

Study of Connective Tissue Disease Associated Pulmonary Hypertension

Thesis

*Submitted For Partial Fulfillment of M.D.degree
in Chest Diseases and Tuberculosis*

By

Mohamed Abd El Monem Mohamed

M.B., B. Ch, M Scin Chest Diseases

Supervised by

Prof./ Mona Mansour Ahmed

Professor of Chest Diseases

Faculty of Medicine / Ain Shams University

Prof./ Iman Hassan ELsayed Galal

Professor of Chest Diseases

Faculty of Medicine / Ain Shams University

Dr./ Ashraf Adel Gomaa

Associate Professor of Chest Diseases

Faculty of Medicine / Ain shams university

Dr./ Ayman Abdel Hamid Farghaly

Consultant Pulmonary Medicine

Military Respiratory Center

Faculty of Medicine - Ain Shams University

2018

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سببنا انك لا تعلم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢



Acknowledgment

*First of all, thanks for **ALLAH** who gave me the power to complete this work.*

*I would like to express my deepest gratitude and sincere appreciation to **Prof. Mona Mansour Ahmed**, Professor of Chest Diseases, Faculty of Medicine, Ain Shams University for her encouragement, her kind support and appreciated suggestions that guided me to accomplish this work. Many thanks & gratitude for her.*

*I am also grateful to **Prof. Iman Hassan Elsayed Galal**, Professor of Chest Diseases, Faculty of Medicine, Ain Shams University, who freely gave her time, effort and experience along with continuous guidance throughout this work.*

*I would like also to express my deepest thanks for **Dr. Ayman Abdel Hamid Farghaly**, Consultant Pulmonary Medicine, Military Respiratory Center, for his continuous follow up and guidance throughout the work.*

*I wish to introduce my deepest thanks to **Dr. Ashraf Adel Gomaa**, Associate Professor of Chest Diseases, Faculty of Medicine, Ain Shams University,, for his kindness, supervision and cooperation in this work.*

*Last but not least, many thanks to **my family and my colleagues** for their continuous support.*

Finally, I would present all my appreciations to my patients without them, this work could not have been completed

List of Contents

Title	Page No.
List of Tables	i
List of Figures	iii
List of Abbreviations	vi
Introduction	1
Aim of the Work.....	3
Review of Literature	
▪ Pulmonary Hypertension	4
▪ Connective Tissue Disease Associated Pulmonary Hypertension	34
▪ Right Heart Catheterization.....	72
Subjects and Methods	94
Results	106
Discussion	124
Limitations of the Study	132
Summary	133
Conclusion.....	137
Recommendations	138
References	139
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table (1):	Comperhensive clinical classification of pulmonary hypertension.....	7
Table (2):	Haemodynamic definitions of pulmonary hypertension.....	8
Table (3):	Updated risk level of drugs and toxins known to induce pulmonary arterial hypertension.....	12
Table (4):	Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension.....	21
Table (5):	Echocardiographic signs suggesting pulmonary hypertension used to assess the probability of pulmonary hypertension in addition to tricuspid regurgitation velocity measurement in Table 4 PA: pulmonary artery.....	22
Table(6):	Risk assessment in pulmonary arterial hypertension.....	29
Table (7):	Key investigations required in the diagnostic work-up of suspected CTD-PAH.	38
Table (8):	Potential reasons for poorer outcome in SSc-PAH than in IPAH.....	47
Table (9):	Key causative mechanisms of PAH in systemic lupus erythematosus.	64
Table (10):	Possible risk factors for the development of PH in systemic lupus erythematosus. ⁽¹⁴⁴⁾	67
Table (11):	Recommendations for right heart catheterization in pulmonary hypertension.....	75
Table (12):	Recommendations for vasoreactivity testing.	89

List of Tables (Cont...)

Table No.	Title	Page No.
Table (13):	Baseline characteristics of the studied population:	106
Table (14):	STEP 1 parameters among studied patients:.....	107
Table (15):	STEP 2 parameters among studied patients:.....	108
Table (16):	RHC results among studied patients:	109
Table (17):	Comparison between step 1 result and confirmed diagnosis with RHC:	110
Table (18):	Comparison between step 2 result and confirmed diagnosis with RHC:	111
Table (19):	Diagnostic performance of Step 1 for diagnosis of PAH among SSc patients:.....	115
Table (20):	Diagnostic performance of Step 1 for diagnosis of PAH among SLE patients:	116
Table (21):	Diagnostic performance of Step 1 for diagnosis of PAH among RA:.....	117
Table (22):	Diagnostic performance of Step 2 for diagnosis of PAH among SSc patients:.....	118
Table (23):	Diagnostic performance of Step 2 for diagnosis of PAH among SLE patients:	119
Table (24):	Diagnostic performance of Step 2 for diagnosis of PAH among RA patients:.....	120
Table (25):	Comparison between all diagnoses regarding mPAP:	120
Table (26):	Distribution of final PAH diagnosis among different diagnoses:	121
Table (27):	Correlation between mPAP and FVC%/DLco% predicted and DLco% predicted:.....	122

