RECENT ADVANCES IN MANAGEMENT OF PULMONARY ARTERIAL HYPERTENSION

Essay

Submitted for partial fulfillment of the Master Degree in Chest and Tuberculosis

Presented by:

Ahmed Mohammed Ahmed Abdel Raheem

M.B., B.Ch. "Sohag University"

Under the supervision of:

Dr. Yasser Mostafa Mohamed

Professor of Chest Diseases

Faculty of medicine – Ain Shams University

Dr. Samar Hassan Sharkawy

Lecturer of Chest Diseases

Faculty of Medicine – Ain Shams University

Dr. Ashraf Mukhtar Madkour

Lecturer of Chest Diseases

Faculty of Medicine – Ain Shams University

Ain Shams University

2010

Acknowledgment

*All greatest greatfullness and deepest appreciation to **ALLAH** for the countless gifts I have been offered.*

*I am greatly honored to express my deep gratitude to **Dr. Yasser Mostafa Mohamed**, professor of chest Diseases, Faculty of Medicine, Ain Shams University for his guidance and encouragement, kind advice and effort.*

*I would like also to express my deep thanks and deepest gratitude to **Dr. Samar Sharkawy**, Lecturer of Chest Diseases, Faculty of Medicine, Ain Shams University and to **Dr. Ashraf Madkour**, Lecturer of Chest Diseases, Faculty of Medicine, Ain Shams University, for his keen and continuous supervision, generous guidance throughout the whole work.*

Finally, I wish to express all my thanks to my father my leader in this life for his kind help.

List of Abbreviations

5HT	5 Hydroxytryptamine
ACE	Angiotensin-converting enzyme
ADMA	Asymetric dimethylarginine
AM	Adrenomedulin
ANP	Atrial natriuretic peptide
AT	Acceleration time
BMP	Bone morphogenetic protein
BNP	Brain natriuretic peptide
CAMP	Cyclic adenolate monophosphate
C-CBs	Calcium-channel blockers
CGMP	Cyclic guanosine monophosphate
COPD	Chronic obstructive pulmonary diseases
CT	Chest computerized tomography
CTEPH	Chronic thromboembolic pulmonary hypertension
DDAH2	Dimethylaminohydrolase
EBCT	Electron beam computerized tomography
ECG	Electrocardiography
ET	Endothelein
FDA	Food and drug admission
GC	Guanylate-cyclase

GDIs	Guanine dissociation inhibitors
GEFs	Guanine nucleotide exchange factors
HIV	Human-immunodeficiency virus
IPAH	Idiopathies pulmonary arterial hypertension
IVS	Interventricular septum
MIG	Myosin light chain
MPAH	Mean pulmonary arterial hypertension
NIH	National Institute of Health
NO	Nitric oxide
NOS	Nitric oxide synthases
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PASP	Pulmonary artery systolic pressure
PCH	Pulmonary capillary haemangiometosis
PDE5	Phosphodiesterase enzymes 5
PDGFR	Platelet derived growth factor receptor
pH	Pulmonary Hypertension
PKG	Phosphokinase G
PVOD	Pulmonary veno-occulsive disease
RHC	Right heart catheterization
RV	Right ventricular
RVOT	Right ventricular outflow tract
SGs	Soluble guanlyte cyclase

TEE	Transesophageal echocardiography
TGF-B	Transforming growth factors-B
TR	Tricuspid regurgitation
TXA2	Thromboxane A2
V/Q	Ventilation-perfusion
VIP	Vasoactive intestinal peptide
WHO	World Health Organization

List of Contents

List of Figures

List of Figures

List of Tables

Introduction

The most serious chronic disorder of the pulmonary circulation is certainly pulmonary arterial hypertension (PAH), a syndrome of diverse etiology and pathogenesis characterized by the persistent increase in pulmonary vascular resistance potentially leading to right heart failure and death *(Filipek, et al., 2004)*.

