VIA MEDICA
REVIEW ARTICLE
Cardiology Journal
2010, Vol. 17, No. 5, pp. 443–447

ISSN 1897–5593

Allergic respiratory disease as a potential co-morbidity for hypertension

Tania Aung[1], John D. Bisognano[2], Mary Anne Morgan[3]

[1]Department of Internal Medicine, University of Rochester Medical Center, Rochester, New York, USA
[2]Divisions of Cardiology, University of Rochester Medical Center, Rochester, New York, USA
[3]Divisions of Pulmonary and Critical Care, University of Rochester Medical Center, Rochester, New York, USA

Abstract

This article examines the relationships between allergic rhinitis and hypertension, chronic sinusitis and hypertension, and asthma and hypertension. Previous studies have demonstrated that men reporting seasonal or chronic rhinitis had on average a 3.5 mm Hg higher systolic blood pressure than those without allergic rhinitis. Proposed mechanisms to the relationship between allergic rhinitis and sinusitis with hypertension may lie in the pathway of obstructive sleep apnea via neurohumoral responses to hypoxemia. Asthmatics were 1.4 times more likely to have heart disease, and 1.3 times more likely to have high blood pressure, than non-asthmatics. The commonality of immunological dysfunction and inflammation between diseases of allergy and those mediated by hypertension and other vascular disorders may explain the correlations observed. Interestingly, obese individuals have higher levels of circulating IL-6, leptin and TNF-alpha skewing the immune system toward the allergen-reactive type 2 helper T-cell. This would mean that obese individuals were predisposed to diseases of chronic inflammation. The implications of allergic rhinitis, chronic sinusitis, and asthma deserve closer attention, especially into the possibility of co-morbidity for hypertension. Although associations between allergic diseases and hypertension have been reported, more studies need to be performed to elucidate the mechanisms behind such associations. (Cardiol J 2010; 17, 5: 443–447)

Key words: allergy, asthma, hypertension, allergic rhinitis

Introduction

Population studies have demonstrated that the prevalence of hypertension and allergic diseases both continue to increase year on year. The concurrent rise in both diseases raises the question of whether there is a relationship between atopic disease and hypertension. The Hagerstown study was originally designed to determine whether urban residence affected respiratory function in non-smokers. The results of the study showed that among the 270 non-smokers, respiratory allergies were associated with a three-fold increased risk of hypertension [1]. In a different study, Stebbings [1] reviewed the relationship between allergic disease and hypertension among New York City transit workers, demonstrating that transit workers with asthma and hay fever had higher systolic blood pressures (SBP) and were prescribed more anti-hypertensives than their non-asthmatic, non-allergenic colleagues [1]. The authors concluded that respiratory allergies may be risk factors for hypertension.

This article will review the existing studies correlating allergic disease and hypertension, the putative mechanisms of such an association, and the clinical implications of such a relationship.

Address for correspondence: Mary Anne Morgan, MD, Assistant Professor of Medicine, Division of Pulmonary and Critical Care, University of Rochester Medical Center, Rochester, New York 14642, USA, e-mail: MaryAnne_Morgan@urmc.rochester.edu

Allergic rhinitis and hypertension

Kony et al. [2] examined whether there was a relationship between allergic rhinitis and elevated arterial blood pressure (BP). The study population consisted of 316 subjects (146 men and 170 women) between the ages of 22 and 44. Subjects were considered to have allergic rhinitis by self reported questionnaire. Subjects were classified as being hypertensive when their SBP was at least 140 mm Hg and/or their diastolic blood pressure (DBP) was at least 90 mm Hg, and/or they reported using an antihypertensive treatment [2]. Treatment was also taken into account. Eighteen of the men had used corticosteroids in the past 12 months. In the 127 men who had not been treated with steroids, a higher SBP was still observed among men with allergic rhinitis than among men without allergic rhinitis (129.8 ± 12.8 *vs* 124.1 ± 12.6 mm Hg, p = 0.05).

Kony et al. [2] concluded that SBP was higher in men with allergic rhinitis than in those without it (130 ± 12.7 *vs* 123.5 ± 13.9 mm Hg, p = 0.002), even after controlling for potential confounding factors such as age, body mass index (BMI), hypercholesterolemia and smoking status. However, there was no association between rhinitis and SBP in women. Kony et al. [2] mentioned that a low cardiovascular morbidity rate in premenopausal women may explain the reported association that was restricted to men. These results were corroborated by data from the Wisconsin Sleep Cohort, which found a significant association between seasonal and chronic rhinitis and elevated SBP in men, after adjusting for age, BMI, hypercholesterolemia, smoking and medications used for respiratory conditions that have potential blood pressure-elevating effects [3]. Men reporting seasonal or chronic rhinitis had on average a 3.5 mm Hg higher SBP than those without allergic rhinitis [2].

