the efficacy of dietary adherence becomes marginal, with much of the improvement in body weight, sodium intake, and BP lost within 36 months.[55] The PREMIER study mirrored these results, with the DASH diet being only moderately effective compared with clinical trials.[56] A meta-analysis was performed, reporting that the efficacy of simply giving instructions and guidance on diet became negligible in clinical trials lasting over 6 months.[57]

Clinical procedures

Logistic problems exist when measuring the physiological parameter of BP. Proper sizing of the arm cuff during manual measurement using a stethoscope and sphygmomanometer is crucial, because an undersized cuff results in consistent overestimation of diastolic BP by approximately 6 mmHg. Inaccurate sphygmomanometers are also common, with 30%–40% of aneroid sphygmomanometers used by physicians being out of calibration by 4 mmHg or more, and about 10% being out of calibration by 10 mmHg or more.[36] Also, gender differences exist with regard to the emotional phenomenon known as "white coat" hypertension, which is characterized by increased sympathetic stimulation and RAAS activity resulting in systolic and diastolic BP elevations of at least 20/10 mmHg, respectively, when a clinician is present. Therefore, there may be an additional need for ambulatory monitoring in women or more care during the clinical assessment of resting BP for more accurate prescriptions.

Conclusion

Antihypertensive medications can reduce BP immediately, yet their prescription would enroll more than 25 million Americans into patienthood and also place a great burden on the health insurance system. Given that exercise has been found to be as effective as medication with little or no side effects and that exercise works on multiple physiological systems, the most effective strategy may be to enroll children into sports to develop exercise habits that will last lifelong as a means to prevent prehypertension. Our goal is to use exercise as a daily medication that fits every individual worldwide. The challenge is to change the current school of thought that exercise, as a therapy, is only used for a short while until symptoms disappear.

Disclosure

The authors report no conflicts of interest in this work.

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