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Studying the relationship between allergo-inflammation and left atrium and pulmonary vein pathological changes in allergic asthma

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Abstract
Allergic asthma is an inflammatory airway disease influenced by genetic and environmental factors and orchestrated by imbalance between T helper 1 cell (Th1) and two immune responses. Inflammation contributes to pathological changes and remodeling in tissues such as the vascular, lung, heart, and beds. The purpose for this study was to evaluate the effects of allergic asthma on heart pathology and remodeling. In methodology, mice were allocated into two healthy and asthma groups, followed by the assessment of airway hyperresponsiveness (AHR), cell enumeration in bronchoalveolar lavage fluid (BALF), measurement of interleukin (IL)-4, IL-33, IL-5, interferon gamma (IFN-γ), and IL-13, total immunoglobulin E (IgE) levels, and analysis of remodeling factors. Also, gene expression analysis was performed for troponin, suppressor of mothers against decapentaplegic (SMAD)2, myocyte enhancer factor 2 (MEF-2), and SMAD3. Finally, histopathological study was conducted. The result revealed that asthma induction augmented AHR and elevated eosinophil percentage, elevated the levels of IL-13, IL-33, IL-5, IL-4, IgE, Helicobacter pylori (HP), and transforming growth factor beta (TGF-β), and the gene expression of SMAD3. Also, eosinophilic inflammation, goblet cell meta/hyperplasia, and mucus secretion were increased in asthmatic versus healthy mice. The level of IFN-γ was lower in the asthma compared to the control group; however, the expressions of troponin, SMAD2, and MEF-2 genes showed no significant differences. It was concluded that allergic asthma changed the balance between type 1 and 2 cytokines, which could possibly lead to profound effects on the cardiovascular system's structure and/or function.

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Introduction

Asthma is a notable inflammatory airway disease—a significant cause of death in the world, especially in developed countries. Patients usually complain of recurring episodes of cough, breathlessness, wheezing, and chest tightness, which is associated with variable degrees of mucosa hypersecretion, inflammation, bronchial hyperresponsiveness, and airways obstruction. Other characteristic features include bronchial gland enlargement, increased smooth muscle mass, and goblet cell hyperplasia. The most common approach for the management of asthma is medical therapy; however, continued use of medications can result in side effects.[1-3]

Pathophysiology and pathogenesis of asthma is influenced by genetic predisposition and environmental factors, which can stimulate the immune system, specifically the Th2 response. Asthma is orchestrated by immune-related allergic responses and an imbalance between Th1 and 2 branches, leading to dysregulated pulmonary immune reactions, disbalanced pro- and anti-inflammatory factors, and respiratory complications.[4,5]

Inflammation contributes to pathological and/or physiological immune processes, recruitment of certain types of immune cells, and local vascular remodeling, contributing to various diseases, including asthma and pulmonary and cardiovascular diseases. Thus, inflammatory responses and related mediators/signaling pathways are usually recognized as potential risk factors, disease initiators, and/or therapeutic targets.[6-8]

The left atrium (LA), due to important mechanical features, has an important role in the modulation of left ventricular (LV) filling and cardiovascular performance. In fact, LA promotes distinct interrelated functions as a reservoir for pulmonary venous comeback during ventricular systole as well as a conduit for pulmonary venous comeback during early ventricular diastole. The LA acts as a booster pump to augment ventricular filling during late ventricular diastole. Notably, there is considerable interplay between ventricular performance and functions of atrium throughout the cardiac cycle. Conduit function is also influenced by atrial compliance during ventricular diastole and is closely related to LV compliance and relaxation.[9,10]

The pulmonary vein (PV) drains oxygen saturated blood from the lungs to the LA, typically existing as four distinct branches. PV stenosis can originate from either intrinsic narrowing or extrinsic compression, and pulmonary hypertension (PH) is another condition that can disturb the lung's blood circulation.[11,12] In this study, the effects of allergic asthma on LA pathological changes and remodeling and their association with allergo-inflammation reactions were investigated in mice models.