Heinrich and Doring [4], in attempting to reproduce the results of Kony's study, studied a large population sample of 4,856 subjects aged 25–64. A Hawksley Random Zero sphygmomanometer was used in this study, as opposed to a digital electronic tensiometer in Kony's study. Three BP recordings were taken after the subject was at rest in a sitting position for an average of 30 minutes. Hypertension was diagnosed as SBP greater than, or equal to, 140 or 90 mm Hg diastolic or use of antihypertensive medication. Neither average SBP nor DBP was significantly different between men with and without allergic rhinitis [4]. There is perhaps more operator--dependent variability in manually measuring BP. In addition, in Heinrich's study, participants' BPs were measured from a sitting position, whereas in Kony's study the measurement was done in the supine position [4]. Such methodological differences could be significant, given that the increment in SBP between men with allergic rhinitis and without allergic rhinitis was approximately 7 mm Hg in the Kony study and only 3.5 mm Hg in the Wisconsin study [4].

An association between allergic rhinitis and hypertension had been identified in men, but not in women, until a recent study by Corbo et al. [5]. This found an association between increased SBP and allergic rhinitis in post-menopausal women. On first thought, one may hypothesize that lower estrogen levels, which increase the risk of hypertension, explain the association of SBP and rhinitis as being stronger in post-menopausal than in premenopausal women. However, the prevalence of snoring is also significantly higher in the post-menopausal age group [5]. In fact, habitual snorers were older, with a larger BMI and a larger waist-to-hip ratio than non-snorers. Post-menopausal women with habitual snoring and allergic rhinitis had the significantly highest SBP [5]. A proposed mechanism is that subjects with nasal congestion due to allergy or nasal obstruction were more likely to be habitual snorers, with frequent episodes of apnea and hypopnea during sleep, triggering sympathetic drive and ultimately leading to higher SBP [5]. Post-menopausal women who snore and have allergic rhinitis should be checked for hypertension and for the presence of sleep-disordered breathing.

Chronic sinusitis and hypertension

In addition to allergic rhinitis, other diseases with an allergic etiology are associated with hypertension. Several studies have demonstrated an association between sinusitis and hypertension. Chronic sinusitis has an estimated prevalence in the U.S. of 14% [6]. In a study by Dales et al. [6], both men and women with chronic sinusitis were more likely to have hypertension than those without sinusitis. This analysis was based on data from 52,992 Canadian subjects (25,324 males and 27,668 females) aged 20–60. The data was adjusted for age, smoking status, alcohol consumption, regular exercise and BMI. The adjusted odds ratio between sinusitis and hypertension for females was statistically significant at 1.42 (95% CI 1.04–1.95). For men, it did not meet statistical significance, although it was increased at 1.12.

There appears to be an association between upper respiratory disorders, such as rhinitis and

sinusitis, and systemic arterial hypertension. This association may be explained through the common ground of obstructive sleep apnea. A recent randomized controlled trial demonstrated that continuous positive airway pressure treatment lowered the BP by approximately 3.3 mm Hg in subjects with upper airway disorders treated with continuous positive airway pressure (CPAP) (95% CI 1.3–5.3), as against those that were not [7]. Interestingly, the sinusitis-hypertension association was stronger among women than men, perhaps because the former have smaller sinus ostia [7]. As with obstructive sleep apnea, increases in airway resistance invoke a sympathoadrenal response marked by episodic hypertension [7]. In addition to anatomical obstruction, chronic inflammation is known to play a role in sinusitis, and the resultant inflammatory mediators may increase susceptibility to hypertension. For example, elevated C-reactive protein (CRP) has been shown to increase the risk of hypertension [7]. Perhaps mediators of chronic sinus inflammation may influence endothelial function, explaining the observed association between chronic sinusitis and chronic hypertension [7].

Asthma and hypertension

Asthma is a chronic inflammatory disorder of the airways. Similarly, it is now recognized that inflammation plays a significant role in the pathogenesis of atherothrombosis [8]. Dogra et al. [8] were interested in quantifying the association between cardiovascular disease (CVD) and asthma. A total of 74,342 participants with a mean age of 56.4 ± 12.5 were divided into two groups: asthmatics and non-asthmatics. The characteristics of each group were examined and three outcomes were used to estimate the relationship between asthma and CVD: high BP, heart disease and stroke. Multiple logistic regression models revealed that asthmatics were 1.4 times more likely to have heart disease, and 1.3 times more likely to have high BP, than non-asthmatics [8].