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Survival in PAH after diagnosis in patients with existing CHD, Portopulm, IPAH, CTD and HIV.....	10
Figure (2):	The pie chart on the left shows the causes of Pulmonary arterial hypertension.....	11
Figure (3):	Schematic diagram of a pulmonary vascular cell showing the possible mechanisms leading to vasoconstriction and/or proliferation of the pulmonary vascular component cells.....	15
Figure (4):	Diagnostic algorithm of PH.....	26
Figure (5):	Evidence based treatment algorithm for pulmonary arterial hypertension patients.....	33
Figure (6):	Patients with PH in association with connective tissue disease may sit in group 1 (pulmonary arterial hypertension), group 2 (PH associated with left heart disease) or group 3 (PH associated with lung disease) while group 4 (chronic thromboembolic pulmonary hypertension) disease must also be excluded.....	36
Figure (7):	Concentric medial hypertrophy and intimal fibrosis can be seen in small pulmonary artery from a scleroderma lung.....	44

List of Figures (Cont...)

Fig. No.	Title	Page No.
Figure (8):	Patient with Systemic sclerosis, interstitial lung disease and pulmonary hypertension Apical four chamber view - Doppler image showing tricuspid regurgitant jet with moderate tricuspid regurgitation.....	52
Figure (9):	Key points to be evaluated when managing SSc-PAH	59
Figure (10):	Pathophysiology of pulmonary hypertension in systemic lupus erythematosus.....	63
Figure (11):	Role of inflammation and Dysregulated immune response in the development of PAH in SLE	65
Figure (12):	The double lumen balloon flotation catheter and its placement at the bedside without fluoroscopy and by monitoring intracardiac pressures	73
Figure (13):	Pulmonary Artery (Swan-Ganz) Catheter.....	77
Figure (14):	Best practice recommendations for right heart catheterization: pressure transducer and zeroing	82
Figure (15):	Representative pressure tracings of a) pulmonary arterial pressure and b) pulmonary arterial wedge pressure (PAWP)	84
Figure (16):	Nomograms for practical application of the DETECT algorithm: determination of the likelihood of pulmonary arterial hypertension and cut-off points for decision to refer a patient to echocardiography and subsequent right heart catheterization.....	97

List of Figures (Cont...)

Fig. No.	Title	Page No.
Figure (17):	Pulmonary artery catheter (7.5 F) used for collecting hemodynamic measurements.....	98
Figure (18):	Cardiac catheterization laboratory outfitted with computerized hemodynamic monitoring systems used by chest specialized hospital Kobry Elkobba Armed Forces.....	101
Figure (19):	Roc curve for detecting cutoff value for step 1	112
Figure (20):	Roc curve for detecting cutoff value for step 2	113
Figure (21):	Shows correlation between mPAP and FVC%predicted/DLco%predicted.....	123
Figure (22):	Shows correlation between mPAP and DLco%predicted	123

List of Abbreviations

Abb.	Full term
%	<i>Percentage</i>
>	<i>More than</i>
5-HTT	<i>5hydroxytryptamine transporter</i>
6MWT	<i>6-minute walking test</i>
ADMA	<i>Asymmetric dimethylarginine</i>
AECAs	<i>Antiendothelial cell autoantibodies</i>
ANA	<i>Anti-nuclear antibody</i>
ANOVA	<i>Analysis of variance</i>
Anti-RNP	<i>Anti-ribonucleic protein</i>
AUC	<i>Area under the curve</i>
BMPR2	<i>Bone morphogenetic protein receptor, type 2</i>
BNP	<i>Brain natriuretic peptide</i>
BSA.....	<i>Body surface area</i>
cAMP	<i>Cyclic adenosine monophosphate</i>
CCB	<i>Calcium channel blocker</i>
CCL5.....	<i>Chemokine Ligand 5</i>
cGMP	<i>Cyclic guanosine monophosphate</i>
CHD.....	<i>Congenital heart disease</i>
CI	<i>Cardiac index</i>
cm.....	<i>Centimeter</i>
CMR	<i>Cardiac magnetic resonance</i>
CO	<i>Cardiac output</i>
COPD	<i>Chronic obstructive pulmonary disease</i>
Cpc-PH	<i>Combined post-capillary and pre-capillary PH</i>
CPET	<i>Cardiopulmonary exercise testing</i>
CREST.....	<i>Calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia</i>
CT	<i>computed tomography</i>
CTD	<i>Connective tissue disease:</i>

List of Abbreviations (cont...)

