Hypertension and Bronchial Asthma: Mechanisms and Management Postprint

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Abstract

Hypertension and bronchial asthma are common chronic diseases of the cardiovascular and respiratory systems, respectively. Genetic susceptibility, inflammatory mechanisms, and unhealthy lifestyles can all increase the risk of developing hypertension and asthma. In recent years, research on the pathogenesis and disease management of hypertension complicated with asthma has become a hotspot. This article reviews the potential pathogenic associations between hypertension and asthma and the scientific management of hypertension complicated with asthma, providing a theoretical basis for clinical research and treatment of patients with hypertension complicated with asthma.

Full Text

Hypertension Complicated with Bronchial Asthma: Mechanisms and Management

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Abstract

Hypertension and bronchial asthma are common chronic diseases of the cardiovascular and respiratory systems, respectively. Genetic susceptibility, inflammatory mechanisms, and unhealthy lifestyles can all increase the risk of developing both conditions. In recent years, research on the pathogenesis and disease management of hypertension complicated with asthma has become a major focus. This review examines the potential pathogenic links between hypertension and asthma and discusses evidence-based management strategies for patients with both conditions, providing a theoretical foundation for clinical research and treatment.

Keywords: hypertension; bronchial asthma; review

China is home to approximately 245 million patients with hypertension [1] and 45.7 million patients with asthma [2]. Notably, a survey of comorbidities among outpatients with asthma in urban China revealed that 16.4% had coexisting hypertension, ranking second among all asthma-related comorbidities [3]. Conversely, 1-4% of hypertensive patients have comorbid asthma, particularly among elderly asthmatics [4]. Traditionally viewed as independent chronic diseases, accumulating evidence suggests these conditions share pathogenic mechanisms and exert mutual influence. Asthma patients have a higher risk of developing hypertension compared to non-asthmatics, independent of conventional risk factors [5], with blood pressure levels correlating with asthma severity [6] and hypertension risk increasing as lung function declines [7]. Furthermore, hypertension is associated with poor asthma control [8], and declining lung function in asthmatics correlates with increased cardiovascular mortality [9]. Given the bidirectional relationship between cardiovascular and pulmonary dysfunction, and the additional health and economic burdens imposed by drug-drug interactions in this population, investigating the mechanistic links and optimizing management strategies for patients with hypertension and asthma represents a critical public health priority.

I. Mechanisms of Interaction Between Hypertension and Asthma

1. Genetic Factors Contribute Significantly to the Comorbidity of Hypertension and Asthma The co-occurrence of hypertension and asthma is primarily driven by underlying genetic variations. Using bioinformatics approaches, Bragina et al. [10] and Zolotareva et al. [11] prioritized genes

potentially involved in this comorbidity, identifying TLR4, CAT, IL-10, and ANG/RASE4 as having the most pronounced impact. TLR4 induces pro-inflammatory responses against invading pathogens and participates in pathogen recognition and innate immune activation. TLR4 deficiency promotes neutrophil infiltration by impairing apoptosis through upregulation of Bcl-2 receptors, thereby exacerbating airway hyperresponsiveness and inflammation [12]. TLR4 also modulates angiotensin II-induced vascular smooth muscle cell proliferation via regulation of the NLRP3 inflammasome, thereby influencing hypertension development [13]. CAT, a component of the antioxidant system, prevents hypertension when overexpressed [14] and shows enhanced activity during asthma treatment [15]. IL-10 exhibits potent anti-inflammatory effects, induces T cell immune tolerance to antigens, and promotes nitric oxide production. Relative IL-10 deficiency occurs in asthmatic populations [16], while its upregulation reduces blood pressure and normalizes endothelial function [17]. The ANG/RASE4 gene primarily induces neovascularization. Collectively, these findings underscore the importance of inflammation, angiogenesis, and oxidative stress in the pathogenesis of both diseases, aligning with clinical observations of shared pathophysiological changes such as vascular remodeling, endothelial dysfunction, and abnormal smooth muscle cell contraction and proliferation.

