

**PROGNOSTIC MARKERS OF PULMONARY HYPERTENSION
IN CHILDREN AND THEIR MODULATION BY TREATMENT**

Thesis

*Submitted for partial fulfillment of Master Degree in
Pediatrics*

By

Ahmed Youssef Sofi

M.B.B.Ch, Cairo University, Fayoum Branch, 2001

Supervised by

Prof. Dr. Alyaa Amal Kotby

Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Dr. Ola Abd El Aziz Elmasry

Assistant Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Dr. Nevin Mamdouh Habib

Assistant Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University

2009

Acknowledgment

*First of all, thanks to **Allah** the most merciful for guiding me and giving me the strength to complete this work the way it is.*

*It is a pleasure to express my deepest thanks and profound respect to my honored professor, **Prof. Dr Alyaa Amal Kotby**, Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her continuous encouragement and valuable supervision and guidance throughout this work.*

*Also, I wish to express my deep gratitude to **Dr. Ola Abd Elaziz Elmasry**, Assistant professor of pediatrics, Faculty of Medicine, Ain Shams University, for her kind support, help and careful supervision. I wish to be able one day to return to her a part of what she had offered to me.*

*I am also deeply grateful and would like to express my sincere thanks and gratitude to **Dr. Nevin Mamdouh**, Assistant professor of pediatrics, Faculty of Medicine, Ain Shams University, for her great help and support and her continuous guidance, correction and explanation.*

Also, I would like to thank my patients and their families for their cooperation and their time.

No words could adequately express my deep appreciation to my family, for their continuous support and guidance. I shall remain indebted to them all my life.

Ahmed Youssef sofi

Contents

	<i>Page</i>
List of abbreviations	i
List of tables	vi
List of figures	x
Introduction	1
Aim of the Work	3
Review of literature.....	4
Definition of pulmonary arterial hypertensionand.....	4
Causes and classification.....	5
Incidence of PAH	8
Pathology of PAH.....	10
Pathogenesis of PAH.....	11
Diagnostic strategy of PAH.....	17
Assessment of severity of PAH.....	29
Therapeutic considerations of PAH	40
Outpatient follow up	53
Prognosis of PAH	54

Contents_(Cont..)

	<i>Page</i>
Patients and methods	55
Results	65
Discussion	128
Summary and conclusion	145
Recommendations	151
References	152
Arabic summary	

List Of Abbreviations

5HT	5 hydroxy tryptamine
6MWD	Six minute walk distance
6MWT	Six minute walk test
ABG	Arterial blood gases
ALK 1	Activin-receptor-like kinase 1 gene
ALT	Alanin transaminase
ANP	Atrial natriuretic peptide
Ao	Aorta
APAH	Associated with pulmonary arterial hypertension
ASD	Arterial septal defect
AST	Aspartate transaminase
AT	Acceleration time
ATP	Adenosine triphosphate
AVP	Arginine vasopressin
BMPR₂	Bone morphogenetic protein receptor type II
BNP	Brain natriuretic peptide
BP	Blood pressure
BSA	Body surface area
CCP	Calcium channel blockers
[Ca²⁺]_i	Intracellular free calcium ion concentration
Cath	Catheterisation
cGMP	Cyclic guanosme nonophosphate
CHD	Congenital heart disease
CNP	C-type natriuretic peptide
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise testing
CPS	Carbamyl phosphate synthase
CT	Computerized tomography
CT ratio	Cardiothoracic ratio
CTD	Connective tissue disease
CTEPH	Chronic thromboembolic pulmonary hypertension