Similarly, Iribarren et al. [9] performed a cohort study among 70,047 men and 81,573 women, 18–85 years old, to determine whether a relationship between asthma and coronary artery disease (CAD) existed. The diagnosis of asthma was through self-report and the primary endpoint was combined non-fatal or fatal CAD. After a median follow-up time of 27 years, and adjusting for age, race/ethnicity, education level, smoking status, alcohol consumption, BMI, serum total cholesterol, white blood cell count, hypertension, diabetes, and history of occupational exposures, asthma was associated with a 1.22-fold (95% CI 1.14–1.31) increased hazard of CAD among women [9]. This association between asthma and CAD has been reproduced in four similar studies [9].

In investigating the mechanism between asthma and CAD, a pro-inflammatory state is common to both disorders. The pathogenesis of atherosclerosis is one of a deregulated immune system and increased inflammatory response. In fact, two pro-inflammatory cytokines that are elevated in asthma, interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha) are also thought to play key roles in the pathogenesis of atherosclerosis [10]. IL-6 has been found in human atherosclerotic plaques, triggers acute phase reactants such as CRP, and activates platelets and mitogenic activity for smooth muscle cells [10]. Elevated CRP levels are associated with age, sex, African-American race, BMI, smoking status, serum lipids, hypertension, presence of diabetes, frequency of exercise and cardio-respiratory fitness [11]. A recent study by Kasayama et al. [11] showed that asthma is an independent risk factor for elevation of CRP levels. The study further demonstrated that plasma CRP levels fell by 30% in response to treatment with inhaled corticosteroids. Thus, one possible mechanism linking asthma to hypertension/CVD may lie in pathways that modulate CRP. In summary, there is an epidemiological relationship between high CRP and incident hypertension but no proof of cause and effect. If the inflammation is successfully treated, one would expect the CRP levels to decline.

Discussion

Among a subset of the population, there may be a relationship between airway-related disease and sodium serum levels. Bronchial reactivity, measured using a histamine challenge test, was associated with elevated 24 hour urine sodium excretion [12]. In fact, extensive study of the plasma of individuals with allergic asthma and/or allergic rhinitis revealed the existence of an unknown serum-borne factor that leads to the accumulation of sodium within platelets, leukocytes, and peripheral blood mononuclear cells [12]. Some have suggested that lysophosphatidylcholine (LPC) may be a likely candidate. Indeed, high serum LPC levels have been associated with increased asthma severity and increased accumulation of $Na+$ in peripheral blood mononuclear cells and leukocytes [12]. Skoner et al. [13] proposed that a defect in $Na+/K+$ pump inhibition therefore leads to intracellular sodium accumulation.

In fact, allergic individuals have been found to have elevated plasma ouabain and altered salt homeostasis [13]. Ouabain is a cardiotonic steroid with a similar mechanism of action as digoxin, ultimately by inhibiting the sodium-potassium ATPase pump. IgE levels were highest in those whose serum contained increased inhibitor activity, suggesting that inhibition of Na+/K+ pump is related to the degree of atopy [13]. Elevated cytosolic levels of sodium promote calcium influx and increases contraction of airway smooth muscle and possibly leading to hypertension. Hypertension in allergic individuals may resolve with a medication that targets the Na+/K+ pump (binding sites for ouabain) [13]. However, there have been no clinical trials to test this hypothesis.

The correlation between allergic disease and hypertension has been established in a few studies. However, the mechanism driving this association has yet to be well elucidated. With regards to sinusitis, allergic rhinitis and asthma, the answer may lie partly in the common ground of obstructive sleep apnea. Allergic individuals with significant nasal congestion/obstruction were more likely to be habitual snorers with frequent episodes of apnea and hypopnea during sleep (i.e. to have obstructive sleep apnea), which then leads to higher SBP and presumably, greater susceptibility to heart disease and stroke. Clinical experience suggests that CPAP plus good control of one's allergies may resolve or facilitate treatment of hypertension.

The effects of sleep-disordered breathing and hypertension are intriguing. Neurohumoral and hemodynamic responses to repetitive episodes of hypoxemia and apnea may offer a pathophysiological basis for patients with disturbed sleep (those with rhinitis, sinusitis, or asthma) having an increased risk for hypertension. The immediate response to hypoxia and hypercapnia is via chemoreceptors which increases minute ventilation and sympathetic responses, ultimately leading to vasoconstriction and marked surges in BPs [14]. The increases in sympathetic activity and BP during sleep in these patients appear to carry over into the daytime, such that patients with disturbed sleep have an increased prevalence of hypertension and high levels of sympathetic nerve activity [14]. Sleep deprivation also has many metabolic consequences, mainly via cortisol activity and insulin resistance, ultimately leading to an increased risk of hypertension, diabetes, and obesity [15].