Materials and Methods

Experimental mouse models

A total of 14 mice (male Bagg Albino [BALB]/c, 6–7 weeks old) were acclimatized to the laboratory animal house. All experimental methods and protocols were carried out according to the animal handling guidelines of the institutional animal ethical committee. The mice were divided into two groups (N = 7 mice in each group): healthy control and asthma groups. All mice during the study received water and also food ad libitum. On days 1 and 14 of study period, the mice were sensitized by ovalbumin (OVA) emulsified in aluminum hydroxide (alum adjuvant) through intraperitoneal injection to induce asthma. On days 24, 26, 28, and 30, the mice were challenged with intranasal OVA solution through a nebulizer. Healthy control animals received normal saline following the same protocol.

Airway hyperresponsiveness assessment

In each group, three mice were used for the assessment of airway hyperresponsiveness (AHR) and others for histopathology and biofactor analyses. The AHR test was assessed in response to the methacholine (MCH) challenge via intubation and measured by determining the enhanced pause (Penh value) reported as a ratio.

Cell enumeration in BALF

One day after the last challenge (on day 31), the mice were euthanized, tracheotomized, and then the bronchoalveolar lavage fluid (BALF) was sampled. Differential cell count was performed on BALF slides to determine the percentage of eosinophil in BALF.

Cytokines

BALF's supernatant was obtained and stored until utilization for measuring the levels of cytokines. The Bioplex-Multiplex method was employed to determine the levels of interleukin (IL)-4, IL-33, IL-5, interferon gamma (IFN-γ), and IL-13 in the supernatant of BALF.

Immunoglobulin E determination

Serum of mice was separated from blood samples, and the level of total immunoglobulin E (IgE) was measured by an enzyme-linked immunosorbent assay (ELISA) kit following the manufacturer's protocol.

Factors of remodeling

To assess tissue remodeling in the lung, hydroxyproline (HP) content, as an important collagen deposition index, was evaluated by a colorimetric modified method, according to a previously described method.[8] Also, transforming growth factor beta (TGF-β), as an anti-inflammatory cytokine and a main remodeling factor, was evaluated in the supernatants of homogenate lung tissue.[8]

Gene expression

To study the gene expression of cardiac-related biomolecules, troponin, suppressor of mothers against

decapentaplegic (SMAD)2, myocyte enhancer factor 2 (MEF-2), and SMAD3 were analyzed using the real-time quantitative polymerase chain reaction (qPCR). For this purpose, the LV of mouse heart was used to extract total ribonucleic acid (RNA), which was reverse transcribed to complementary deoxyribonucleic acid (cDNA) by using specific primers, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the internal control gene.

Histopathological assessments

After the tissue (heart and lung) collection and fixation, histological section slides were prepared and stained and then evaluated using light microscopy for tracking changes in the heart atrium. In the lung tissue, eosinophilic infiltration around airways and vessels, hyperplasia of goblet cell, and mucus hypersecretion were assessed.

Statistical analysis

Data were shown as mean ± SD (standard deviation) through the usage of GraphPad Prism. To analyze the difference between groups, the paired *t*-test was applied in SPSS (Statistical Package for the Social Sciences) software and then compared. A *p*-value of less than 0.05 was considered to indicate statistically significant variations.

Results

AHR

This was observed when the Penh value increased in the asthma group compared to the healthy control group for all MCH concentrations (Figure 1); this elevation was statistically significant ($p < 0.05$) in most of the MCH concentrations.

Cell counting in BALF

Eosinophil percentage was significantly higher in the asthma group (82% ± 3%) than the healthy group (4% ± 1%) ($p < 0.05$).

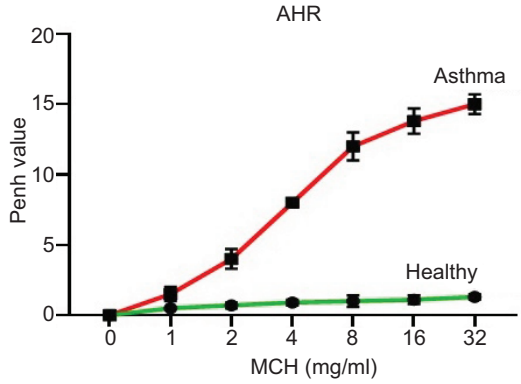

Figure 1 Airway hyperresponsiveness. The methacholine challenge test in the study groups. The symbol * shows significant difference between two groups.