cTnT	Cardiac troponin T
CXR	The chest radiograph
DBP	Diastolic blood pressure
DL_{co}	Decreased lung diffusion capacity for carbon monoxide
DORV	Double outlet right ventricle
ECE	Endothelin-converting enzyme
ECG	Electrocardiogram
EF %	Ejection fraction
ET-1	Endothelium-1
EVE	Endogenous vascular elastase
FEV1	Forced expired volume in one second
FGF-2	Fibroblast growth factor
FPAH	Familial pulmonary arterial hypertension
FS %	Fraction shortening
GER	Glomerular filtration rate
HB	Hemoglobin
HCT	Hematocrit
HIV	Human immunodeficiency virus
HR	Heart rate
HRCT	High resolution computerized tomography
ILD	Interstitial lung disease
IP₃ channel	Inositol 1,4,5-trisphosphate-gated calcium channel
IPAH	Idiopathic pulmonary arterial hypertension
IQR	Interquartile rang
IV	Intravenous
IVSd	Interventricular septum thickness in diastole
IVSd Z score	Z scores in Interventricular septum thickness in diastole
IVSs	Interventricular septum thickness in systole
KLD	Kinase-like domain
LA	Left atrium
LVIDd Z	Z scores in Left ventricular internal diameter in

score	diastole
LVIDs	Left ventricular internal diameter in systole
LVIDs Z	Z scores in Left ventricular internal diameter in systole
score	
LVPWd	Left ventricular posterior wall thickness in diastole
LVPWd Z	Z scores in Left ventricular posterior wall thickness in
score	diastole
LVPWs	Left ventricular posterior wall thickness in systole
LVS	Left ventricular systolic
MMPs	Metalloproteinases
mPAP	Mean pulmonary artery pressure
NEPs	Neutral endopeptidases
NO	Nitric oxide
NOS	Nitric oxide synthase
NPR-A	Natriuretic peptide receptor A
NPR-B	Natriuretic peptide receptors B
NPR-C	Natriuretic peptide receptor C
NPRs	Natriuretic peptide receptors
NYHA	New York heart association
PaCO₂	Arterial carbon dioxide tension
PAH	Pulmonary arterial hypertension
PaO₂	Arterial oxygen tension
PAP	Pulmonary artery pressure
PASP	Pulmonary artery systolic pressure
PCH	Pulmonary capillary hemangiomatosis
PCWP	Pulmonary capillary wedge pressure
PDA	Patent ductus arteriosus
PDE	Phosphodiesterase
PFT	Pulmonary function test
PGI₂	Prostaglandin I ₂
PLAT	Platelet
PH	pulmonary hypertension
PM	Pulmonary microvasculopathy
POV	Pulmonary occlusive venopathy

PPH	Primary pulmonary hypertension
PPHN	Persistent pulmonary hypertension of the newborn
PT	Prothrombin time
PTT	Partial thromboplastin time
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
PVS	Right ventricular systolic pressure
PWP	Pulmonary wedge pressure
PWT	Posterior wall thickening
RAP	Right atrial pressure
RBC	Red blood cells
RHC	Right heart catheterization
ROCC	receptor-operated calcium channels
RR	Respiratory rate
RVOT	Right ventricular outflow tract
RVS	Right ventricular systole
RVSP	Right ventricular systolic pressure
SBP	Systolic blood pressure
SD	standard deviation
SERCA	sarcoplasmic/endoplasmic reticulum Ca^{2+} -ATPase
TEE	Trans-esophageal echocardiography
TR	Tricuspid regurgitation
TRmax	Tricuspid regurgate maximum pressure gradient
PG	
TRVmax	Tricuspid regurgate velocity maximum
TTE	Transthoracic Doppler-echocardiography
TXA₂	Thromboxane A ₂
U_{Na}V	Urinary sodium excretion
UR	Uric acid
URO	Urodilatin
UV	Urinary volume
VO₂	Oxygen consumption
VOCC	Voltage-operated calcium channels
V/Q	Ventilation perfusion lung scan

VSD	Ventricular septal defect
WBC	White blood cells
WHO	World health organization

List Of Tables

<i>Table No.</i>	<i>Title</i>	<i>Page</i>
1	Clinical classification of pulmonary hypertension – Venice 2003.....	5
2	Risk factors of pulmonary arterial hypertension	6
3	Pathological classification of vasculopathies of pulmonary hypertension.....	10
4	The Borg scale.....	26
5	6MWD sources of variability.....	26
6	Prognostic parameters in patients with pulmonary arterial hypertension	29
7	NYHA/WHO Classification of functional status of patients with pulmonary hypertension	30
8	Etiology of PAH in studied group.....	65
9	Comparison between patients and controls as regards the measured demographic data	67
10	Comparison between patients and controls as regards the clinical data.....	68

List Of Tables_(Cont..)

