BRONKOPULMONER HASTALIKLARDA PLAZMA ENDOTELİN-1 KONSANTRASYONLARI

PLASMA ENDOTHELIN-1 CONCENTRATIONS IN BRONCHOPULMONARY DISEASES

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Özet

Son zamanlarda bulunmuş bir vazokonstriktör olan ve damarın yeniden şekillenmesinde rol alan endotelin-1 (ET-1)'in üretimi hipoksiye kronik maruz kalmadan dolayı artabilir. Biz plazma ET-1 konsantrasyonlarını pnömoni (n=13), tüberküloz (n=12), akciğer kanseri (n=10), kronik obsrüktif akciğer hastalığı (n=15), kor pulmonale (n=12) ve bronşiyal astımı (n=10) kapsayan bronkopulmoner hastalıklarda ölçtük. Yirmi sağlıklı kişi kontrol grubu olarak alındı. Plazma ET-1 hazır ticari kitle radioimmunoassay yöntemiyle ölçüldü. Plazma ET-1 konsantrasyonları kronik obsrüktif akciğer hastalığında, kor pulmonalede, bronşiyal astımda ($p < 0.001$, her grup için), tüberkülöz ve kanserde ($p < 0.01$, her ikisi için) ve pnömonide ($p < 0.05$) kontrol grubuna göre daha yüksekti. Dolaşımda artmış ET-1 konsatrasyonu çeşitli patolojik durumlarda akciğerlerden artmış salınıma, akciğerlerde azalmış klirense veya her ikisine bağlı olabilir.

Anahtar kelimeler: *Endotelin-1, bronkopulmoner hastalıklar*

Summary

Endothelin-1 (ET-1), a recently described vasoconstrictor, might play a role in pulmonary vascular remodeling that may be produced by chronic exposure to hypoxia. We measured plasma ET-1 concentrations in patients with bronchopulmonary diseases including pneumonia (n=13), tuberculosis (n=12), lung cancer (n=10), chronic obstructive lung disease (n=15), cor pulmonale (n=12), and asthma bronchiale (n=10). Twenty healthy volunteers were taken as the control group. Plasma ET-1 was measured by radioimmunoassay method using a commercially available kit (Amersham). Plasma ET-1 concentrations were significantly higher in chronic obstructive lung disease, cor pulmonale, asthma bronchiale ($p < 0.001$, for all groups), tuberculosis and cancer ($p < 0.01$ for both groups), pneumonia ($p < 0.05$) than those of the control group. Increased circulating concentration of ET-1 could result from either an increase in the release of endothelin-1 from lungs or a decrease in its clearence from lungs in various pathologic conditions or both.

Key words: *Endothelin-1, bronchopulmonary diseases*

AÜTD 1997, 29:399-402 **MJAU 1997, 29:399-402**

Introduction

Endothelin-1 (ET-1), being the most vasoconstrictor known, was originally isolated by Yanagisawa et al. from porcine aortic endothelial cell culture. It has 21 amino acid residues derived from a larger peptide, big endothelin (1). The synthesis of ET-1 is not limited to endothelial cells and its biological actions clearly extend beyond its vasoconstrictor potential. ET-1 is released from vascular endothelial cells (1), tracheal and bronchial epithelial cells (2), pleural mesothelial cells (3), and from lung macrophages (4). ET-1 contracts isolated pulmonary vessels (2,5) and increases pulmonary vascular resistance (6). In humans, ET-1 also causes bronchoconstriction in an isolated bronchus (7). In addition to bronchoconstriction, ET-1 may be a significant contributing factor in the development of airway inflammation because it has been shown to stimulate arachidonate 15-lipoxygenase activity in animals (8). Hypoxia stimulates synthesis and release of ET-1 from endothelium (2,9) and this peptide could play a major role in pulmonary vascular remodeling responses to chronic hypoxia (9). It has been shown that lung and plasma ET-1 concentrations increase in paralel to the severity of hypoxemia in rats (10). Recent observations indicate increased plasma ET-1 concentrations of subjects with pulmonary hypertension (11,12) and bronchoalveolar lavage fluid ET-1 concentrations of patients with bronchial asthma (13). In one of our studies, we found that plasma ET-1 increased in smorkers and the degree of increase was related to number of cigarette consumed (14).In this study, we aimed to investigate plasma ET-1 concentrations in patients with bronchopulmonary diseases including pneumonia, tuberculosis, lung cancer, chronic obstructive lung disease, cor pulmonale, and asthma bronchiale.

Table 1. *Plasma ET-1 Concentrations in Controls and Patients*

Group	Plasma ET-1 (pg/ml)	p<
Control (n=20)	2.93±1.11	
Tuberculosis (n=12)	3.88±0.50	0.01
Pneumonia (n=13)	3.73±1.07	0.05
Cancer (n=10)	4.78±1.99	0.01
Chronic obstructive lung disease (n=15)	5.83±1.61	0.001
Cor pulmonale (n=12)	5.38±2.14	0.001
Asthma bronchiale (n=10)	5.91±0.99	0.001