2. Systemic Inflammation as a Common Pathogenic Basis Systemic inflammation underlies the pathogenesis of both hypertension and asthma and contributes to adverse outcomes and disease burden [18]. Studies have shown that C-reactive protein levels—a systemic inflammatory marker associated with interleukin-6 and hypertension—correlate with the rate of lung function decline [19], suggesting a potential link between hypertension and asthma mediated by systemic inflammation affecting both disease courses.

Asthma is currently classified into two major endotypes: Type 2-high inflammation and Type 2-low inflammation. Research indicates that the comorbidity of hypertension and asthma is characterized by the Type 2-low inflammatory endotype [20]. Asthma patients with Type 2-low inflammation exhibit higher hypertension prevalence compared to those with Type 2-high inflammation [20]. Interferon-γ (IFN-γ), a cytokine associated with Type 2-low inflammation, promotes M1 macrophage secretion, directly contributing to blood pressure elevation and adverse outcomes, while elevated IFN-γ levels in asthma patients correlate with airway hyperresponsiveness and severe asthma [21]. Conversely, hypertension predisposes T cells toward increased IFN-γ responses and decreased T helper 2 (Th2) cell responses [21]. Therefore, hypertensive patients with asthma predominantly display innate and adaptive immune features of the Type 2-low inflammatory endotype, which facilitates airway hyperresponsiveness, smooth muscle hypertrophy and hyperplasia, structural remodeling, and mucus secretion while simultaneously promoting vascular tone elevation and blood pressure increase [22]. Consequently, asthmatics with hypertension often present with late-onset, corticosteroid-insensitive, refractory asthma.

Interleukin-17 (IL-17) also plays a crucial role in hypertension development and end-organ damage. IL-17 induces a pro-inflammatory phenotype in vascular smooth muscle cells by increasing release of mediators including IL-6, IL-8, IL-10, and C-reactive protein [23]. IL-17 is intimately involved in asthma pathogenesis, with elevated levels associated with neutrophil infiltration, airway hyperresponsiveness, and corticosteroid insensitivity. IL-17 also induces pro-inflammatory cytokine secretion from lung structural cells and airway smooth muscle, including tumor necrosis factor-α, IL-1β, IL-6, and eotaxin, which are critical in airway inflammation and remodeling.

The interplay among cytokines such as IFN-γ, IL-17, and IL-6 drives the development and progression of both hypertension and asthma. These cytokines promote smooth muscle cell proliferation and fibrin deposition through shared inflammatory pathways, constituting the pathological basis for vascular remodeling and endothelial dysfunction in both airway and cardiovascular diseases, and playing pivotal roles in their pathogenesis.

3. Smooth Muscle Activation Smooth muscle function is essential for both airway and vascular physiology. Calcium and potassium channels expressed on vascular smooth muscle cell (VSMC) membranes determine arterial lumen diameter and vascular tone, serving as the final effectors of airway tone and targets of various inflammatory factors. The large-conductance calcium-activated potassium channel (BK^+Ca) is the most abundant potassium channel on VSMCs, critically regulating bronchodilation, airway hyperresponsiveness, and the dynamic balance between vasoconstriction and vasodilation [24]. Upregulated BK^+Ca channel expression in smooth muscle cells impairs vasodilatory function, with primary hypertensive patients showing significantly higher BK^+Ca channel activity than non-hypertensive individuals [25]. Various cytokines and inflammatory mediators such as IL-4 and bradykinin, as well as neurotransmitters including acetylcholine and serotonin, can activate BK^+Ca channels, participating in airway smooth muscle contraction and proliferation [24].

BK^+Ca activity is closely associated with hypoxic responses. Hypoxia induced by bronchial asthma leads to increased reactive oxygen species (ROS) production, elevated intracellular calcium, and dysregulated hypoxia-inducible factor-1α (HIF-1α) signaling, which reduces BK $ 1$subunitexpression, decreasesBKchannelCa\hat{}\{2+\}$ sensitivity, maintains membrane depolarization, and triggers L-type Ca^{2+} channel activation, ultimately causing hypertension [25]. Targeting BK^+Ca channels significantly reduces airway smooth muscle cell reactivity, serum cytokine levels, nitric oxide production, and inflammatory cell infiltration, positioning BK^+Ca channels as promising therapeutic targets for allergic airway inflammation [24].

