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SMALL AIRWAYS IN ASTHMA

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MALI DISAJNI PUTEVI U ASTMI

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ABSTRACT

Asthma is a chronic inflammatory lung disease characterized by reversible obstruction of airways and bronchial hyperresponsiveness. In recent years there has been a growing interest in the role of the small airways in asthma and there is increasing evidence that they contribute significantly to the clinical expression of asthma. Numerous studies have shown that inflammation is present in the small airways of patients with asthma and that it may be more intense than that found in the large airways, particularly in severe asthma, nocturnal asthma, coexisting asthma and obesity and asthma in smokers. Currently there is no accepted single lung function parameter to detect small airways dysfunction. Recent data show that impulse oscillometry is a promising diagnostic tool to assess the involvement of the small airways. The use of corticosteroids in extrafine formulation, whether alone or in fixed combinations with long-acting b2 agonists, improves drug distribution throughout the bronchial tree, enhancing the therapeutic effect with lower doses of drugs.

Key words: *asthma; bronchioles; inflammation.*

SAŽETAK

Astma je hronična inflamatorna bolest pluća koju karakterišu hiperreaktivnost bronhijalnog stabla i reverzibilna opstrukcija disajnih puteva. Poslednjih godina pažnja se fokusira na ulogu malih disajnih puteva u astmi i nađeni su mnogobrojni dokazi o njihovom značajnom uticaju na kliničke manifestacije bolesti. Brojne studije su pokazale da postoji inflamacija u malim disajnim putevima i da je intenzivnija od one u većim disajnim putevima, posebno kod bolesnika sa teškom astmom, noćnom astmom, kod gojaznih pacijenata i pušača. Trenutno ne postoji prihvaćena pojedinačna dijagnostička metoda za preciznu procenu disfunkcije malih disajnih puteva. Najnoviji podaci pokazuju da je impulsna oscilometrija dijagnostička metoda koja mnogo obećava u proceni malih disajnih puteva u astmi. Upotreba kortikosteroida u formi ekstrafinih čestica, bilo posebno bilo u fiksnoj kombinaciji sa dugodelujućim beta 2 agonistima, poboljšava distribuciju leka kroz bronhijalno stablo, a time se nižim dozama leka postiže bolji terapijski učinak.

Ključne reči: *astma; bronhiole; zapaljenje.*

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways, characterised by both hyperresponsiveness of the bronchial tree and reversible obstruction of the airways. According to WHO (May, 2011), around 235 million people suffer from asthma. It is estimated that the global prevalence of asthma ranges from 1 to 18% of the total population of different countries. The results of the study conducted in Serbia in 2009-2010, show that asthma was newly diagnosed in 13% of the cases (1). It is estimated that asthma accounts for 250,000 deaths worldwide each year (2).

The pathophysiology of asthma has traditionally been attributed to an inflammatory process that occurs predominantly in the large airways

The tracheobronchial tree is a system of airways that allows the passage of air from the trachea to alveoli. At each generation branching is dichotomous, that is - each airway is being divided into two smaller daughter airways (3,4), but in peripheral areas branching is mostly trichotomous. The respiratory tree consists on average of 23 generations: the conducting zone with airway generations 0-16, the respiratory zone 17-23 generations, with alveolar ducts and alveolar sacks as an actual respiratory zone (Fig 1).

With each division, the air passages become narrower, but as their number geometrically progresses as they continue to divide, the total airway cross section increases exponentially from 2.5 cm^2, in the trachea to 1.2 m^2 prior to entering the alveoli.

The first seven branching generations make up the large airways, and are followed by small airways with inner diameter of 0.5 to 2 mm (3). However, due to the heterogeneity of the airways, the small airways are found as early as from 4th branching generation, whereas the large airways can spread as far as the 12^{th} branching generation. Small airways are histologically characterised by non-cartilaginous wall, but are conversely comprised of a thin layer of active smooth muscles, fibrous and elastic fibres. Support is provided by alveolar connections, hence, the small-airway collapses due to the loss of alveolar attachment or changes in muscle tone.

