Winter Hypertension: Potential mechanisms

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Abstract:

Hypertension exhibits a winter peak and summer trough in countries both north and south of the equator. A variety of explanations have been proposed to account for the seasonal nature of hypertension. It is likely that this reflects seasonal variations in risk factors. Seasonal variations have been demonstrated in a number of risk factors may play essential roles for seasonality of hypertension such as noradrenalin, catecholamine and vasopressin, vitamin D, and serum cholesterol. However, a number of studies have also suggested a direct effect of environmental temperature and physical activity on blood pressure. This paper was design to review the available evidence on seasonal variations in hypertension and possible explanations for them.

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Introduction:

Seasonal influence on arterial blood pressure has been demonstrated by various studies based on single or repeated measurements among adults, the elderly, and children as well as healthy and hypertensive subjects. [1-5] In all of these studies, both systolic and diastolic mean blood pressures showing a seasonal peak during winter and trough in summer. This variation is likely to affect the prevalence of hypertension in different seasons because of the fact that increase in blood pressure in winter will shift the proportion of the subjects from normotensive to the hypertensive category. This variation linked with multiple risk factors, such as temperature, physical activity, air pollution, and ultraviolet radiation. Other potentially important seasonal risk factors such as seasonal variation in the serum level of cholesterol, noradrenalin, catecholamine, and vasopressin which tend to rise in the winter. The aim of this article is to review the current knowledge about seasonal variations in hypertension, as well as their possible common underlying risk factors.

Possible risk factors

Temperature

Several studies have found relationship between blood pressure (BP) and external temperature, with the highest pressures recorded in cold temperature and lowest pressures recorded in relative warm temperature. In some studies BP measurements were recorded in a population of hypertensive subjects [7, 8, 9, 14] whereas in other studies normotensive. [6, 10, 11, 15] In about twenty normotensive volunteers, Jansen and colleagues [6] demonstrated a moderate but significant influence of ambient temperature on BP. A significant increase in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) was seen when moving from higher to lower ambient temperature. In study conducted in United States (US), DBP in association with a 5°C decrease in 7-day moving averages of temperatures increased by 1.01% to 2.09% and 1.55% to 2.49% for ambient and apparent temperature, respectively. [14] The association of blood pressure with outdoor temperature was also found in the 8801 elderly subjects participating in study conducted in three French cities. [7] In that study, SBP decreased with increasing temperature, with an 8.0–mm Hg decrease between the lowest (<7.9°C) and the highest (≥21.2°C) temperature quintile. In another study performed in individuals aged 65 to 74 years was based on only 96 subjects recruited in 1 general practice found a 1 degree C decrease in living-room temperature was associated with rises of 1.3 mmHg in SBP and 0.6 mmHg in DBP. (27) A 1 degree C decrease in the mean outdoor temperature was also found to be associated with rises of 0.43 mmHg in SBP and 0.29 mmHg in DBP in fifteen healthy elderly Japanese. [15] Another study found very similar results, reporting in 2007 that a 1 degrees C increase in indoor temperature reduced SBP by an average of 0.31 mmHg), whereas, A 1 degrees C increase in outdoor temperature reduced blood pressure by the smaller average of 0.19 mmHg. [16] Furthermore, Komulainen and colleagues [9] reported that BP increased 30/20 mmHg and heart rate decreased 12 beats/min after three minutes to changes in ambient temperature. In a study Zimbabwe [10] showed that SBPs and DBPs were significantly higher when recorded at 15ºC than at 25ºC (a mean difference of 32.2 ± 4.2 mmHg and 19.5 ± 3.0 mmHg for SBPs and DBPs, respectively). In another study was carried out on a rural Ghanaian population, found that SBP fell by 5 mmHg per 10ºC rise in ambient temperature. [11]

Mechanisms that could explain the association between blood pressure and temperature remain undetermined. Activation of the sympathetic nervous system and secretion of catecholamine are increased in response to cold temperatures. This could result in an increase in blood pressure through increased heart rate and peripheral vascular resistance. [12] Endothelium-dependent mechanisms could also be involved in the relationship between temperature and vasodilatation, as suggested by a recent study. [13] On the other hand, some relatively recent studies have suggested that alterations in temperature might also influence vascular function through an effect on endothelial nitric oxide synthase and the bioavailability of nitric oxide. In rats, Acute and short-term exposure of rats to elevated environmental or core body temperatures has been shown to increase endothelial nitric oxide synthase expression.