Abb.	Full term
<i>CTDs</i>	<i>Connective tissue diseases</i>
<i>CTEPH</i>	<i>Chronic thromboembolic pulmonary hypertension</i>
<i>CTPA</i>	<i>CT pulmonary angiogram</i>
<i>CX3CLI</i>	<i>Chemokine Ligand 1</i>
<i>dcSSc</i>	<i>Diffuse cutaneous systemic sclerosis</i>
<i>DLco</i>	<i>Diffusion lung capacity for carbon monoxide</i>
<i>DPAH</i>	<i>Drug-induced PAH</i>
<i>DPG</i>	<i>Diastolic pressure gradient</i>
<i>ECG</i>	<i>Electrocardiogram</i>
<i>EGF</i>	<i>Endothelial growth factor</i>
<i>EIF2AK4</i>	<i>Eukaryotic Translation initiation factor 2 alpha kinase 4</i>
<i>EMG</i>	<i>Electromyogram</i>
<i>ESC/ERS</i>	<i>European Society of Cardiology and the European Respiratory Society</i>
<i>ET-1</i>	<i>Endothelin-1</i>
<i>ETA</i>	<i>Endothelin A</i>
<i>ETB</i>	<i>Endothelin B</i>
<i>FVC</i>	<i>Forced vital capacity</i>
<i>HFpEF</i>	<i>Heart failure with preserved ejection fraction</i>
<i>HIV</i>	<i>human immunodeficiency virus.</i>
<i>HPAH</i>	<i>Heritable pulmonary arterial hypertension</i>
<i>i.v</i>	<i>Intravenous</i>
<i>IIF</i>	<i>Indirect immunofluorescence</i>
<i>IJ</i>	<i>Internal jugular</i>
<i>IL-1</i>	<i>Interleukin-1</i>
<i>IL-6</i>	<i>Interleukin-6</i>
<i>ILD</i>	<i>Interstitial lung disease</i>

List of Abbreviations (cont...)

Abb.	Full term
<i>IPAH</i>	<i>Idiopathic PH</i>
<i>Ipc-PH</i>	<i>Isolated post-capillary PH</i>
<i>LA</i>	<i>Left atrium</i>
<i>lcSSc</i>	<i>Limited cutaneous systemic sclerosis</i>
<i>LHD</i>	<i>Left heart disease</i>
<i>LV</i>	<i>left ventricle</i>
<i>LVEDP</i>	<i>Left ventricular end-diastolic pressure</i>
<i>MAP</i>	<i>Mitogen-activated kinase; BMPR: Bone morphogenetic protein receptor</i>
<i>MCTD</i>	<i>Mixed connective tissue disease</i>
<i>mSAP</i>	<i>Mean systemic arterial pressure</i>
<i>N</i>	<i>Number</i>
<i>NFAT</i>	<i>Nuclear factor of activated T cells</i>
<i>NO</i>	<i>Nitric oxide</i>
<i>NPV</i>	<i>Negative predictive value</i>
<i>NS</i>	<i>No statistically significant difference</i>
<i>NT-proBNP</i>	<i>N-terminal pro-brain natriuretic peptide</i>
<i>PA</i>	<i>Pulmonary angiography</i>
<i>PAC</i>	<i>Pulmonary arterial catheter</i>
<i>PAH</i>	<i>Pulmonary arterial hypertension</i>
<i>PAPm</i>	<i>Mean pulmonary arterial pressure</i>
<i>PASP</i>	<i>Pulmonary artery systolic pressure</i>
<i>PAWP</i>	<i>Pulmonary arterial wedge pressure</i>
<i>PCA</i>	<i>Prostacyclin analogues</i>
<i>PCH</i>	<i>Pulmonary capillary haemangiomatosis</i>
<i>pCO₂</i>	<i>Partial pressure of carbon dioxide</i>
<i>PDE-5-I</i>	<i>Phosphodiesterase- 5-inhibitors</i>
<i>PDGF</i>	<i>Platelet derived growth factor</i>

List of Abbreviations (cont...)