<i>Table No.</i>	<i>Title</i>	<i>Page</i>
11	Comparison between patients and controls as regards the measured ECG and CXR data.....	72
12	Comparison between patients and controls as regards the measured M-mode and 2D echocardiographic data.....	74
13	Indices of pulmonary artery pressure and RV pressure in the patient group.....	76
14	Classification of patients according to severity of PAH as calculated by TR jet	77
15	Comparison between patients and controls as regards the measured laboratory data	78
16	Comparison between patients before and after sildenafil therapy as regards the measured clinical data.....	84

List Of Tables_(Cont..)

<i>Table No.</i>	<i>Title</i>	<i>Page</i>
17	Comparison between patients before and after sildenafil therapy as regards NYHA class.....	87
18	Comparison between patients before and after sildenafil therapy as regards the measured ECG data.....	88
19	Comparison between patients before and after sildenafil therapy as regards the measured M-mode and 2D echocardiographic data.....	90
20	Comparison between patients before and after sildenafil therapy as regards the measured Doppler echocardiographic data.....	92
21	Comparison between patients before and after sildenafil therapy as regards the measured laboratory data	95
22	Comparison between survivors and non-survivors as regards the measured demographic data.....	101

List Of Tables_(Cont..)

Table No.	Title	Page
23	Comparison between survivors and non-survivors as regards the clinical data	102
24	Comparison between survivors and non-survivors as regards the measured ECG and CXR data	103
25	Comparison between survivors and non-survivors as regards the measured M-mode and 2D echocardiographic data.....	106
26	Comparison between survivors and non survivors as regards the measured Doppler echocardiographic data.....	109
27	Comparison between survivors and non-survivors as regards the measured laboratory data	111
28	Predictors of death as a dependent variable (a) and sum up of six variables (b)	117
29	Predictors of death as a dependent variable (a) and sum up of six variables (b)	118
30	Correlation between BNP and TRVmax	119
31	Correlation between uric acid and TRVmax.....	121

List Of Figures

<i>Figure No.</i>	<i>Title</i>	<i>Page</i>
1	Mechanisms of nitric oxide (NO)/cGMP-induced vasodilation.....	12
2	Cartoon illustrating factors driving the evolution of PAH and the rationale of present and potential therapies	14
3	Pulmonary arterial hypertension: potential pathogenetic and pathobiological mechanisms.....	16
4	Pulmonary arterial hypertension diagnostic approach.....	17
5	Chest radiograph of a patient with idiopathic pulmonary arterial hypertension	20
6	<u>Top</u> : Apical four-chamber view (systole) showing enlarged right-side chambers with compressed and geometric distortion of an intrinsically normal LV secondary to marked RV pressure overload; severe TR. <u>Bottom</u> : Peak TR velocity of 4.68 m/s, with a peak gradient of 87.8 mm Hg indicating severe PAH.....	21

List Of Figures_(Cont..)

<i>Figure No.</i>	<i>Title</i>	<i>Page</i>
7	Amino Acid Sequences of the Three Human Natriuretic Peptides.....	32
8	Action of Atrial Natriuretic Peptide at Target Cells.....	34
9	Physiologic Effects of Natriuretic Peptides Released from the Heart When Venous Return Is Increased.....	36
10	Algorithm of the treatment of paediatric pulmonary arterial hypertension	40
11	Endothelin system in vascular disease	46
12	Management of prostaglandin therapy and lung transplantation	52
13	Etiology of PAH in studied group.....	66
14	Comparison between patients and controls as regards the oxygen saturation.....	69
15	Comparison between patients and controls as regards the 6MWD	70
16	Comparison between patients and controls as regards the clinical data.....	71