Role of Exhaled Nitric Oxide in Chronic Obstructive Pulmonary Disease (COPD): Correlation With Pulmonary Function Tests

Thesis

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LIST OF ABBREVIATIONS

AAT	Alpha-1-antirypsin
AHR	Airway hyperresponsiveness
ARDS	Adult respiratory distress syndrome
BAL	Bronchoalveolar lavage
BTS	British thoracic society
Ca^{2+}	Calcium
CF	Cystic fibrosis
cGMP	Cyclic guanosine monophosphate
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DNA	Di nucleic acid
DPB	Diffuse panbronchiolitis
ECP	Eosinophil cationic protein
EDRF	Endothelium derived relaxing fctor
EGF	Epidermal growth factor
eNANC	Excitatory non adrenergic non cholinergic
ENO	Exhaled nitric oxide
eNOS	Endothelial nitric oxide synthase
EPO	Eosinophil peroxidase
ET-1	Endothelin-1

ETS	Environmental tobacco smoke
FEF_{25-75}	Forced expiratory flow 25-75
FEV_1	Forced expiratory volume in the first second
FMN	Flavin mononucleotide
FVC	Forced vital capacity
GM-CSF	Granulocyte-macrophage colony stimulating factor
H_2O_2	Hydrogen peroxide
H_4B	Tetrahydroprotein
HDM	House dust mites
IFN-γ	Interferone-γ
IgE	Immunoglobulin E
IL-10	Interleukin-10
IL-12	Interleukin-12
IL2	Interleukin-2
IL4	Interleukin-4
IL5	Interleukin-5
IL-8	Interleukin-8
iNANC	Inhibitory non-adrenergic non-cholinergic
iNOS	inducible nitric oxide synthase
IV	Intravenous
LAA	Laboratory animal allergy
L-NAME	N^G-nitro-L—arginine methyl ester

LTB4	Leukotrien B4
MBP	Major basic protein
MCP-1	Macrophage chemotactic protein-1
MIP-1α	Macrophage inflammatory protein 1-α
mRNA	Messenger ribonucleic acid
NADPH	Nicotinamide adenine dinucleotide phosphate
NANC	Non-adrenergic non-cholinergic
NK	Natural killer
NMDA	N-methnyl-D-aspartate
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NO_2^-	Nitrate
NO_2	Nitrogen dioxide
NO_3	Nitrite
NOS	Nitric oxide synthase
O_3	Ozone
$oNOO^-$	Peroxynitrite
$PaCO_2$	Partial pressure of oxygen in arterial blood
PaO_2	Partial pressure of arterial CO_2
PCD	Priamry ciliary dyskinesia
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
RS-NO	Nitrosothiols

SLP	Secretory leukoproteinase inhibitor
TGF-B	Transforming growth factor-B
$TIMP_5$	Tissue inhibitors of MMP_5
TNF	Tumor necrosis factor-α
US	United States
VC	Vital capacity
VCAM-1	Vascular cell adhesion molecule-1
VIP	Vasoactive intestinal peptide
WHO	World Health Organization

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major health problem. It is the fourth leading cause of chronic morbidity and mortality in the United States. COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Symptoms, functional abnormalities, and complications of COPD can all be explained on the basis on this underlying inflammation and the resulting pathology ***(Global Initiative for Chronic Obstructive Lung Disease, 2004).***

Chronic inflammation is a critical feature of chronic obstructive pulmonary disease, cystic fibrosis, and asthma. This inflammation is associated with the increased production of reactive oxygen species or oxidative stress in the lungs. Oxidative stress may have several adverse effects and may amplify the inflammatory process; however, monitoring oxidative stress is difficult and may not be reflected by changes in blood markers. Therefore they developed several noninvasive markers in the exhaled breath that may indicate oxidative stress in the lungs, and studied these in relationship to the severity of chronic inflammatory lung diseases. They analyzed the exhaled breath for the content of nitric oxide as a marker of inflammation ***(Paredi et al., 2002).***

In the past nitric oxide (NO) was regarded exclusively as an atmospheric contaminant. Currently, however, it is

thought to play an important endogenous signaling role in the physiological control of airway diseases ***(Gaston et al., 1994).***

NO is produced endogenously in the human respiratory tract where it can act as a dilator of bronchial and vascular smooth muscle, a neurotransmitter and an immune response mediator ***(Moncada et al., 1991).***

Measurement of NO in exhaled air is a simple method of investigating endogenous NO production ***(Gustafsson et al., 1991).***

NO is synthesized by various pulmonary cells, including epithelial, endothelial cells and infiltrating inflammatory cells. NO can easily be measured in exhaled air, Where its concentration depends on local production by the respiratory system ***(Rolla et al., 2000).***

Exhaled NO is a well-studied marker of airway inflammation and oxidative stress and is decreased in healthy chronic smokers ***(Kharitonov et al., 1995).*** Exhaled NO is also increased during COPD exacerbations; whereas conflicting results have been reported in stable COPD patients. Moreover, The levels of exhaled NO were significantly correlated with lung function as assessed by FEV_1 ***(Maziak et al., 1998).***

Exhaled NO levels- in COPD may be correlated with disease severity ***(Clini et al., 1998)***

AIM OF THE WORK

Measurement of NO concentration in the exhaled breath of patients with chronic obstructive pulmonary disease and its value as a noninvasive marker of airway inflammation and to correlate between it and pulmonary function tests.