Conversely, repeated cold exposure of rats (4°C for 4 hours per day for 1 week) led to the development of hypertension and impaired endothelial vasodilator function in isolated arterial tissue. [17] Cold exposure also produces other relevant changes in the endothelial phenotype, including activation of the pro-inflammatory transcription factor nuclear factor-κB. [18] Thus, experimental studies suggest that cold temperature may alter endothelial biology. In contrast, summer seems to be a lower risk period for hypertension. It has been suggested that warm ambient summer temperatures may contribute to reduced vascular resistance. The other explanation has been linked between serum vitamin D status and hypertension. [19] However, hypertension patients should always be well-prepared for cold weather, taking precautions to limit exposure to the cold.

Vitamin D

Significant seasonal vitamin D level variations were observed in several communities, which reveal a variation of values for 25-(OH) D, increased during summer and spring, while gradually decreasing in autumn and winter. Several clinical and epidemiological studies [20, 30] have shown that there association between hypertension and low vitamin D level, and there are some plausible biological mechanisms as well. In humans, skin exposure to ultraviolet B radiation, which is the major source of vitamin D, has been associated with lower blood pressure. Krause et al. randomly assigned 18 patients with mild hypertension to receive Ultraviolet B (UV-B) or Ultraviolet A (UV-A) exposure, 3 times weekly for 6 weeks. [31] In this study, he found that there was a 162% rise in plasma 25(OH)D in the UV-B group along with a drop in both systolic and diastolic blood pressure by 6 mm Hg. Furthermore, a single interventional study conducted in 148 vitamin D–deficient elderly women demonstrated a 9.3% decrease in systolic blood pressure with supplemental vitamin D and calcium compared with calcium alone. [32] Despite the evidence of clinical and epidemiological studies, the mechanisms that could explain the association between blood pressure and vitamin D deficiency remain controversial. Recent study conducted by Li and colleague [33] demonstrate that Vitamin D is a potent endocrine suppressor of renin biosynthesis to regulate the renin–angiotensin system (RAS). Mice lacking the Vitamin D receptor (VDR) have elevated production of renin and angiotensin II (ANG II), leading to hypertension, cardiac hypertrophy and increased water intake. These abnormalities can be prevented by treatment with an angiotensin-converting-enzyme inhibitor (ACE inhibitor) or angiotensin receptor antagonist (AT_1). Vitamin D repression of renin expression is independent of calcium metabolism, the volume- and salt-sensing mechanisms and the Ang II feedback regulation. In normal mice, Vitamin D-deficiency stimulates renin expression, whereas injection of 1,25-dihydroxyvitamin D(3) [1,25(OH)(2)D(3)] reduces renin synthesis. In cell cultures, 1,25(OH)(2)D(3) directly suppresses renin gene transcription by a VDR-dependent mechanism. Furtheremore, Laboratory studies demonstrate that 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] inhibits renin expression in the juxtaglomerular apparatus [33,34,36] and blocks proliferation of vascular smooth muscle cells (VSMCs). [35] vascular smooth muscle cells revealed several mechanisms by which 1,25-dihydroxyvitamin D3 might contribute to the pathogenesis of vascular lesions, because vitamin D3 dose-dependently activates p38 mitogen-activated protein kinase and phosphatidylinositol kinase. [37,38] Upon activation, these signal transducers induce cell dedifferentiation, promote cell migration, and increase oxidative stress (together with cytokines and growth factors, including angiotensin II), thus leading to vascular wall stiffening which could influence systemic blood pressure. Thus, vitamin D-deficiency may increase the risk of hypertension, and vitamin D supplementation may be beneficial to the cardiovascular system. Further understanding of these complex relationships may improve the understanding of the role of vitamin D in blood pressure physiology.