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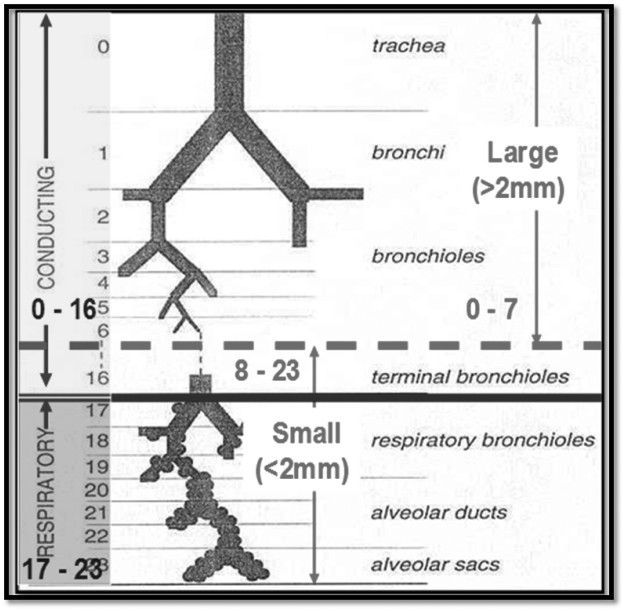

Figure 1. Schematic diagram of the small airways division

PATHOPHYSIOLOGICAL RESEARCH

The concept of small airways was developed by Weibel in the 1960s, and it is based on the quantitative study of the lung anatomy (3). In vivo canine study, using both bronchoscopy (so-called 'wedge technique') and balloon catheterisation, showed that small airways resistance comprises from 10 to 20% of total respiratory system resistance (6). Therefore, the small-airway disease and the presence of comorbidities may be presented with a slight deviation in standardised lung function testing (such as spirometry) with a few or no symptoms, so consequently Mead in his later work dubbed them the 'quiet zone' of the lungs (7).

Nevertheless, the study revealed a striking difference in peripheral airway resistance between asthmatics and healthy individuals, which was sevenfold higher in patients with mild asthma compared to the control group (8). In the same clinical study, a bronchoprovocational test with metacholine showed a significantly increased resistance in small airways. (8). Kraft et al. confirmed that patients with nocturnal asthma have a higher peripheral airway resistance at night than during daytime (9).

Although small airways were initially understood as the 'quiet zone' of the lungs, after a large body of research confirmed an increased resistance in them, they have come to be recognized as the major site of airway obstruction, especially in specific asthma phenotypes.

PATHOHISTOLOGICAL RESEARCH

Up until now, a relatively small number of studies have dealt with pathohistological features as well as specific changes in small airways in patients with asthma. The application of fiberoptic bronchoscopy, namely transbronchial biopsy, bronchoalveolar lavage, along with the development of molecular biology, has led to an advanced understanding of the pathogenesis of bronchial asthma (10). During the examination of the lung tissue specimens of patients who died after a sudden severe asthmatic attack, a large number of bronchioles had an increased amount of lumen occlusion, smooth muscle thickness and both mononuclear cells and eosinophils compared to the control group – the patients who died of other causes, with negative anamnesis for respiratory diseases (11). A study that provided us with more specific information dealt with central and peripheral airways inflammation, using lung resection specimens from the patients suffering from asthma as well as from those who did not suffer from the disease. Inflammatory cells that have a central role in asthma - Th2 cells and eosinophils were found in both large and small airways. The number of activated eosinophils, as well as those of a major basal protein however, were significantly greater in the small airways (12). In addition, IL-5 expression of one of the most important cytokines that takes part in the inflammation in asthma is significantly present in small airways (13). Haley demonstrated that localisation, density as well as the type of the inflammatory cells was different in small and large airways with patients who suffer from asthma. The greatest density of the inflammatory cells in the small airways (including eosinophils, chymase-positive mast cells) is found on the outside region of the airway wall (i.e., between the smooth muscle and the alveolar attachments), whereas most of the eosinophils in the large airways were found in the "inner" airway wall region (i.e., between the basement membrane and the smooth muscles) (14). This difference in the distribution of cells between the large and small airways are disease specific (characteristics of asthma), as they were not observed in cystic fibrosis.