Abb.	Full term
<i>PEA</i>	<i>Pulmonary endarterectomy</i>
<i>Peak VO₂</i>	<i>Peak oxygen uptake</i>
<i>PFTs</i>	<i>Pulmonary function tests</i>
<i>PH</i>	<i>Pulmonary hypertension</i>
<i>P_{imax}</i>	<i>Maximal inspiratory pressure</i>
<i>PPH</i>	<i>Primary PH</i>
<i>PPHN</i>	<i>Persistent PH of the newborn</i>
<i>PPV</i>	<i>Positive predicted value</i>
<i>pSS</i>	<i>Primary Sjogren's syndrome</i>
<i>PVCs</i>	<i>Premature ventricular contractions</i>
<i>PVOD</i>	<i>Pulmonary veno-occlusive disease</i>
<i>PVR</i>	<i>Pulmonary vascular resistance</i>
<i>R</i>	<i>Correlation</i>
<i>RA</i>	<i>Rheumatoid arthritis</i>
<i>RANTES</i>	<i>Regulated upon activation, normal T cell expressed and secreted</i>
<i>RAP</i>	<i>Right atrial pressure</i>
<i>RBBB</i>	<i>Right bundle-branch block</i>
<i>RHC</i>	<i>Right heart catheterization</i>
<i>ROC</i>	<i>Receiver operating characteristic</i>
<i>R_t</i>	<i>Right</i>
<i>RV</i>	<i>Right ventricular</i>
<i>RVP</i>	<i>Right ventricular pressure</i>
<i>RVSP</i>	<i>Right ventricular systolic pressure</i>
<i>S</i>	<i>Statistically significant</i>
<i>Scl70</i>	<i>Scleroderma 70</i>
<i>SD</i>	<i>Standard deviation</i>
<i>SLE</i>	<i>Systemic lupus erythematosus</i>

List of Abbreviations (cont...)

Abb.	Full term
<i>SNPs</i>	<i>Single nucleotide polymorphisms</i>
<i>SPSS</i>	<i>Statistical package for social science</i>
<i>SSc</i>	<i>Systemic sclerosis</i>
<i>SSc-PAH</i>	<i>Systemic sclerosis associated pulmonary arterial hypertension</i>
<i>SvO2</i>	<i>Mixed venous oxygen saturation</i>
<i>SVR</i>	<i>Systemic vascular resistance</i>
<i>TAPSE</i>	<i>Tricuspid annular plane systolic excursion</i>
<i>TGF-b</i>	<i>Transforming growth factor-b</i>
<i>TPG</i>	<i>Transpulmonary pressure gradient</i>
<i>TR</i>	<i>Tricuspid regurgitant jet</i>
<i>TTE</i>	<i>Transthoracic echocardiogram</i>
<i>UK</i>	<i>United Kingdom</i>
<i>USA</i>	<i>United States of America</i>
<i>V/Q</i>	<i>Ventilation / perfusion</i>
<i>VE/VCO2</i>	<i>Ventilator equivalents for carbon dioxide</i>
<i>VEGF</i>	<i>Vascular endothelial growth factor</i>
<i>VF</i>	<i>Ventricular fibrillation</i>
<i>VIP</i>	<i>Vasoactive intestinal peptide</i>
<i>VO2</i>	<i>Oxygen consumption</i>
<i>VO2/HR</i>	<i>Oxygen pulse</i>
<i>VPAC</i>	<i>VIP receptors</i>
<i>VT</i>	<i>Ventricular tachycardia</i>
<i>WHO</i>	<i>World Health Organization.</i>
<i>WHO-FC</i>	<i>World Health Organization functional class.</i>
<i>WSPH</i>	<i>World Symposium on PH</i>
<i>WU</i>	<i>Wood units</i>

INTRODUCTION

Pulmonary hypertension (PH) is a substantial global health issue in which all age groups are affected with rapidly growing importance in elderly people.⁽¹⁾

PH embraces a variety of diseases that have little in common apart from elevated blood pressure in the pulmonary circulation.⁽²⁾

Precise diagnostic classification of pulmonary hypertension is essential, not least for reasons of treatment and prognosis, because treatment options that are efficacious in some forms of pulmonary hypertension may be ineffective or even disadvantageous in other forms.⁽²⁾

Pulmonary arterial hypertension (PAH) affects 0.5–15% of patients with connective tissue diseases (CTDs) and is one of the leading causes of mortality in systemic sclerosis (SSc) and mixed connective tissue disease (MCTD). Despite increasing recognition of PAH in CTDs, the diagnosis is often delayed, which may lead to unfavorable outcomes in these patients.⁽³⁾

Screening for PAH in SSc allows for earlier detection and treatment that prolongs survival and improves symptoms but it is important that clinicians who follow SSc patients screen and act upon the results, such as referring suspected PAH for right heart catheterization (RHC) and treatment at an expert center.⁽⁴⁾