Cytokines

The main type 1 (IFN-γ) and type 2 (IL-13, IL-33, IL-5, and IL-4) cytokines had changes in both groups. On the one hand, the levels of type 2 cytokines in the asthma group were significantly ($p < 0.05$) higher than in the healthy group (Figure 2); but on the other hand, the level of IFN-γ was significantly lower in the asthma group than in the healthy group ($p < 0.05$).

Total immunoglobulin E

The main allergic immunoglobulin (total IgE) showed a significantly elevated level in asthmatic mice (2811 ng/mL ± 268 ng/mL) compared to healthy animals (209 ng/mL ± 11 ng/mL), denoting a significant difference ($p < 0.05$).

Tissue remodeling factors

In the asthma group, the HP level, as a main tissue remodeling factor, was significantly elevated ($p < 0.05$) compared to the healthy control group. Also, the mean level of TGF-β, as another tissue remodeling factor, was significantly higher in the asthma group ($p < 0.05$) than in the healthy group (Figure 3).

Gene expression

To evaluate the potential effects of asthma induction on the gene expression of cardiac-related biofactors (involved in cardiac pathological conditions), the expression was measured. At the gene expression level, troponin, SMAD2, and MEF-2 showed no significant ($p > 0.05$) changes in the asthma and healthy groups (Figure 4); however, SMAD3 was significantly upregulated ($p < 0.05$) in the asthma group compared to the healthy group.

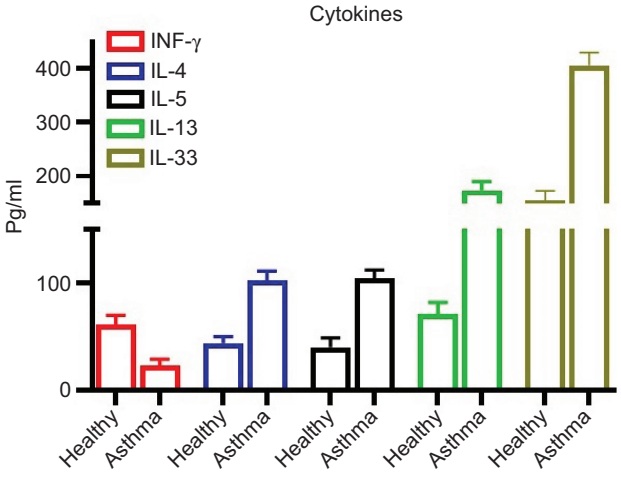

Figure 2 Cytokines. The levels of IFN-γ, ILs-4, ILs-33, ILs-5, and ILs-13 were evaluated in all groups. The symbol * shows significant difference between two groups.

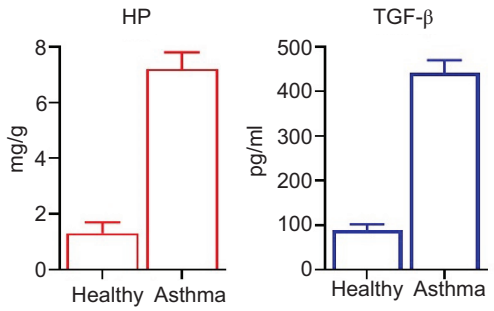

Figure 3 Remodeling factors. TGF-β and HP were evaluated in all groups. The symbol * shows significant difference between two groups.