4. Obesity and Metabolic Dysfunction Obesity represents a major risk factor for both asthma and hypertension and significantly impacts asthma control. Meta-analyses of over 100,000 participants have demonstrated that maternal obesity and gestational weight gain increase the risk of childhood asthma

and wheezing in offspring, beginning in utero [26]. Obesity is also a key driver of hypertension development, increasing the risk of hypertension 3.5-fold through mechanisms including sodium retention, renin-angiotensin and sympathetic nervous system activation, and adipokine dysregulation, with approximately 60% of hypertension attributable to obesity [27]. Mechanistic studies reveal that obesity increases airway hyperresponsiveness risk, with many obese asthmatics exhibiting Th1-activated responses mediated by systemic inflammation, insulin resistance, and/or altered lipid metabolism [28]. Obesity polarizes CD4 cells toward Th1 and promotes infiltration of pro-inflammatory M1 macrophages, directly elevating blood pressure [29]. Furthermore, IL-6 secreted by adipocytes and inflammatory macrophages in white adipose tissue can directly contribute to both asthma and hypertension through methylation and other processes [30].

5. Dietary Salt Dietary salt intake correlates with cardiovascular disease development, with the relationship between high salt intake and blood pressure elevation well-established. Beyond effects on the kidneys, sympathetic nervous system, and vasculature, high salt intake profoundly influences the immune system via Th17 cells. Studies show that high-salt diets promote Th17 cell generation through alterations in gut microbiota, thereby modulating the relationship between salt intake and hypertension and asthma [31]. Th17 cytokines recruit neutrophils to airways by increasing epithelial-derived neutrophil chemoattractant secretion, with epithelial cell-derived IL-1β and IL-23 inducing neutrophilic inflammation upon Th17 stimulation [32]. Th17 cytokines also induce mucous cell metaplasia and exert pleiotropic effects on airway smooth muscle, causing airway narrowing and irreversible obstruction. Additionally, Javaid et al. found that increasing dietary salt intake in asthmatic patients significantly elevated histamine levels, while salt restriction improved asthma symptoms and reduced bronchodilator use [33].

II. Management of Patients with Hypertension and Asthma

Management of patients with hypertension and asthma requires a multifaceted approach, including controlling both diseases, treating comorbidities, and implementing lifestyle modifications. Because antihypertensive or asthma control medications may affect blood pressure or asthma control, maximizing preventive measures, minimizing and cautiously using specific drug classes, and emphasizing non-pharmacological interventions are particularly important. Calcium channel blockers (CCBs) reduce extracellular Ca^{2+} influx, relaxing vascular smooth muscle while inhibiting bronchial smooth muscle contraction, preventing mast cell histamine release, reducing pulmonary vascular resistance, and dilating pulmonary vessels, making them first-line agents for hypertensive patients with asthma. Renin-angiotensin system inhibitors demonstrate significant efficacy in suppressing airway remodeling and warrant clinical promotion. Non-selective beta-blockers should be contraindicated in patients with unstable

asthma, while cardioselective β_1-blockers should be used conditionally.

1. Antihypertensive Therapy in Patients with Hypertension and Asthma The Chinese Hypertension Prevention and Treatment Guidelines [34] indicate that five major classes of antihypertensive drugs can be used as initial therapy, but recommend individualized treatment based on specific populations and comorbidities. For hypertensive patients with asthma, treatment selection must consider asthma-related issues with each medication class (Table 1).

Table 1: Antihypertensive Drugs–Indications, Side Effects, Considerations for Asthma, and Positioning

Drug Class	Indications/Side Effects & Precautions	Asthma-Specific Considerations	Positioning
Thiazide diuretics	First-line or add-on; may cause hypokalemia or hyponatremia	Caution required: SABA, theophylline, and corticosteroids can lower serum potassium; risk increases with higher doses	First-line or add-on for CKD, CHF, and MI; may elevate potassium and creatinine; angioedema; contraindicated in pregnancy

