Evaluation of some Inflammatory Markers in Exhaled Breath Condensate in Patients with Bronchial Asthma

Thesis

Submitted for Partial Fulfillment of the Master Degree In

Chest Diseases

By

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(M.B.,B.Ch, Ain Shams University, 2005)

Under Supervision of

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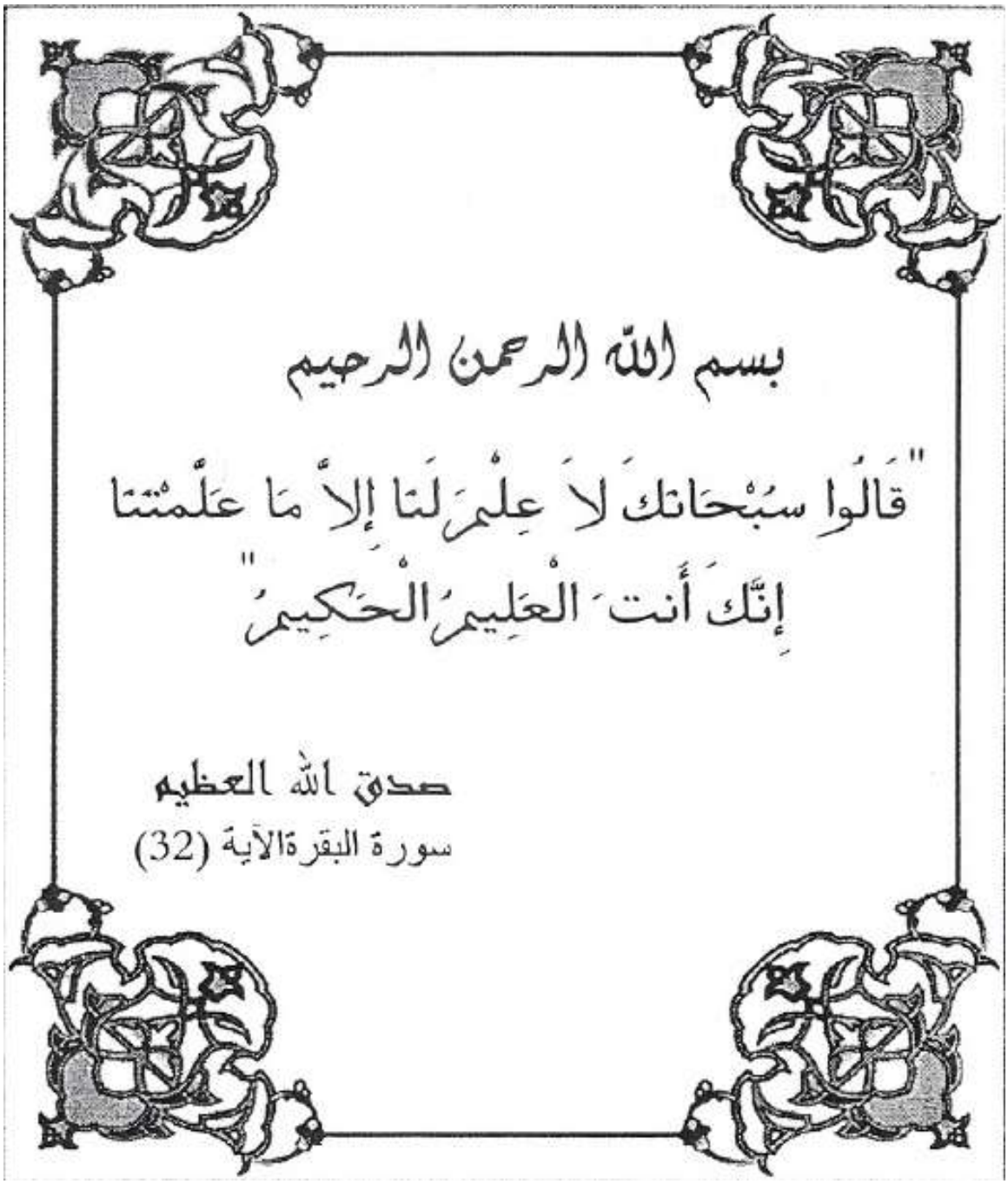
2009



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تقييم بعض دلالات الالتهاب في هواء الزفير المكثف في مرضى الربو الشعبي

رسالة

توطئة للحصول على درجة الماجستير في الأمراض الصدرية

مقدمة من

ط / أحمد محمد غريب

بكالوريوس الطب والجراحة ـ جامعة عين شمس (٢٠٠٥)

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LIST OF ABBREVIATIONS

AHR	Airway hyper responsiveness
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
COPD	Chronic obstructive pulmonary disease
Cys-LTs	Cysteinyl leukotrienes
EBC	Exhaled breath condensate
F_ENO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume in the 1^{st} second
FVC	Forced vital capacity
GINA	Global initiative for asthma
H2O2	Hydrogen peroxide
IFNγ	Interferon γ
IgE	Immunoglobulin E
IL	interleukin
LO	Lipooxygenase
LT	Leukotriene
NO	Nitric oxide
NO2	Nitrite
NO3	Nitrate
NOS	Nitric oxide synthase
NOS1, nNOS	Neuronal nitric oxide synthase
NOS2, iNOS	Inducible nitric oxide synthase
NOS3, eNOS	endothelial nitric oxide synthase
PEF	Peak expiratory flow
PGE-2	prostaglandin E2
ROS	Reactive oxygen species
sIL-2R	soluble interleukin-2 receptor
Th1	T- helper 1
Th2	T- helper 2
TNF-α	tumor necrosis factor α