Hormones

Hormones and vasoactive substance such as Vasopressin (AVP), norepinephrine (NE), epinephrine (E) and angiotensin II, aldosterones and catecholamine have suggested play a role of seasonal variation in blood pressure. In a study conducted in Japan, mean plasma noradrenaline, urinary

excretion of catecholamines and sodium significantly higher in winter than in summer was found in hypertensive patients. No comparable differences were found in either plasma renin activity or plasma aldosterone concentrations. [39] Furthermore, Cold air exposure of 4º C for 30 min was found reduces the plasma vasopressin levels in human subjects. [40] In another study, Plasma aldosterone (PA) was found significantly increased 59% from summer to winter, whereas plasma norepinephrine (PNE), plasma epinephrine, and plasma renin activity (PRA) increased 19, 2, and 17%, respectively. [41] In twenty healthy male volunteers exposed to a temperature of 10 degrees C for 120 min , Leppäluoto and colleagues [42] demonstrated a significant increase in serum level of noradrenaline from 4.5 to 6.3 nmol l. A German study found that Endothelin-1 levels displayed a significant variation, with a sinusoid pattern throughout the year: nadir values occurred in January, peak values in July. Angiotensin II demonstrated a significant correlation with endothelin-1 and paralleled its rhythmicity. In contrast, plasma catecholamines exhibited an opposite pattern. [43] In an attempt to study effects of cold on blood pressure and the renin-angiotensin-aldosterone system, 34 healthy young subjects with or without a family history of essential hypertension were exposed to moderate cold (4 degrees C for 1 h) or severe cold (immersion of the hands to 0 degrees C for 10 min). Moderate cold was found elevated blood pressure, aldosterone, cortisol and noradrenaline when the subjects wore summer clothing but not when the subjects wore winter clothing. Regardless of the clothing worn, skin blood flow and plasma renin activity decreased significantly in response to moderate cold but angiotensin II decreased insignificantly. Severe cold elevated blood pressure, cortisol, aldosterone and noradrenaline. This study suggested that, among the various hormones studied, noradrenaline is the only hormone responsible for an elevation of blood pressure in response to cold. [44]

Serum cholesterol level

Several studies have been done on the association between cholesterol and blood pressure. [45, 46, 47] Serum cholesterol is strongly associated with endothelial dysfunction and reduced nitric oxide bioavailability, [48, 49, 50] which may lead to functional arterial stiffening. In cholesterol-fed rabbits, increased oxidative stress has been found, attributable to endothelial dysfunction. [51] Oxidative stress reduces the function of renal dopamine receptors in rats, leading to sodium retention and high blood pressure. [52] Interestingly, a significant seasonal variation in plasma levels cholesterol with higher values in winter has been reported in many studies. [53-58] in a Lipid Research Clinics Coronary Primary Prevention Trial Placebo Group study [59] showed significant seasonal cycles, characterized by wintertime peaks in plasma levels of total cholesterol (TOT-C) and low-density lipoprotein cholesterol (LDL-C) (mean changes 7.4 and 6.4 mg/dL respectively), but no variation for triglycerides. A similar temporal pattern was confirmed in an elderly population [60] and in young, healthy subjects. [61] In this cohort, however, the seasonal variation, which was characterized by a wintertime peak and a summertime low, was slight, with amplitudes of 1.8% and 2.5% of the average cholesterol values respectively. Interestingly, the annual rhythm of blood cholesterol has been found to be independent of age, gender, body mass index (BMI), overall diet, or physical activity. [62] In study conducted in Norway found similar result, that the free fatty acids and glycerol was high in January-March, low in April-July and high again in August-September. [63]

Physical activity

In both sexes, overall levels of physical activity are significantly higher in summer than in winter. [64] Physical inactivity is strongly positively associated with hypertension, [65] and intervention studies have demonstrated that increased physical activity is effective in the treatment of high blood pressure in a variety of populations. [66, 67] In view of this, physical activity is widely advocated in the treatment of hypertensive disease. [68] How physical activity positively affects BP remains unclear. One of the primary mechanisms through which physical activity is thought to affect blood pressure is through improves endothelial function. The endothelium acts to maintain normal vasomotor tone, enhance the fluidity of blood, and regulate vascular growth. Abnormalities in these functions contribute to many disease processes, including angina,

myocardial infarction, coronary vasospasm, and hypertension. Exercise causes increases in blood flow leading to increased shear stress, which is the force acting parallel to blood vessels. Enhanced shear stress results in endothelium-dependent, flow-mediated dilation of vessels. Chronic increases in shear stress have been found to improve endothelial function in animal studies as well as in some limited human studies. [69] Another mechanism proposed that the physical activity may also reduce the elevated sympathetic nerve activity that is common in essential hypertension. [70]

