Original Article

Arrhythmia And Asthma Relationship

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Abstract

Uncontrolled asthma can be complicated by cardiac conduction disturbances and arrhythmias. Medications used to treat asthma have been associated either directly or indirectly with cardiac rhythm disorders. There is limited data on the burden, predictors and impact of arrhythmia in hospitalized asthmatic children. Therefore, we conducted this study to examine these issues.

Introduction:

Asthma was independently associated with an increased risk of developing future arrhythmia. Inhaled corticosteroids, oral corticosteroid as well as bronchodilator were independently associated with increased risk of arrhythmia. New users of corticosteroids and bronchodilator in 6 months had the highest risk of arrhythmia **(1)**.

Relationship between Arrhythmia and Asthma:

Cardiovascular disease is the most frequent cause of death among hospitalized asthma patients. Several studies suggested that asthma is an independent risk factor for cardiovascular disease (CVD) and arrhythmias. Previous studies described high prevalence of tachycardia, premature ventricular contractions and AFib among patients with asthma **(2, 3)**.

Taha et al. identified a total of 12 988 129 patients admitted with primary diagnosis of asthma disease from 2010 to 2014. Among those, cardiac arrhythmia was reported in 2 014 459 (16%) patients. The most frequent arrhythmias in the descending frequency were atrial fibrillation (8.95%), followed by non-AFib arrhythmia including: nonspecific arrhythmia (3.86%), atrial flutter (0.93%), ventricular tachycardia (0.88%), sinoatrial nodal dysfunction (0.44%), and paroxysmal supraventricular tachycardia (0.35%). In-hospital mortality rate in asthma hospitalizations was higher in patients with atrial fibrillation (3.40%) followed by ventricular tachycardia (3.25%) **(1)**.

The main reason is that these studies followed up asthma patients in clinic who generally had mild disease compared to our hospitalized patients and arrhythmias have been found to be associated with disease severity **(4)**.

Previous study demonstrated that asthma is not just a local inflammatory disease but rather a systemic inflammatory disease with high serum levels of inflammatory markers (**5)**.

This systemic inflammation can increase the risk of arrhythmias directly or indirectly by enhancing the formation and rupture of coronary atherosclerotic plaques **(1)**.

It is also known that the cardiac conduction system is affected by hypoxia, causing pronounced electrophysiological changes in the myocardium (impaired repolarization, decreased electrical activity). Myocardial

dystrophy develops, accompanied by reduced cardiac output and impaired acid-base balance, which is a trigger for arrhythmias **(6)**.

Leukotrienes mediate bronchoconstriction, mucus secretion, and local edema in the bronchioles. Leukotrienes have systemic effects; leukotriene receptors are highly expressed in the heart and intricately associated with the conduction system **(7)**.

Prior studies have demonstrated that pharmacological reduction of leukotrienes with a 5 lipo-oxygenase inhibitor decreases heart rate, enhances heart rate variability, and in the setting of permanent AF, improves heart rate control. These leukotrienes may represent a set of upstream inflammatory markers, resulting in downstream effects because leukotriene B4 is a potent inducer of IL-6 production **(8)**.

The exact mechanism of arrythmia in asthma disease is poorly understood and likely multifactorial. The pathogenesis of asthma is characterized by chronic inflammation of airways. This inflammation may play a role in developing arrythmias in asthmatics as inflammation is a well-established risk factor for arrhythmias. Other than inflammation, respiratory failure and bronchodilator therapy are also possible mechanisms of arrythmias in asthma disease **(9)**.

The first mechanism is related to respiratory failure associated with asthma exacerbation. A higher risk of arrhythmia and mortality among asthma patients with respiratory failure requiring invasive or noninvasive ventilation **(10)**.

The second mechanism is based on the association between inflammation and arrhythmias. Chronic airway inflammation is the pathogenesis of asthma disease. Inflammatory cells accumulate in the airway, activate cytokines, and enhance airway remodeling **(11)**.

The third mechanism is related to asthma therapy. Several studies provided evidence that asthma therapy like bronchodilators and corticosteroids increased the risk of arrhythmias and this might confound the association between asthma and arrhythmia **(12)**.

There are other plausible mechanisms for an increased risk of AF. Dysfunction of the airway autonomic nervous system may be involved in the airway hyperresponsiveness observed in patients with asthma. Similarly, dysfunction of the autonomic nervous system may induce significant and heterogeneous changes of atrial electrophysiology, causing cardiac arrhythmia**(13)**.

Distension and dilation of the atria are among the important pathophysiological mechanisms for the formation of supraventricular cardiac arrhythmias. As demonstrated by **Schotten et al.**, this leads to the uneven supraventricular spread of impulses from the sinus node, as well as the formation of re-entrant circuits inside the atrium (14).

Electrocardiographic changes that accompany an increase in airway obstruction may also be due to autonomic mechanisms. Respiratory homeostasis is known to be controlled by the sympathetic and parasympathetic nervous systems. In BA, there is an increase in the tone of the parasympathetic nervous system, meanwhile the abnormal activity of the parasympathetic nervous system can be closely associated with the pathogenesis of asthma and is reflected in heart rate variability **(15)**.

Parasympathetic influences slow down the heart rate and prolong PQ. However, our data indicate only PQ lengthening without associated bradycardia. The vagal effect is probably not the only mechanism of delayed conduction of supraventricular impulses **(16)**.

Previous studies of COPD patients identified frequent occurrence of cardiovascular events including arrhythmias **(17)**. Pilot studies using continuous ECG monitoring in COPD patients suggested high prevalence of

ventricular premature beats and ventricular arrhythmias (VT) but these studies were limited in size (largest N=75) hence limiting their ability to stratify COPD by its objectively documented severity (PFT) or accounting for confounding variables **(4)**.