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INTRODUCTION

Asthma is an inflammatory disorder of the airways associated with airflow obstruction and bronchial hyper-responsiveness that vary in severity across the spectrum of the disease. Although asthma is considered to be a chronic inflammatory disease, evaluation and therapy guidance are mainly based on clinical symptoms and lung function tests that remain the corner stones of clinical practice. ***(Kharitonov and Barnes, 2006)***

The assessment of inflammatory respiratory disorders in presence of different basic diseases such as Asthma was dependant on invasive methods such as bronchoscopy. Sputum induction is considered to be a semi invasive technique that has helped clinical researchers to identify the inflammatory process of many airway diseases including asthma. ***(Kostikas et al, 2008)*.**

However, it is sometimes difficult to accomplish and involves some discomfort for the patients, it requires dedicated personnel and special equipment and may not be used repeatedly in part due to its pro-inflammatory effect. Additionally, sputum induction is associated with broncho spasm in a considerable proportion of asthmatic patients and all the above render its introduction in everyday clinical practice difficult.
(Green et al, 2002)

The collection of exhaled breath condensate (EBC) is achieved by freezing the exhaled air with the use of special condensing devices. Despite some methodological problems of this procedure, its non invasive nature

gives the opportunity for repeated measurements on the same person and provides valuable information for the assessment of airway inflammation. ***(Montuschi, 2005)***

EBC contains a large number of mediators including adenosine, ammonia, hydrogen peroxide H2O2, isoprostanes, leukotrienes, prostanoids, nitrogen oxides, peptides and cytokines. Concentrations of these mediators are influenced by lung diseases and are modulated by therapeutic interventions. In the respiratory system H2O2 may be released both from inflammatory and structural cells including neutrophils, eosinophils, macrophages and epithelial cells. H2O2 is a volatile molecule, which has been demonstrated in EBC by several investigators. An increased content of H2O2 has been described in exhaled condensate in adults, both healthy and with asthma. ***(Horva´th et al, 2001)***

Leukotrienes (LTs) are potent pro-inflammatory mediators that contribute to pathophysiology of asthma. The cysteinyl leukotrienes (Cys-LTs) LTC4, LTD4 and LTE4 are generated by different cells, and are able to contract airway smooth muscle, stimulate mucous secretion and decrease mucociliary clearance. They have vasodilating properties and increase vascular permeability, recruit eosinophiles into the airways and sputum, as well as activate NO release from human polymorphonuclear granulocytes. Detectable levels of LT C4, D4, and E4 have been reported in exhaled condensate of asthmatic. ***(Leff, 2000)***

The field of non invasive techniques for assessing airway inflammation has developed rapidly since nitric oxide (NO) was recognized as an important mediator in exhaled air. The balance between nitrite/ nitrate, S nitrosothiols and nitrotyrosine in lung epithelial lining fluids reflected by exhaled breath condensate gives us insight of NO synthesis and its role in airway inflammation and oxidative stress. High levels of nitrite have been shown in exhaled breath condensate collected relatively easy by the patients themselves and could be a home marker for acute asthma. ***(Hunt et al, 1995)***

Aim of the Work

The aim of this study is to measure the concentrations of hydrogen peroxide, nitric oxide and Leukotrienes C4, D4 and E4 in exhaled breath condensate in asthmatic patients and determine their value as non invasive markers of airway inflammation

Bronchial Asthma

Definition

Asthma has significant genetic and environmental components, but since its pathogenesis is not clear, much of its definition is descriptive. Based on the functional consequences of airway inflammation, an operational description of asthma is:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.

The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment. (GINA, 2008)

Epidimiology

Asthma is a serious global health problem. People of all ages in countries throughout the world are affected by this chronic airway disorder that, when uncontrolled, can place severe limits on daily life and is sometimes fatal. The prevalence of asthma is increasing in most countries, especially among children. ***(GINA, 2008)***

Asthma is a problem worldwide, with an estimated 300 million affected individuals. Nonetheless, based on the application of standardized methods to measure the prevalence of asthma and wheezing illness in

children and adults, it appears that the global prevalence of asthma ranges from 1% to 18% of the population in different countries. ***(Masoli et al , 2004)***.

Risk factors:

Factors that influence the risk of asthma can be divided into those that cause the development of asthma and those that trigger asthma symptoms; some do both. The former include host factors (which are primarily genetic) and the latter are usually environmental factors ***(Busse and Lemanske, 2001)***

Host factors

Genetic

The search for genes linked to the development of asthma has focused on four major areas: production of allergen specific IgE antibodies (atopy); expression of airway hyper responsiveness; generation of inflammatory mediators, such as cytokines, chemokines, and growth factors; and determination of the ratio between Th1 and Th2 immune responses (as relevant to the hygiene hypothesis of asthma) (***Strachan, 1989).***

Multiple genes may be involved in the pathogenesis of asthma, and different genes may be involved in different ethnic groups. ***(Holloway et al, 1999)***