In addition, the higher prevalence of obesity and a sedentary lifestyle in both asthmatics and hypertensives may muddy the relationship between the two. Obesity has been shown to induce decreased immune tolerance [16]. A greater body weight increases the level of circulating IL-6, leptin and TNF-alpha, skewing the immune system toward the allergen-reactive type 2 helper T-cell [16]. It is well established that this Th2 cytokine profile triggers the activation and/or recruitment of IgE antibody producing B cells, mast cells and eosinophils: the triad involved in allergic inflammation [16]. Because there is a significant increase in this response in obese people, therefore, there is a higher prevalence of diseases of chronic inflammation. These diseases include CVD, type II diabetes, stoke and atopic diseases such as asthma and allergies.

Since allergic rhinitis appears to be a potential co-morbidity for hypertension, the question arises as to whether allergic rhinitis plays a role in other vascular disorders such as myocardial infarction or stroke. In fact, the relationship between allergic rhinitis and stroke was recently the subject of two studies. In the first, by Low et al. [17], increased hospital admission rates for stroke were positively correlated with the presence of upper respiratory infection, pollen allergy, and increased air pollution. In a second study by Matheson et al. [18], a population of 9,272 participants with an average age of 62 was followed over 4.4 years. Patients with a history of stroke or CAD were excluded because of their high risk of stroke. Of the 125 participants who had had strokes, 2.2% of those with a history of hay fever suffered a stroke, compared to 1.25% of those with no history of hay fever ($p = 0.02$) [18]. Participants with a history of hay fever had an unadjusted hazard ratio (HR) of 1.72 (95% CI 1.08–2.27) for stroke *versus* participants without hay fever. Risk of stroke remained significant (HR 1.87; 95% CI 1.17–2.99) after controlling for age, sex, race, smoking status, BMI, diabetes, hypertension, alcohol use, and hyperlipidemia [18].

The mechanism behind this association was initially thought to be through hypertension induced by hay fever. However, even after controlling for diagnosed hypertension, this association remained. Hay fever is associated with the release of inflammatory mediators such as histamine, leukotrienes, prostaglandins and cytokines [18]. Perhaps it is this heightened systemic inflammation that increases the risk of stroke. Another possibility could be the effects of the use of antihistamines. Patients with hay fever who use antihistamines may be at increased risk of stroke because of severe hay fever or an iatrogenic response to antihistamines [18]. Judging by this study, a history of hay fever seems to be a risk factor for stroke. Given the high prevalence of hay fever, (10.8% of patients ages 45–64),

this association may be an area for future research and investigation [18].

Conclusions

The implications of allergic rhinitis, chronic bronchitis, and asthma deserve increased focus on the possibility of co-morbidity for hypertension. Allergic disease and hypertension are increasingly prevalent with each year that goes by. Their common foundation — that of inflammation — and their demonstrated association prompt the question of whether controlling atopy would improve BP control, and *vice versa*. Another interesting question posed is whether the chronic inflammation of poorly controlled atopy would increase vulnerability to cerebrovascular thrombotic events and stroke. Although current data is sparse, it does provide an intriguing hypothesis and an avenue for future approach. If hypertension is indeed partly related to an allergic phenomenon, such an association could significantly change the clinical management of hypertension. As clinicians, one possibility is to screen patients with asthma, sinusitis, or allergic rhinitis for elevated BP or *vice versa*.

In addition to the commonality of inflammation for all of these allergic disorders, another commonality may be the use of sympathomimetic agents, such as nasal decongestants, to relieve allergic symptoms. These medications are clearly capable of producing elevated BP. More research needs to be done to delineate whether allergic disorders are indeed related to hypertension. Confounders such as sympathomimetic agents may be playing a role.

In conclusion, there is mounting evidence that allergic diseases may play a role in the pathogenesis of hypertension. Although associations between allergic diseases and hypertension have been reported, more studies must be performed to elucidate the mechanisms behind such associations. A lot more work needs to be done to prove a causal relationship. A randomized, prospective trial in which two normotensive groups — one with and one without allergies — are compared over time for incidence of hypertension might be useful. As alluded to earlier, the use of vasoconstrictors would have to be monitored. Ultimately, given the epidemiological relationship between allergy and hypertension, therapies that target allergic diseases may also be of benefit in hypertension.

Acknowledgements

The authors do not report any conflict of interest regarding this work.

Helpful comments for this manuscript from Mark Ping Chao (MD Candidate, Stanford University Medical School), Michelle Kim (MD, MD Anderson Cancer Center) and Andre Ba Aung (BA Candidate, Northwestern University).

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