Recent retrospective study (N=7441) confirmed that the prevalence of VT on Holter monitoring correlated with COPD severity, but whether this association was merely a reflection of the reduced LVEF caused by ischemic cardiomyopathy commonly seen in COPD patients, or whether mortality could be correlated with VT remained unclear **(18)**.

For this reason, a substantial caution has to be exercised when interpreting these data, even though limited evidence showed that non-sustained VT detected in the ambulatory setting carried prognostic value for the occurrence of sudden cardiac death **(19)**.

5 lipo-oxygenase activity differs significantly based on sex, with male neutrophils producing less leukotrienes compared with female neutrophils. Thus, this pathway may be a plausible explanation for the differing strength of the asthma and AF association by sex. Other potential AF triggers in asthma may include specific asthma treatments, such as oral glucocorticoids and β-agonists and methylxanthines. Because asthma treatment is based on asthma severity and the severity of asthma is associated with higher levels of systemic inflammation, the role of controller medications is difficult to discern. As new biologic agents emerge in the treatment of asthma, this may reduce the corticosteroid burden and allow for a different perspective in delineating the association of asthma and AF **(20)**.

Clinically, the prevalence of undiagnosed and silent AF remains high and undetected AF can lead to deleterious consequences, such as thromboembolic events, heart failure, and progression of AF as a chronic disease state **(21)**.

Thus, identification of populations at higher risk for AF development can lead to (1) earlier diagnosis/management of AF and (2) guide secondary (and possibly primary) preventive efforts. Traditional cardiovascular disease risk factors of hypertension, obesity, and obstructive sleep apnea also are strong modifiable risk factors for AF **(22)**. Additionally, addressing obesity through weight reduction programs and treating sleep apnea in asthmatic patients has been demonstrated to improve asthma symptoms **(23)**.

That said, insufficient control of BA, in turn, can cause the formation of various pathological conditions. For example, there are studies showing the risk of cardiac arrhythmias and conduction disorders in patients with uncontrolled BA due to functional changes or pathological remodeling of the myocardium **(**24,25).

Atrial remodeling, which is the pathomorphological basis of serious supraventricular cardiac arrhythmias, has a more rapid progression with poor BA control and is formed as a result of excessive stretching of the atrial wall, as well as other adverse factors **(26)**.

The connection between bronchial asthma (BA) and supraventricular arrhythmias, including atrial fibrillation (AF), was noted in studies by **Warnier et al., Goudis et al.,** and **Cepelis et al. (2;27; 28)**. Available data indicate that in the adult population, cardiac arrhythmias are significantly more common in patients with BA than in those without it **(24; 28)**. The results of a Norwegian population study HUNT study, demonstrate that the risks of supraventricular arrhythmias and AF are increased in patients with an uncontrolled BA **(27)**.

Despite the fact that AF is diagnosed primarily in adult patients with BA, other supraventricular arrhythmias are described in patients with childhood BA **(29)**. At the same time, there are a number of studies demonstrating the development of atrial remodeling and changes in the electrophysiological properties of the atria of children with BA **(30)**.

Consequently, it should be noted that in the study of **Çiftel et al.** it was found that patients with BA are characterized by disorders of electrophysiological properties of the right atrium, which consist of an increase in the intra-atrial and interatrial conduction time. This, according to the authors, can be considered as a predictor of supraventricular arrhythmias in patients with BA, the risk of which increases as the severity and duration of uncontrolled asthma increases **(31)**.

Electrocardiography (ECG) is the universal screening method for assessing the state of the atrial myocardium and the conducting system of the heart. According to **German et al.** ECG analysis can make a significant input to the assessment of the risk of formation of supraventricular rhythm and conduction disorders. Therefore, the analysis of the atrial component of the ECG, and atrioventricular conduction in patients with BA is an important component of the management of these patients, especially in pediatric practice. Consequently, the study of the characteristics of the ECG and its supraventricular component in children with BA is relevant **(32)**.

Considering the available data on the reduced rate of atrial conduction in patients with an insufficient level of asthma control, it is important also to study the relationship between ECG parameters that characterize the atrial complex and atrioventricular conduction, that reflect the severity of bronchial obstruction, an important component in the formation of clinical manifestations of asthma **(33,34)**.

Parameters of the supraventricular component of the ECG (PQ, sPQ segment, rPQ) were statistically significantly higher in patients who had severe manifestations of bronchial obstruction (Tiffeneau index lower than 75%) compared with children who had no bronchial obstruction or were from mild to moderate (Tiffeneau index higher than 75%), all $p < 0.05$. At the same time, in **Gordina et al.** study, no differences in the amplitude, shape, and duration of the P wave in patients with different degrees of severity of bronchoconstriction were observed; the median values of P-wave duration in all three groups with different values of the Tiffeneau index were close to 0.08 sec, all $p > 0.05$ **(35)**.

This is consistent with the data of **Ghandi et al.**, in whose study, on comparing patients with BA with healthy children, it was found that the maximum and minimum duration of the P-wave were identical in subjects of both groups, although the dispersion of the P-wave was higher in patients with asthma **(29)**.

Currently, new data have been made available about the oneness of the cardiopulmonary system, including the presence of cardiomyocytes in pulmonary vein tissue, as described in a review by **Folmsbee and Gottardi**. The relationship between certain BA phenotypes and the electromechanical properties of the heart has also been demonstrated. This may, in the future, serve as a starting point for treatment aimed at achieving BA control, being targeted toward corresponding cardiorespiratory mechanisms **(36)**.

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