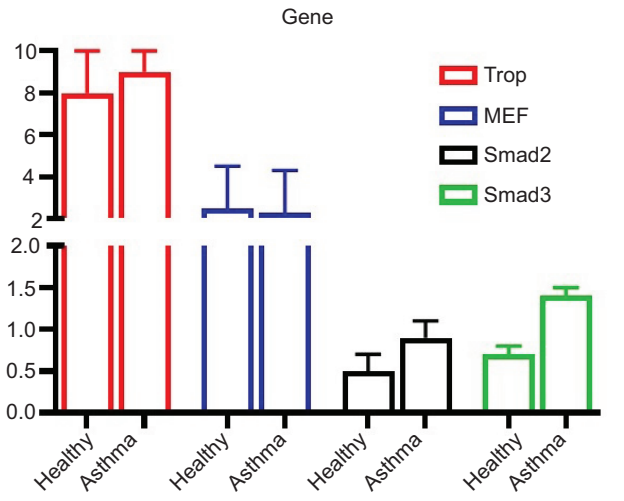

Figure 4 Gene expression. The expression of troponin, SMAD2, MEF-2, and SMAD3 were evaluated in all groups. The symbol * shows significant difference between two groups.

Histopathology

Histopathological studies of the heart and lung tissues revealed no significant changes in LV histopathology in the healthy or asthmatic mice (Figure 5). In the lung, eosinophilic inflammation around airways and vessels, goblet cell hyperplasia, and mucus secretion were significantly enhanced in the asthma group ($p < 0.05$) compared to the control group (Figure 5).

Discussion

Lung has a strong effect on the heart and also heart has a strong effect on the lung. One of the main interaction is observed in cardiac asthma. Cardiac asthma refers to a type of asthma characterized by LV failure, which is already damaged due to coronary artery sclerosis, hypertension, or aortic valve diseases. In a small group of patients in an earlier study, however, paroxysmal dyspnea results from stenosis of mitral without myocardial failure, while in others the attacks are usually precipitated by emotional distress, exertion, or paroxysmal tachycardia.[9-11,13-16]

When the rate of heart is accelerated due to various reasons, blood is expelled by the hypertrophied right ventricle into pulmonary circulation more rapidly than it could pass through the narrowed mitral orifice. The resulting congestion causes paroxysmal dyspnea and acute PH, which may be accompanied by asthmatic breathing that may progress to acute pulmonary edema.[17,18] Cardiac dyspnea is often confused with asthma or bronchospasm induced by exercise. Cardiac asthma is the consequence of pulmonary edema due to PV hypertension (PVH) rather than asthmatic bronchoconstriction; for distinguishing cardiac from pulmonary dyspnea, cardiopulmonary stress tests are necessary.[18] Cardiac asthma results in breathing difficulties caused by cardiogenic pulmonary edema and asthmatic bronchoconstriction, in reality a reflexive bronchoconstriction and a manifestation of pulmonary congestion PVH. As a matter of fact, cardiac asthma is only a presentation of cardiac dyspnea. Heart failure is defined as systolic failure with reduced diastolic dysfunction due to a stiff heart or LV ejection fraction (HFrEF [heart failure with reduced ejection fraction]) and/or a valvular heart disease but with preserved LV ejection fraction (HFpEF [heart failure with preserved ejection fraction]).[18] In PVH, prolonged and chronic elevation of hydrostatic pressure disrupts the alveolar-capillary units of protective layers. The disrupted integrity of the capillary membrane allows water and also proteins to flux across the capillary into the alveolar sac, culminating in pulmonary edema.[18,19]

Increased hydrostatic pressure and PVH can promote precapillary vascular changes and trigger the remodeling of precapillary arterioles, primarily associated with an increase in vascular tone and medial hypertrophy due to "muscularization." Vascular remodeling progresses to intimal and adventitial hyperplasia and plexiform lesions as well as the development of obstructive vasculopathy. Moreover, progression of vascular remodeling is associated with increased pulmonary vascular resistance. Hyperplastic remodeling is irreversible and portends a poor prognosis.[20,21] Pulmonary function can be influenced by lung water content, and also interstitial edema affects breathing, which may lead to airflow obstruction through airway resistance. In this condition, several mechanisms can be involved for the increased airway resistance. Elevated capillary hydrostatic pressure and edema cause reflex bronchoconstriction, reduced lung volume decreases geometric bronchial size, intraluminal edema obstructs bronchi, and finally, bronchial mucosal edema exerts a profound effect on airway resistance.[22,23] In asthma, key remodeling factors are considerably elevated, which can subsequently affect other tissues' functional output (such as the cardiovascular system).