Drug Class	Indications/Side Effects & Precautions	Asthma-Specific Considerations	Positioning
ACEI	May cause cough; can trigger/worsen asthma—use with caution	Can reduce bronchial reactivity; potential first-line option for asthma-hypertension comorbidity	First-line or add-on for CKD, CHF, and MI; may elevate potassium and creatinine; angioedema; contraindicated in pregnancy
ARB	First-line or add-on; may cause edema; constipation and cardiac conduction block possible with β-B combination	May benefit smooth muscle contraction and triggers; recommended as first-line in asthma-hypertension comorbidity	First-line or add-on
CCB	Not recommended for monotherapy; indicated for CHF, MI, and arrhythmias; may cause bradycardia, fatigue, insomnia; peripheral circulation and glucose/lipid metabolism impairment	Can trigger bronchospasm; contraindicated in unstable asthma and severe airflow obstruction	-
β-blockers	-	-	-

Note: ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; CCB: Calcium channel blockers; β-B: Beta-blockers

Beta-blockers: Beta-blockers are classified as non-selective (targeting both β_1 and β_2 adrenergic receptors) or relatively cardioselective (primarily targeting β_1 receptors). A meta-analysis found that short-term β-blocker therapy caused a small decrease in forced expiratory volume in one second (-6.9%) in asthmatic patients, with symptom exacerbation occurring only with non-selective agents

[35]. Beta-blockers also reduce asthmatic patients' responsiveness to β_2-agonists: cardioselective agents diminish drug efficacy, while non-selective agents abolish it entirely [35], indicating adverse effects on asthma pharmacotherapy. However, some studies suggest cardioselective β-blockers do not affect clinical symptoms, lung function, or rescue medication use in mild-to-moderate chronic airway disease [36]. Given their bronchoconstrictive effects and impact on β_2-agonist therapy, β-blockers should be contraindicated in unstable asthma or severe airway obstruction. Moreover, β-blockers are generally not recommended as first-line monotherapy for hypertension; in patients with compelling indications such as arrhythmia, myocardial infarction, or congestive heart failure, cardioselective β-blockers (preferably low-dose) may be used [34].

Angiotensin-Converting Enzyme Inhibitors: ACEI use may cause drug-related cough, leading to discontinuation in nearly one-fifth of patients due to impaired breakdown of bradykinin and other inflammatory peptides and increased bradykinin-dependent sensitivity of airway sensory nerve fibers. A case-control study in hypertensive patients with asthma found ACEI use associated with increased asthma incidence, higher short-acting β-agonist use, more emergency visits/hospitalizations, and greater systemic corticosteroid requirements [8]. Despite being a major antihypertensive class generally well-tolerated by most asthmatics, ACEI is not contraindicated in asthma-hypertension comorbidity and can be used as first-line therapy, though clinicians must monitor for potential adverse effects in susceptible individuals.

Angiotensin Receptor Blockers: ARBs lower blood pressure by blocking angiotensin type I receptors. Studies show elevated angiotensin II and renin levels during asthma exacerbations compared with stable periods [37], suggesting a pathogenic role for the renin-angiotensin system in asthma. Angiotensin II receptor antagonism significantly reduces immune cell counts in bronchoalveolar lavage fluid and decreases Th2 (IL-4, IL-5, IL-13) and Th1 (IL-2, IFN-γ) cytokine expression in allergic asthma mouse models, demonstrating potential anti-allergic effects [38]. Angiotensin II receptor blockade also attenuates bronchial hyperresponsiveness and reduces bronchial smooth muscle contraction. ARBs do not cause cough or increase airway reactivity and have fewer adverse effects. The ACE2/Ang(1-7)/Mas receptor pathway has emerged as a potential therapeutic target in asthma, alleviating allergic airway inflammation, reducing hyperresponsiveness, and slowing remodeling [39,40]. Given that ARBs simultaneously target pathways relevant to both hypertension and asthma without affecting ACE kininase function or causing cough, they represent promising first-line agents for hypertensive patients with asthma.

Calcium Channel Blockers: Ca^{2+}-dependent excitation-contraction and stimulus-secretion coupling mechanisms are central to asthma pathophysiology, with Ca^{2+} involved throughout bronchial constriction, mast cell mediator release, vagal reflex stimulation, airway mucosal gland secretion, eosinophil chemotaxis, and even smooth muscle remodeling [41]. CCBs reduce smooth muscle contraction, relieve bronchospasm, and induce mild bronchodilation,

demonstrating definitive anti-asthmatic effects. Studies show CCBs improve lung function [42] and airway remodeling in severe asthma, making them the preferred therapy for asthma-hypertension comorbidity [34], particularly with concomitant coronary artery disease.