Alveolar tissue inflammation is also seen in patients who suffer from nocturnal asthma, which could be of significance in asthma pathogenesis. Patients with nocturnal asthma had increased numbers of eosinophils in their lung parenchyma at night compared to patients with non-nocturnal asthma Moreover, NA patients had a greater number of eosinophils and macrophages in their alveolar tissue at night than during the day. (9).

Airway remodelling is a common finding in asthma. Collagen deposition and an increase in volume of smooth muscles in peripheral airways in patients who suffer from asthma shows that a certain degree of remodelling exists in small airways as well (15). As it has been reported, the outer wall of small airways is the major site of remodelling in fatal asthma, with an increase in both collagen type 1, and fibronectin, decreased collagen 3, decrease in elastic

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fibres, and increased matrix metalloproteinase (16). Moreover, it has been confirmed that the decrease in elastic fibres along with the alveolar collapse result in the rupture of alveolar attachments. (17). Asthma is characterised by an increased airway smooth muscle mass which leads to an acute bronchoconstriction and contributes to bronchial hyperreactivity. As it has been previously noted, increased smooth muscle mass in small airways is a common feature of asthma, and with specific stimuli present, it can contribute to hyperreactivity.

The aforementioned inflammatory phenomena, remodelling and smooth muscle contractions lead to the small airway obstruction and hyperreactivity. Airway obstruction leads to the airflow obstruction, as one of the main characteristics of asthma.

DIAGNOSTIC METHODS FOR SMALL AIRWAY ASSESSMENT

The need for a non-invasive method for the assessment of small airways is an imperative for the everyday clinical practice. Basically, two groups of non-invasive methods are recognised: lung function tests and imaging (visualisation).

Pathophysiology of the small-airways diseases is mainly characterised by the premature airway closure, air trapping, lung hyperinflation and regional distribution of ventilation inequalities. Tests that focus on these characteristics can be useful surrogates to detect and quantify small airways disease. The total cross-sectional area of the airways increases toward the lung periphery, airflow velocity decreases and airflow itself becomes laminar (turbulent in large airways). The obstruction of small airways affects ventilation distribution, whereas air trapping occurs due to the closure of small airways. There is still no single pulmonary function test with acceptable cut-off values for assessment and evaluation of the levels of severity of small airways obstruction. The majority of tests are indirect markers or so-called surrogate parameters of the small airways.

Pulmonary function tests that assess small airways can be classified as: tests for measuring airflow and resistance of the airways, air-trapping and hyperinflation assessment tests, and tests for assessing non-homogeneity of ventilation distribution (Table 1)

Table 1. Small airways assessment tests

Diagnostic Tests (Parameters)	**Evaluation**
Spirometry (FEV1, FVC)	airway airflow
Curve flow / volume (MEF25%, MEF 50%, FEF 25-75%)	
Static volume and capacity measurements (TLC, FRC, RV, VC, IC, SVC)	hyperinflation, air trapping
Impulse Oscillometry (R20, R5, X5)	airway resistance
Visualisation methods (HRCT, He-MRI)	hyperinflation, air trapping

The most widely used test for pulmonary function assessment is spirometry. In obstructive pulmonary disease (COPD), spirometry records a decreased forced expiratory volume in 1 second (FEV1), below 80%, but the parameter itself does not provide enough information on the small airway obstruction. Furthermore, it is confirmed that FEV1 can have normal values even with a substantial obstruction of small airways present (8). In the second half of the test, toward the end of forced expiration, forced vital capacity (FVC) depends substantially on the degree of airflow limitation, thus logically, the indicators of flow rate at low lung volumes (MEF 50% and especially MEF 25%) would be reliable predictors of obstruction of small airways. These parameters, however, show a significant inconsistency when making multiple measurements and are considerably affected by large airways obstruction. Hence, the flow rate at low lung volumes (the end of the expiration) may reflect the status of small airways provided that lung elasticity is preserved, and with no large airway constriction present (preserved FEV1). FEF 25-75% is often mentioned as a good indicator of small airway obstruction. However, its value is largely affected by the obstruction in the large airways; it lacks specificity due to its inconsistency during multiple measurements, and as such is less reliable (19).