Asthma and atrial fibrillation (AF) with distinct phenotypes share common inflammatory pathophysiological pathways. Inflammation plays a key role in the initiation and progression of AF. Coagulation markers such as D-dimer and fibrin degradation products are elevated in both asthma and AF. The products of fibrin degradation enhance inflammation via stimulating monocyte differentiation and releasing IL-6.[24-28] There are currently no clear inflammatory/coagulation biomarkers interconnecting AF and asthma subtype. Asthma is one of the potential risk factors of AF. Furthermore, long- and short-acting β2 agonists as

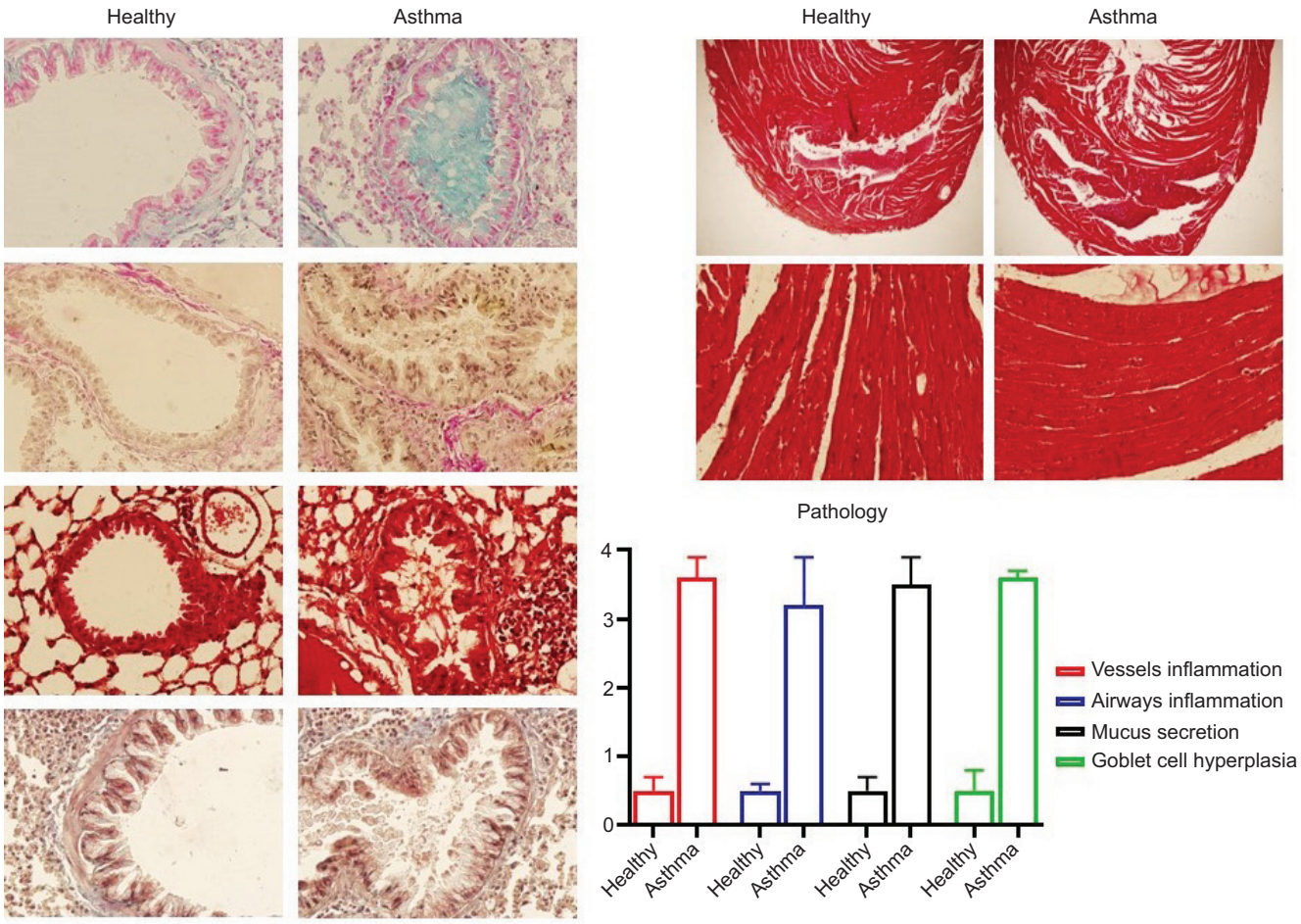

Figure 5 Histopathology. Pathological changes were evaluated in the heart and lung, showing eosinophilic inflammation around airways and vessels, hyperplasia of goblet cells, and mucus hypersecretion in the lung. The symbol * shows significant difference between two groups. The black arrow shows mucus secretion, the green arrow shows goblet cells, the yellow arrow shows berivascular inflammation, and the blue arrow shows beribronchial inflammation.

the most common prescribed asthma medications influence the heart rate and increase the risk of arrhythmias. It has been proposed that these medications may explain the association between AF and asthma.[29-31] In this study, the increase of Penh value was observed in the asthma group after the MCH challenge. This increase indicates breathing difficulties in the asthma group, which could have affected heart-related vascular beds.

Primary vasculature inflammation and vascular leak are characteristic features of severe asthma; however, allergic inflammation drives angiogenesis and angiogenic mediators can lead to asthmatic inflammation. Moreover, the epithelial cells of the airway produce growth factors and vascular inflammatory mediators as well. Also, eosinophils directly promote angiogenesis via releasing proangiogenic mediators.[32,33] In this study, histopathological assessments in the heart tissue revealed no significant changes in the LV of the healthy and asthmatic mice. In the lung tissue, eosinophilic inflammation around airways and vessels, goblet cell meta/hyperplasia, and mucus secretion were enhanced in the asthma group. Also, the percentage of eosinophils in BALF was increased in asthmatic mice, indicating eosinophilic inflammation in the pulmonary system.