Air pollution: Hypothesis

Several epidemiologic studies have reported positive associations between short-term fluctuations in ambient particulate matter (PM) levels and arterial blood pressure. [71-74] In a study conducted in USA by Johnson and Parker [75] used data from a large, nation-wide survey in the United States in which subjects were 30 years or older. This study found that PM 2.5 was associated with a small elevated risk of hypertension. In another study Auchincloss and colleague [76] examined cross-sectional associations between short-term ambient PM 2.5 and systolic and diastolic blood pressure, mean arterial pressure, and pulse pressure, and found that systolic blood pressure and pulse pressure were positively associated with ambient levels of PM 2.5 and the associations were stronger in the presence of roadway traffic. During the air pollution episode in Europe in January 1985, an association between blood pressure and air pollution was observed. Continuous concentrations of total suspended particulates and sulfur dioxide were associated with an increase in systolic blood pressure of 1.79 mm Hg per 90 micrograms/m3 total suspended particulates and 0.74 mm Hg per 80 micrograms/m3 sulfur dioxide. In subgroups with high plasma viscosity levels and increased heart rates, systolic blood pressure increased by 6.93 mm Hg and 7.76 mm Hg in association with total suspended particulates. [77] Guo and his team, found elevated levels of ambient particulate matters are associated with an increase in emergency hospital visits (EHVs) for hypertension in Beijing, China. [78] In animal experimental studies, Bartoli and colleague used dogs and concentrated ambient air particles to investigate the effect of ambient particles on systemic hemodynamics, and found that exposure to concentrated ambient air particles ranging from 94.1 to 1557.0 μg/m 3 increased systolic blood pressure by an average of 2.7 mmHg, diastolic blood pressure by 4.1 mmHg, mean arterial pressure by 3.7 mmHg, heart rate by 1.6 beats per minute, and decreased pulse pressure by 1.7mmHg. [79] In another study , found a significant association between O_3 and blood pressure in the cold-weather season. [80]

A number of biological mechanisms have been proposed to explain this association Exposure to air pollution has been shown to cause arterial vasoconstriction. [81] A study on the acute effect of inhaled urban air-pollution particles in the rat showed increased plasma levels of endothelin-1, which is thought to have an active role in the maintenance of basal systemic vascular tone. [82] In the animal model, injection of endothelin-1 leads to dose-related increases in sympathetic nerve activity, therefore alteration in the central endothelin-1 system could result in blood pressure elevation. [83] However, these studies have been performed in animal models and therefore, the mechanisms require confirmation in the human population.In a controlled experimental design, found evidence that air pollution actually has a causal role in elevating blood pressure. [84] In a study on healthy adults, showed that inhalation of $PM_{2.5}$ and O_3 causes acute arterial vasoconstriction. A potential biological mechanism for vasoconstriction was suggested to include a reflex increase in the sympathetic nervous system activity. Oxidative stress and subsequent systemic inflammation caused by air pollution is also suggested as a possible mechanism for many cardiovascular diseases including hypertension. [85]

Seasonal variations of PM, PM10 and PM2.5 have been observed to be maximum during winter months [86] In a study conducted in Beijing, China found the PM2.5 increased up to 57% in winter . [87] In Turkey, The concentration of PM2.5, and PM10 was found to be higher in winter than in summer. As expected, the low temperature is associated with an increase in the number of episodic events. This is may be as a result of the

extensive use of fuel during winter-time for heating purposes and also due to stagnant air masses formed because of low temperature and low wind speed over the study area. [88] To date, no one has seriously considered air pollution as a factor may play an important role in seasonal appearance of hypertension. The result from epidemiological and experimental studies showed previously support this hypothesis.

Conclusion:

Significant increase in systolic and diastolic blood pressure during winter compared to summer was clearly documented. There are several possible reasons of the seasonality of hypertension: external temperature, physical activity, seasonal variation in noradrenalin, catecholamine and vasopressin, vitamin D, and serum cholesterol are important factors which can play a role in blood pressure variability. However, the evidence suggests that a number of simple precautions to reduce the risk of hypertension in winter could be taken. These include adequate indoor heating, wearing protective clothing, especially for elderly patients. Attempts should also be made to ensure that our lifestyles, in relation to diet, regular exercise, are at least as healthy in winter as they are in summer.

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