Assessment of Endothelial Dysfunction In Idiopathic Pulmonary Fibrosis

Thesis

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List of Abbreviations

5-LO	5 Lipoxygenase
FLAP	5 Lipoxygenase activating protein
α-PI	Alpha-1 proteinase inhibitor
6MWD	6 minutes walk distance
6MWT	6 minutes walk test
ABG	Arterial blood gases
ACEI	Angiotensin converting enzyme inhibitors
AECs	Alveolar epithelial cells
AIP	Acute interstitial pneumonia
ALK	Activin- like kinase
ALAT	Latin American Thoracic Association Statement
AM	Adrenomedullin
AMP	Adenosine monophosphaste
AP-1	Activated protein-1
ARDS	Acute Respiratory Distress Syndrome
AT II	Alveolar type II cells
ATP	Adenosine Triphosphate
ATS	American Thoracic Society
AZA	Azathioprine
BAD	brachial artery diameter
BAD_{basal}	brachial artery diameter at rest
BAD_{FMD}	brachial artery diameter follow mediated dilatation
BAL	Bronchoalveolar lavage
bFGF	basic fibroblast growth factor

BH4	Tetrahydrobiopterin
BMPR-2	Bone morphogenic protein receptor - 2
Cyclic AMP	Cyclic adenosine monophosphate
Cyclic GMP	cyclic guanosine monophosphate
CD	Cluster of differentiation
CMV	Cytomegalovirus
CO2	Carbone Dioxide
CP	Cyclophosphamide
CPET	Cardiopulmonary exercise testing
CT	Computed tomography
CTGF	Connective tissue growth factor
CXC	Chemokines
CXCL	Chemokine linked
CXCR	Chemokine receptor
DAD	Diffuse alveolar damage.
DBL	baseline diameter of brachial artery
Dend	diameter change of brachial artery at the end of the post cuff deflation period
DIP	Desquamative interstitial pneumonia
DLCO	Diffusing capacity for carbon monoxide
DLCO/VA	Diffusing capacity for carbon monoxide corrected to the alveolar volume
Dmax	maximum diameter of brachial artery after cuff release.
DNA	Deoxy ribonucleic acid
DPLD	Diffuse parenchymal lung diseases
DTPA	99Tc-diethylenetriamine penta acetate
EBV	Epstein Barr virus

ECs	Endothelial Cell
ECM	Extracellular matrix
EDHF	Endothelium-derived hyperpolarizing factor
EF	Endothelial function
ELF	Epithelial lining fluid
ENA-78	Epithelial neutrophil activating protein-78
eNOS	Endothelial NO synthase
EPAP	Estimated pulmonary artery pressure
ERD	Endothelial reactive dilatation
ERS	European Respiratory Society
ET-1	Endothelin-1
ETA	Endothelin receptor A
ETB	Endothelin receptor B
FEF	Forced expiratory flow
FEV1	Forced expiratory volume in 1^{st} second
FF	Fibroblastic foci
FGF	Fibroblast growth factor
FMD	Flow-mediated vasodilatation
FPF	Familial pulmonary fibrosis
FRC	Functional residual capacity
FS	Fibrosis score
FVC	Forced Vital Capacity
Gamma-GCS	Gamma glutamyl cysteine synthetase
GCP	Granulocyte chemotactic protein
GERD	Gastroesophageal reflux disease
GGO	Ground glass opacity

GGS	Ground glass score
GM-CSF	Granulocyte monocyte colony stimulating factor
GMP	Guanosine monophosphate
GROs	Growth related genes
GTP	Guanosine Triphosphate
H	hour(s)
HB-EGF	Heparin binding EGF
HC	Honeycombing
HCV	Hepatitis C virus
HGF	Hepatocyte growth factor
HIF	Hypoxia inducible factor
HIV	Human immunodeficiency virus
HRCT	High resolution computed tomography
hTERT	Telomerase reverse transcriptase
ICAM	Intercellular adhesion molecule
Id1	Inhibitor of differentiation 1
IIPs	Idiopathic interstitial pneumonias
ILs	Interleukins
ILD	Interstitial lung diseases
INF	Interferon
IP-10	Interferon gamma inducible protein 10
IPAH	Idiopathic pulmonary arterial hypertension
IPF	Idiopathic pulmonary fibrosis
ITAC	IFN-γ-inducible T-cell a chemoattractant
JTS	Japanese Respiratory Society
Kg	Kilogram
Kc	calcium-activated potassium channel
LBW	Leane body weight

LDI	Laser Doppler Imaging
LTs	Leukotrienes
m	meter
mm	millimeter
MCP-1	Monocyte chemoattractant protein-1
Mg	milligram
MHz	Mega hertz
MIG	Monokine induced by IFN-γ
Min	minute (s)
MIP	Macrophage inflammatory protein
mm Hg	millimeters of mercury pressure
MMPs	Matrix Metalloproteinases
MMRC	Modified Medical Research Council
mPAP	Mean pulmonary arterial pressure
NAP-2	Neutrophil activating protein-2
NF-κB	Nuclear factor kappa B
(NK) cells	Natural killer Cells
NO	Nitric oxide
NSIP	Nonspecific interstitial pneumonia
O2	Oxygen
OSA	Obstructive sleep apnea
α-PI	alpha-proteinase inhibitor
P(A-a) O_2	Alveolar arterial oxygen difference
P2	Pulmonary component of second heart sound
$PaCO_2$	Partial pressure of arterial carbon dioxide
PAD	Peripheral artery disease.
PAH	Pulmonary arterial hypertension
PAECs	pulmonary artery Ecs