TGF-β is a key player in the process of pathological pulmonary fibrosis, and the TGF-β1/SMAD3 pathway is one of the important mechanisms promoting pulmonary fibrosis.[34,35] By binding to TGF type II receptor, TGF-β recruits SMADs 2/3, and the phosphorylated complex is translocated to the nucleus, where it modulates gene transcription via cyclic adenosine monophosphate (cAMP) response element binding protein (CBP)/p300 histone acetyltransferases, leading to cell proliferation and fibronectin production.[36-40] In our study, TGF-β as a main remodeling factor was increased in asthmatic mice, indicating tissue remodeling and fibrosis in the lung and heart. However, the level of IFN-γ as the main type 1 cytokine was decreased in the asthma group compared to the control group while the levels of type 2 cytokines (IL-13, IL-33, IL-5, and IL-4) were increased in asthmatic animals. These changes reflect the initiation and empowerment of inflammation, especially allergic inflammation, in the lung. Moreover, IgE as another allegro-inflammatory factor was increased in asthmatic animal compared to healthy models, explaining atopic reactions.

A transcription factor, MEF-2, regulates the structural development of various tissues, including the cardiac

muscle. MEF-2A-D, as a member of the MEF-2 family, play critical roles in muscle differentiation and cardiovascular function.[41] In neurons and lymphocytes, MEF-2 is highly expressed, acting as a regulator of immune and neuronal cell differentiation and function. MEF-2 is necessary for IL-2 transcriptional activation during the activation of peripheral T cells and plays an important role in T cell apoptosis via regulating the expression of nuclear receptor subfamily 4, group A, member 1 (NUR77). MEF-2 is coupled with a variety of regulatory proteins: p300, p/CAF, calcineurin-dependent 2 (NFATC2), nuclear factor of activated T cells, mitogen-activated protein kinase 7 (MAPK7), nuclear receptor coactivator 2 (NCOA2), myogenic differentiation 1 (MYOD), class II histone deacetylases (HDAC4-9), and calcineurin binding protein 1 (CABIN1). Further, this transcription factor is regulated by calcium-dependent and MAPK signaling cascades. MEF-2 integrates a number of overlapping cellular signaling pathways, which are influenced by calcium signaling. The deficiency of MEF-2C is associated with defects in the production of T, B, natural killer (NK), and common lymphoid progenitor cells.[42,43] In this research, while evaluating the potential effects of asthma on the gene expression of cardiac-related pathological markers, we noticed no significant changes in the gene expressions of troponin, SMAD2, and MEF-2 between the asthma and control groups; however, the expression of SMAD3 was significantly upregulated in the asthma group, suggesting the initiation of lung tissue remodeling.