Definition:

Pulmonary hypertension refers to the hemodynamic state in which the pressure measured in the pulmonary artery is elevated. By expert consensus, PAH is regarded as a mean pulmonary artery pressure (mPAP) greater than 25 mm Hg in the setting of normal or reduced cardiac output and a normal pulmonary capillary wedge pressure *(Barst et al., 2004).*

Epidemiology

Pulmonary hypertension (PH) is an uncommon disorder, with an estimated yearly incidence of 2 per million people. Pulmonary hypertension (PH) is defined as an abnormal elevation of pressure in the pulmonary

artery [mean pulmonary artery pressure (MPAP) > 25 mmHg at rest or > 30 mmHg during exercise], Secondary pulmonary hypertension is relatively common but is underdiagnosed. Reliable estimates of the prevalence of this condition are difficult to obtain because of the diversity of identifiable causes *(Barst et al., 2004)*.

Recent improvements in our understanding of this syndrome have been quite remarkable, including the identification of a gene responsible for inherited forms of PAH, a better understanding of the pathobiological pathways involved in the development of pulmonary hypertension*, (Farber et al., 2004)* and the development of medical therapies targeting these different pathways *(Humbert et al., 2004).* However, pulmonary hypertension still challenges physicians with both its diagnosis and treatment.

Methods

Search in all available English written literature during period between 1990-2009 using terms recent advances in management of pulmonary arterial hypertension, pulmonary arterial hypertension, pulmonary hypertension, pulmonary vascular diseases will be conducted.

The searching sites will include medline and pubmed internet sites as well as eminent pulmonary and respiratory journal.

Aim of the Work

To present the recent available data on clinical presentation, prognosis, and especially management strategies for patients with pulmonary arterial hypertension (PAH).

Historical Background

THE DISCOVERY OF THE PULMONARY CIRCULATION

The discovery of the pulmonary circulation is an interesting and debated subject. It is commonly believed that the discovery of the pulmonary circulation had its inception in Europe in the sixteenth century by Servetus, Vesalius, Colombo, then Harvey. However, in view of the discovery of ancient manuscripts, the real credit for the discovery of the pulmonary circulation belongs to an eminent physician of the thirteenth century: Ibn Nafis.

Abu-Alhassan Alauldin Ali Bin Abi-Hazem Al-Quarashi, known as Ibn Nafis, was born about 1210 in Damascus. He learned medicine under the guidance of such distinguished physicians as Aldakwar and studied the books of famous pioneers as Rhazes, Avicenna and Maimonides. In 1236 Ibn Nafis moved to Egypt and worked in Al-Mansouri Hospital where he became chief of physicians and the sultan's personal physician. On December 17, 1288 he died at the age of 78 after an unknown illness *(Farber and Loscalzo, 2004).*

The theory that was accepted prior to Ibn Nafis was put forth by Galen in the second century, who said that the blood reaching the right side of the heart went through invisible pores in the septum to the left side of the heart where it mixes with air to create spirit and then is distributed to the body. According to Galen's views, the venous system is quite separate from the arterial system, except when they come in contact by the unseen pores *(Farber and Loscalzo, 2004)*.

However, Ibn Nafis, based on his knowledge in anatomy and scientific thinking, postulated that "...the blood from the right chamber of the heart must arrive at the left chamber but there is no direct pathway between them. The thick septum of the heart is not perforated and does not have visible pores as some people thought or invisible pores as Galen thought. The blood from the right chamber must flow through the vena arteriosa (pulmonary artery) to the lungs, spread through its substances, be mingled there with air, pass through the arteria venosa (pulmonary vein) to reach the left chamber of the heart and there form the vital spirit..." *(Farber and Loscalzo, 2004)*.

In another site he said, "The heart has only two ventricles...and between these two there is absolutely

no opening. Also dissection gives this lie to what they said, as the septum between these two cavities is much thicker than elsewhere. The benefit of this blood (that is in the right cavity) is to go up to the lungs, mix with what is in the lungs of air, then pass through the arteria venosa to the left cavity of the two cavities of the heart..." *(Farber and Loscalzo, 2004)*.

In describing the anatomy of the lungs, Ibn Nafis stated, "The lungs are composed of parts, one of which is the bronchi, the second, the branches of the arteria venosa and the third, the branches of the vena arteriosa, all of them connected by loose porous flesh". Then he added, "... the need of the lungs for the vena arteriosa is to transport to it the blood that has been thinned and warmed in the heart, so that what seeps through the pores of the branches of this vessel into the alveoli of the lungs may mix with what there is of air therein and combine with it, the resultant composite becoming fit to be spirit when this mixing takes place in the left cavity of the heart. The mixture is carried to the left cavity by the arteria venosa" *(Fuster et al., 1984).*