Lung hyperinflation is assessed by measurements of static lung volumes and lung capacity. The increase in total lung capacity (TLC) and functional residual capacity (FRC) is commonly recognized in patients with COPD and severe asthma due to lung hyperinflation. Residual volume (RV) increases due to the collapse of peripheral airways at the beginning of expiration (air-trapping), with a decrease in VC and inspiratory capacity (IC) as a direct consequence. IC is a good predictor of a degree of air trapping and exercise tolerance. Persistent retention of air in the lungs after expiration, due to the obstruction of small airways is reflected in an increase in RV/ TLC ratio. A decrease of FVC if RV is increased can indicate air trapping. The difference between inspiratory slow vital capacity (SVC) and FVC, as well as the FVC/SVC ratio have been used as surrogate markers of small airways collapsibility. It is reported that there is a considerable decrease of a FVC/TLC ratio irrespective of the change in FEV1 with patients with obstructive bronchiolitis who undergo a lung transplantation (20). The result indicates that decreasing FVC/SVC ratio reflects the changes in the obstruction of small airways. Nonetheless, further research is necessary to evaluate the sensitivity of the parameter. Moreover, air-trapping can be expressed through a decrease in FVC during bronchoprovocation challenge testing with a dose of methacholine causing a 20% fall in FEV1 (21).

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Impulse oscillometry (IOS) is a method employed to determine the mechanical properties of the lung and respiratory system, by measuring respiratory impedance (22). It is a non-invasive method, suitable for function testing, and requires only passive cooperation by the patient. Increased resistance at lower frequencies (5Hz, R5) without any change in resistance at higher frequencies (20Hz, R20) and an increase of a respiratory reactance (X5) indicate an increased resistance in peripheral airways. Increased resistance in peripheral airways measured by IOS is an indicator of heterogeneous ventilation. The parameters of IOS show that there is a significant increase in peripheral airways resistance in patients who have severe asthma (23).

Thoracic High resolution computed tomography (HRCT) together with helium MRI are currently the most accepted imaging tools for evaluation of small airways. Currently available thoracic HRCT does not permit visualization of airways <2-2.5 mm in diameter, which consequently makes it impossible to directly verify small airways abnormalities. HRCT can be used to evaluate air trapping and inhomogeneous ventilation distribution, thus providing indirect information on small airways. The HRCT findings of small airways disease consist of patchy areas of high and low attenuation of the lung parenchyma – called mosaic perfusion – which is thought to be the consequence of reflex vasoconstriction in under-ventilated areas of the lung (24). This is specifically accentuated in HRCT scans obtained at the end of expiration of the patient (Fig 2). The problem with this method and its wider application in routine clinical practice is patient radiation exposure. In technical terms, it is demanding and expensive.

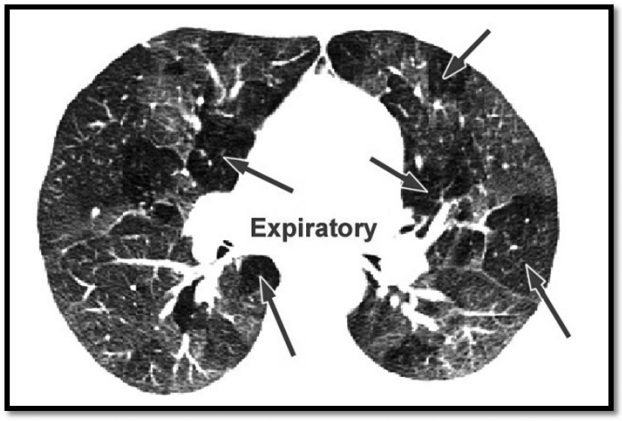

Figure 2. Thoracic HRCT - mosaic perfusion, indirect indicator of obstruction of the small airways