Materials and Methods

For comparison of plasma ET-1 concentrations between normal control subjects and the patients with bronchopulmonary diseases, 20 normal volunteers (average age: 45 years, range: 24 - 61 years) were invited to participate in this study. Patients' ages ranged from 20 to 90 years with a mean of 50 years (38 males, 34 females). Among them, 12 patients had tuberculosis, 13 pneumonia, 10 lung cancer, 15 chronic obstructive lung disease, 12 cor pulmonale, and 10 asthma bronchiale. None of them had diabetes mellitus or any renal disease, being conditions releated to increased plasma ET-1 concentrations. Central venous blood was collected from the volunteers and patients resting in a supine position for 10 minutes before blood sampling. Five ml of blood were collected into tubes containing 100 µL EDTA/ml and 400 kallikrein inhibitor units/ml aprotinin (Trasylol®). Blood samples were centrifuged at 2000g for 10 minutes at 4°C and stored at -70°C within 30 minutes after sampling. Plasma ET-1 was measured by radioimmunoassay method in acidified plasma samples after extraction with Amprep C2 columns (code RPN 1913, Amersham), which were preequilibrated with methanol and water. Endothelin was eluted with 5 ml of 0.1 % trifluoroacetic acid in water and 80 % acetonitrile in water plus 0.1 % trifluoroacetic acid. The radioimmunoassay of plasma ET-1 was performed using a commercially available kit (Endothelin 1-21 specific [^{125}I] assay system, Amersham, U.K.). Results are presented as mean ± standart deviation. Student's test was used for the comparison of plasma ET-1 values of patients and controls. Differences at $p<0.05$ were considered significant.

Results

Plasma ET-1 concentrations in controls and patients and the statistical evaluation are shown Table 1. The plasma ET-1 concentrations of the normal volunteers (ranging from 1.1 to 5.6 pg/mL with a mean of 2.93 ±1.11 pg/ml) showed a statistically significant difference when compared to the patients with chronic obstructive lung disease, cor pulmonale, and asthma bronchiale ($p<0.001$ for all groups). There were also significant differences in plasma ET-1 concentrations between tuberculosis and control groups and between cancer and control groups ($p<0.01$ for both). On the other hand, significant difference existed in plasma ET-1 concentrations between the normal volunteers and the patients with pneumonia ($p<0.05$).

Discussion

Experimental studies have established that ET-1 causes potent vasoconstriction (7-10). In addition to the potent vasoconstrictor and pressor actions, endothelin has been reported to produce a wide spectrum of biological effects. ET-1 may contribute to bronchoconstriction and promote airway inflammation (2,7,8). Little is known, however, about its actual role in the pathophysiology of various diseases. We report that patients with bronchopulmonary diseases including tuberculosis, lung cancer, chronic obstructive lung dissease, cor pulmonale, and asthma bronchiale, have elevated plasma ET-1 concentrations. Recent studies have attemped to elucidate a relationship between ET-1 and pulmonary hypertension. Elevated ET-1 concentrations have been demonstrated in children (12) and adults (15,16) with pulmonary hypertension, and in children with pulmonary hypertension associated with congenital heart defects (17). However, the mechanisms for increased plasma ET-1 concentrations in these patients have not been demonstrated, yet. Hypoxia increases plasma and lung ET-1 concentrations (10). Mechanism that might explain the effect of hypoxia on plasma ET-1 concentration is injury of endothelial cells by hypoxia (18). Another possible mechanism is altered renal hemodynamics by hypoxia (19). Alveolar hypoxia is a hallmark in a variety of pulmonary diseases, such as chronic obstructive lung disease. Because hypoxia stimulates synthesis and/or release of ET-1, this potent vasoconstrictor peptide could play a major role in hypoxic pulmonary disease. Mattoli and colleagues (20) have demostrated that patients with symptomatic asthma and chronic airflow obstruction release increased amounts of ET-1 in the airway mucosa. Other studies show that ET-1 is released into the circulation as well as into the bronchoalveolar lavage fluid in vivo model of adult respiratory distress syndrome (21). Feng and

colleagues (22) showed that plasma ET-1 concentrations of stable patients with chronic obstructive lung disease did not significantly change, but were significantly higher during attacks than that in healthy subjects. The concentrations of plasma ET-1 in the patients with cor pulmonale were significantly higher than those in the healthy subjects and chronic obstructive lung disease patients. ET-1 is shown to act as a potent mitogen in various types of cells including vascular smooth muscle cells, mesangial cells, fibroblasts, osteoblastic cells, and human epithelial carcinoma cells (23,24). In the present study, we also demonstrated that plasma ET-1 concentrations increased in patients with lung cancer. ET-1 may be a significant contributing factor in airway inflammation (2,8). We found that the plasma ET-1 concentrations increased in patients with pneumonia and pulmonary tuberculosis. The concentrations of plasma ET-1 in pulmonary tuberculosis and pneumonia were signgficantly higher than those in the healthy controls. Under physiological conditions, lungs may play an important role in protecting peripheral vasculature from the potent vasoconstriction caused by ET-1 (2). At the low concentrations occurring physiologically, the major ET-1 clearing sites appear to reside in the lungs. When pulmonary binding capacity is saturated by ET-1 other vascular beds may take over the function of clearing endothelin from the circulation (2,17,25). Mechanisms contributing to increased plasma ET-1 concentrations found in tuberculosis, pneumonia, chronic obstructive lung desease, cor pulmonale, lung cancer, and asthma bronchiale could result from increased lung production and/or decreased clearance.

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