Allergen exposure is linked to circulatory system inflammation, and the inflammatory gene expressional changes correlate with inflammatory markers in circulation. Therefore, allergen exposure may be the one risk factor for cardiovascular injury and inflammation of the circulatory system.[44] In clinical situations, we have a less-understood perception of the link between cardiovascular complications and pulmonary ventilation diseases. A number of potential pathophysiological mechanisms can induce AF in patients with asthma. Among these, hypoxia plays a dominant role by promoting oxidative stress, which contributes to electrophysiological abnormalities in atrial muscle cells and finally, to the development of AF.[45] Chronic intermittent hypoxia promotes tissue remodeling in the atrium and alters atrial autonomic structure, predisposing to AF. Among the pathophysiological mechanisms involved in chronic intermittent asthma, hypoxemia and hypercapnia can lead to pulmonary arteriole contraction, increasing pulmonary artery and right atrium pressure. The latter (i.e., elevated right atrial pressure) can then cause the right atrium to expand, resulting in endocardial vessels' hemodynamic alterations, blood flow reset, atrial contraction, and increased susceptibility to arrhythmia.[46,47] Due to the presence of β2 receptors on the cardiac muscle, inhalation of β2 agonists by asthma patients is considered another potential predisposing factor to cardiac electrophysiology disturbance.[48-50] Inflammation may play a role in promoting the development of vein wall fibrosis. Allergic reactions can cause inflammation in the heart and PVs and disrupt the normal electrical conduction in the PVs, potentially increasing the likelihood of ectopic beats and AF. Inflammation can also lead to structural changes in the LA, such as increased left atrial wall thickness and altered PV size, further contributing to AF. Understanding the role of inflammation is crucial for diagnosis and management of these conditions.[51-54] Understanding the relationship between cardiovascular complications and chronic pulmonary ventilation diseases plays a key role in the management of this disease.

Allergo-inflammation may contribute to the pathology of LA and PVs, potentially leading to conditions like AF and/or PV stenosis. Allergic reactions can cause inflammatory reaction in the heart and surrounding tissues, including the PVs that can disrupt normal electrical activity and lead to abnormal heart rhythms. Additionally, inflammation may contribute to the development of PV stenosis, a narrowing of the PVs, which can impair blood flow from the lungs to the heart. While PV stenosis can occur due to other factors like catheter ablation for AF, allergic inflammation can also play a role in its development. Inflammation can damage the delicate lining of the PVs, leading to scarring and narrowing. PV stenosis can cause symptoms like shortness of breath, coughing up blood (hemoptysis), and chest pain. The PVs are often the source of electrical impulses that trigger AF. These veins contain muscle tissue that can develop abnormal electrical activity, which leads to ectopic beats and ultimately AF.[51-54] In this study, several limitations are noteworthy. We could not evaluate the prolonged chronic effects of asthma on LV and PV in the long run. Also, we could not evaluate other important cardiac and pulmonary biomarkers. Specific tissue staining techniques, functional studies, and evaluation of signaling pathways were not performed in the heart. Also, we could not study the blood circulatory effects of the heart on asthmatic lungs.

Ethics Approval and Consent to Participate

This research was approved by the ethics committee of animal house of ix.med.vet.dep, 2024 (No. IX.MED.VET.DEP.REC.2024.0200011.2).

Consent for Publication

Not applicable.

Availability of Data and Materials

Data are available on request from the corresponding author.

Acknowledgments

Not applicable.

Authors' Contributions

DZ, HX, SSA, and XH have participated in all stages of the study.

Conflicts of Interest

There are no conflicts of interest.

Funding

None.

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