TREATMENT OF SMALL AIRWAYS ASTHMA: CHARACTERISTICS

Asthma treatment guidelines were created by GINA and are organised into five steps based on the control level. Inhaled corticosteroids (ICSs) and long-acting Beta2 agonists are the first-line therapy. In order to reach the small airways, the average particle diameter of an inhaled drug should range from 1 to 2μm. The new 'generation' of inhalers with extrafine particles considerably increases the deposition of the drug in the lungs. Initial clinical studies confirmed that drugs in the form of extrafine particles when compared to conventional form of ICS, had lower oropharyngeal deposition (20-30% vs 80%) and higher lung deposition (50-60% vs 10-20%) (25).

It has been shown that patients with asthma treated with ICS with extrafine particles exhibited a similar increase in FEV1 with 2.5-fold lower dose when compared with conventional (non-extrafine) form of ICSs (26). Administration of the drug in extrafine formulation enables a maximum drug release at the desired site (lungs) with a maximum decrease in drug dose. In this way, it is possible to achieve substantial benefits of topical application and reduce the risks of systemic adverse effects at the same time.

A recent published study on selective research of ICS effect on small airways using IOS dealt with the comparison of the effects of ICS with extrafine particles (HFA-BDP) to those of conventional ICS (CFC-BDP) on small airways, when administered to mild-to-moderate asthmatics. It was shown that after 12 weeks R5-R20 (peripheral obstruction markers measured by IOS) progressively improved with HFA-BDP. The effect on R20 and spirometric parameters was similar in both groups (27).

It leads us to a conclusion that extrafine particles considerably decrease hyperinflation which reflects the obstruction of the small airways.

CONCLUSION

A number of clinical studies confirmed that inflammation in asthma affects all parts of the tracheobronchial tree. The main focus in the last few years has been turned to the small airways inflammation due to the fact that poor control of this inflammation significantly contributes to the disorder of the lung function and remodelling of the airways as the main characteristics of asthma. It is still not known whether all patients with asthma have small airways involvement or if a "small airways phenotype" exists. Small airways are thought to be more affected in severe asthma, nocturnal asthma, asthma in smokers and coexisting asthma and obesity. Recognizing physiological characteristics of the small airways and pathological changes in them, respectively, has facilitated the discovery of the diagnostic methods for small airways assessment. Impulse oscillometry is a sensitive method for computing peripheral resistance. Further studies are required to evaluate all these tests and

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their diagnostic relevance, as well as therapeutic response and follow-up in case small airways are affected by a pathological process in asthma. A characteristic of therapy for small airways in asthma is in application of ICS with extrafine particles, as separate drug or in a fixed combination with long-acting beta 2-agonists, which enables their improved deposition in lungs. Further clinical trials are required in order to estimate whether this type of medication can achieve clinical advantage in long-term disease control.

ABBREVIATIONS

BAL - Bronchoalveolar lavage

CC - Closing capacity

COPD - Chronic obstructive pulmonary disease

CV - Closing volume

FEF 25-75% - Forced expiratory flow with 25-75% FVC

FEV1 - Forced expiratory volume in 1 second

FRC - Functional residual capacity

FVC - Forced vital capacity

GINA - Global Initiative for Asthma

HRCT - High-resolution computed tomography

IC - Inspiratory capacity

ICSs - Inhaled corticosteroids

IOS - Impulse oscillometry

LABA - long-acting beta2-agonists

MRI - Magnetic resonance imaging

NA - Nocturnal asthma

RV - Residual volume

SVC - Slow inspiratory vital capacity

TLC - Total lung capacity

VC - Vital capacity

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