PAI	Plasminogen activator inhibitor
PaO_2	Partial pressure of arterial oxygen
PASP	Pulmonary artery systolic pressure
PCWP	Pulmonary Capillary Wedge Pressure
PDEI	Phosphodiesterase inhibitor
PDGF	Platelet derived growth factor
PEDF	Pigment epithelium-derived factor
PET	Positron emission tomography
PF	Platelet factor
PFTs	Pulmonary function tests
PGs	Prostaglandins
PH	Pulmonary hypertension
PMNs	Polymorph nuclear neutrophils
PPH	Primary Pulmonary hypertension
P-value	Probability value
PVR	Pulmonary vascular resistance
REM	Rapid eye movement
RONS	Reactive Oxygen and Nitrogen Species
ROS	Reactive oxygen species
RPM	Rapamycin
RV	Residual volume
RVSP	Right ventricular systolic pressure
S	Second(s)
S3	Third heart sound
SaO_2	Arterial oxygen saturation
SLPI	Secretory leukoprotease inhibitor
SMCs	Smooth Muscles

SP	Surfactant protein
SPAP	Systolic pulmonary artery pressure
TBLB	Transbronchial lung biopsy
TDI	Tissue Doppler imaging.
TGF	Transforming growth factor
Th-1	T-helper cell type 1 lymphocytes
Th-2	T-helper cell type 2 lymphocytes
TIMPs	Tissue inhibitors of matrix metalloproteinases
TLC	Total lung capacity
TNF-α	Tumor necrosis factor alpha
TTE	Transthoracic echocardiography
UIP	Usual interstitial pneumonia
$\dot{V}$ max	The maximal expiratory flow rate
V/Q	Ventilation perfusion ratio
V_A	Alveolar volume
VC	Vital Capasity
V_D	Dead space volume
VEGF	Vascular endothelial growth factor
VIP	Vasoactive intestinal peptide
VOP	Venous Occlusion Plethysmography
V_T	Tidal volume
VSMCs	vascular smooth muscle cells
vWF	von Willebrand factor
XOR	Xanthine oxidoreductase

Abstract

Background: IPF is defined as a specific form of chronic fibrosing interstitial pneumonia limited to the lung, with the histopathology of UIP on surgical lung biopsy. Pulmonary hypertension (PH) is frequently seen in patients with IPF and is commonly attributed to hypoxic vasoconstriction and capillary destruction. Pathology findings include endothelial proliferation and medial hypertrophy that exceed those expected in the setting of hypoxia. PH in patients with IPF is associated with decreased exercise capacity and worse survival ***(Patel et al., 2007).***The endothelium of the bronchial circulation shares characteristic features of other systemic vascular beds. Namely, leukocyte recruitment and vascular leak occur at postcapillary sites, and there is a vigorous angiogenesis response to tissue ischemia. This is in direct contrast to the pulmonary vasculature. both bronchial endothelium and pulmonary endothelium are exposed to mechanical stress imposed by lung ventilation ***(Wagner, 2009).***Together these findings support the notions that under ischemic and/or hypoxic conditions, ELR^+ CXC chemokines are involved in promoting angiogenesis in the lung and that both the bronchial and pulmonary circulations of the lung are important in promoting vascular remodeling ***(Strieter et al., 2007).***

Aim of the work: to assess the prevalence of endothelial dysfunction in patients with Idiopathic Pulmonary Fibrosis and its correlation with pulmonary hypertension.

Subjects and methods: the study included two groups; target population and control group. The target population subdivided in to 2 subgroups included 30 IPF patients: Subgroup I (15 IPF cases) with pulmonary artery hypertension; Subgroup II (15 IPF cases) without pulmonary artery hypertension. The control group included 10 normal healthy individuals. They were subjected to written informed consent, demographic data acquisition, detailed history taking, thorough clinical examination, collagen profile, ABG (PaO_2, $SaO_{2)}$, PFTs (spirometry), 6MWT, HRCT chest scan, echocardiography, and brachial artery duplex to assess endothelial dysfunction.

Results: Subgroup (I) & Subgroup (II) showed a statistically highly significant difference in BAD_{FMD} and ERD compared to the control group. Whereas, BAD_{basal}, BAD_{FMD} and ERD were affected in both Subgroup (I) and Subgroup (II), But with no statistically significant difference. EPSP was correlating indirectly with BAD_{basal} and BAD_{FMD} whereas EPSP was correlating directly with ERD, but these relations were found to be statistically insignificant.

Conclusion: This work concluded that BAD_{FMD} &ERD more affected in IPF patients regardless PAH presence or absence than normal population.

Key words: IPF, brachial artery flow mediated dilatation, estimated pulmonary artery systolic pressure, ERD.