Thiazide Diuretics: Low-dose thiazides (alone or in combination) are first-line for hypertension. However, in hypertensive patients with asthma receiving diuretics plus short-acting β-agonists, theophylline, and corticosteroids, the risk of hypokalemia increases further. Diuretics also increase hematocrit and reduce bronchial mucus secretion, impairing sputum clearance. Therefore, thiazide diuretics should be used cautiously in asthmatics receiving corticosteroids, theophylline, and high-dose β_2-agonists.

III. Asthma Pharmacotherapy in Hypertensive Patients

Asthma medications include β_2-agonists, corticosteroids, leukotriene modifiers, theophylline, anticholinergics, antihistamines, mast cell stabilizers, selective Th2 cytokine inhibitors (suplatast), recombinant humanized anti-IgE monoclonal antibody (omalizumab), anti-IL-5 antibodies (mepolizumab), among others, some of which affect blood pressure [43]. β-agonists can elevate or worsen existing hypertension, with frequent short-acting β_2-agonist use associated with increased cardiovascular risk. High-dose oral corticosteroids can induce sodium and water retention, with hypertension being a major cardiovascular complication of systemic corticosteroid therapy, necessitating close blood pressure monitoring in asthmatics requiring oral corticosteroids. Systemic corticosteroids can also worsen hypertension or impair efficacy of other antihypertensive agents, so their use should be minimized.

Inhaled corticosteroids have minimal blood pressure effects. Low-dose inhaled corticosteroids control airway inflammation and may reduce blood pressure in mild asthma [8]. Anticholinergics and theophylline are widely used in asthma with minimal blood pressure impact. Anticholinergic bronchodilators are recommended for asthmatics who cannot tolerate β_2-agonists or experience β-blocker-induced asthma exacerbations.

IgE participates in vascular remodeling by activating mast cell Fc RI receptors, with IL-6 serving as a key mediator that promotes reactive oxygen species production and reduces phosphorylated endothelial nitric oxide synthase (p-eNOS) levels in endothelial cells, causing endothelial dysfunction and blood pressure elevation [44]. The anti-IgE monoclonal antibody omalizumab blocks IgE binding to Fc RI and CD23 receptors on inflammatory cells, attenuating Th2-type inflammatory immune responses [45], reducing asthma symptoms and exacerbations while significantly decreasing oral corticosteroid requirements [46]. Therefore, anti-IgE therapy may inhibit angiotensin II–induced pathological vascular remodeling and hypertension, representing a novel therapeutic avenue for hypertensive patients with elevated serum IgE or allergic disease history.

IV. Non-Pharmacological Management of Asthma and Hypertension

Unhealthy lifestyles (high salt intake, obesity, smoking, alcohol consumption, sedentary behavior, reduced physical activity) increase the prevalence of both hypertension and asthma. Lifestyle modifications (sodium restriction, dietary changes, alcohol moderation, healthy eating, regular exercise, weight control, smoking cessation) serve as first-line antihypertensive measures, enhancing blood pressure control, improving prognosis in hypertensive patients, and exerting beneficial effects on asthma control and outcomes [47,48].

V. Summary and Outlook

The comorbidity of hypertension and asthma is associated with shared genetic dysregulation, systemic inflammation, and unhealthy lifestyles. Abnormal smooth muscle contraction and proliferation, vascular dysfunction, and systemic inflammation represent common features of both diseases. Type 1 and Type 17 inflammatory pathways warrant particular attention in the pathogenesis of hypertension-asthma comorbidity. Pharmacological management must consider drug-drug interactions between antihypertensive and asthma control medications, with CCBs and ARBs recommended as first-line antihypertensive agents. If blood pressure control is inadequate or other comorbidities exist, low-dose thiazide diuretics and selective β-blockers may be considered. Healthy lifestyle modifications are crucial for managing both conditions.

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Note: Figure translations are in progress. See original paper for figures.