Asthma is the most common chronic disease in children and has also a high prevalence among all ages. The disease has a substantial economic impact and affects significantly the quality of life of asthmatic patients. It is well established that asthma is a specific type of chronic inflammation in the airways, although the precise etiology of this inflammation is not well understood. Multiple aspects of the inflammatory syndrome in asthma require more studies, including the precise role of each inflammatory cell type and the best way to evaluate the severity of the disease and the response to treatment. The understanding of asthma as a chronic inflammatory syndrome has influenced the development of multiple experimental and clinical studies concerning the pathophysiology of airway inflammation, the relationship between this inflammation and bronchial hyperresponsiveness, and the development of programs of long term care of asthmatics.

The central focus of our project was the pulmonary inflammation in asthma and we will perform studies with animal models of pulmonary allergic inflammation, studies with lungs and cell cultures from the lungs of people that died from asthma and also clinical studies with children and adults with asthma.

In this project we focus on:

1. The effects of nitric oxide and capsaicin-sensitive nerve fibers in the modulation of pulmonary inflammation in guinea pig and murine models of chronic airway inflammation.

2. The modulation of chronic airway inflammation by corticosteroids and leukotrienes using a guinea pig model of chronic airway inflammation.

3. The pulmonary expression and activity of nitric oxide synthase in experimental models of asthma and chronic obstructive pulmonary disease (COPD) and in people who died with asthma and COPD.

4. Evaluating the characteristics of airway inflammation in people who died from asthma or chronic obstructive pulmonary disease and correlation with clinical data.

5. The effects of physical training on airway inflammation, functional status and quality of life in children and adults with moderate and severe persistent asthma as well as its effect on airway inflammation in animal models of asthma.
Our main findings were:

1) Aerobic training (AT) in asthmatic children reduced the severity of exercise-induced bronchoconstriction, post-exercise breathlessness and daily doses of inhaled steroids as well as improved health-related asthma quality of life scores. In asthmatic adults, AT increased the number of days without asthma symptoms and decreased the levels of eNO and eosinophil cells in the sputum.

2) In a murine model of chronic asthma induced by ovalbumin (OVA), AT decreased eosinophil counting in the bronchoalveolar lavage fluid and in the airway walls, and reduced the expression of IL-4 and IL-5 by peribronchial inflammatory cells. OVA-sensitized animals submitted to AT presented an increase the expression of IL-10 and a reduction in airway remodeling.

Conclusion: These findings suggest that AT is associated with beneficial effects on disease control and quality of life in asthmatic children and reduces airway allergic inflammation in asthmatic patients and in a murine model of asthma.

3) Airway inflammation in patients that have died due to asthma (fatal asthma) was investigated and we observed an increase in the number of eosinophils and mast cells in the outer area of larger airways, small membranous bronchioles and in peribronchiolar parenchyma. The number of CD3+, CD4+ and CD20+ cells was increased in the intrapulmonary airways. Increased neutrophil counting was also observed in peribronchiolar parenchyma.

Conclusion: Our findings provide further evidence of the importance of the lung periphery in the pathophysiology of fatal asthma.

4) The role of constitutive nitric oxide synthase (cNOS) and inducible NOS (iNOS) isoforms were investigated in a model of chronic allergic inflammation in guinea pigs. The inhibition of both NOS isoforms increased resistance of the respiratory system and collagen deposition on airways and decreased airway inflammation (edema and cell mononuclear cell migration). Specific inhibition of iNOS reduced resistance of the respiratory system, eosinophilic and mononuclear cell recruitment, and collagen and elastic fibers content in airways.

Conclusion: Our findings suggest that both NOS isoforms modulates bronchoconstriction and airway inflammation and remodeling.


