بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

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MONA MAGHRABY

Role of plasma connective tissue growth factor levels in assessment of pulmonary arterial hypertension in Children with congenital heart disease

Thesis

Submitted for Partial Fulfillment
of Master's Degree in ***Pediatrics***

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2021

سورة البقرة الآية: ٣٢

Acknowledgment

First and foremost, I feel always indebted to **ALLAH,**
the Most Kind and Most Merciful.

I'd like to express my respectful thanks and profound gratitude to **Dr. Waleed Mohamed El Gendy,** *Assistant Professor of Pediatrics Faculty of Medicine– Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to **Dr. Iman Mohamed El Sayed,** *Lecturer of Pediatrics Faculty of Medicine– Ain Shams University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

Muhammad Amin

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List of Abbreviations

Abb.	Full term
+LR	Positive likelihood ratio
BNP	B-type natriuretic peptide
CHD	Congenital heart disease
CTGF	Connective tissue growth factor
ECHO	Echocardiography
ElISA	Enzyme immunoassay
–LR	Negative likelihood ratio
mPAP	Mean pulmonary artery pressure
NPV	Negative predictive value
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PADP	Pulmonary artery diastolic pressure
PAH	Pulmonary artery hypertension
PASP	Pulmonary artery systolic pressure
PPV	Positive predictive value
Qp	Pulmonary artery flow
Qp/Qs	Pulmonary-to-systemic flow ratio
Qs	Systemic artery flow
Rp/Rs	Pulmonary-to-systemic resistance ratio
RVDP	Right ventricular diastolic pressure
RVSP	Right ventricular systolic pressure
SPSS	Statistical package for the social sciences

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a severe progressive disease with high mortality and morbidity leading to elevated pulmonary vascular resistance, right heart failure and death ***(Simonneau et al., 2004).*** Clinically, the disease is defined as a mean pulmonary artery pressure of >25mmHg at rest ***(Barst et al., 2004).*** The incidence of PAH secondary to congenital heart disease is estimated as 1.6-12.5 case/million/year ***(Olgunturk, 2010).*** The increased pulmonary blood flow in congenital heart disease (CHD) with left-to-right shunts induces endothelial cell injury and apoptosis and increases pulmonary arterial pressure with neo-intimal development and pulmonary vascular remodeling ***(Gatzoulis et al., 2009, Voelkel et al., 2012).***

Specific PAH-target drugs have improved the quality of life and survival by preventing pulmonary vascular remodeling ***(Montani et al., 2014, Rhodes et al., 2009).*** PAH carried a poor prognosis in children with CHD ***(Rosenzweig et al., 2004).***

In the past years, some blood biomarkers in PAH such as B-type natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), endothelin-1, growth differentiation factor-15 and miRNAs have been used to diagnosis and prognosis ***(Bienertova-Vasku et al., 2015, Giannakoulas et al., 2014),*** but none of them was validated to be an ideal biomarker.

Connective tissue growth factor (CTGF), also known as CCN2, is a 38-kDa, cysteine-rich secreted peptide and belongs to the member of the CCN (acronym of Cyr61/CEF-10, CTGF/Fisp-12 and Nov) family of growth factors that was originally isolated from umbilical vein endothelial cells ***(Bradham et al., 1991).*** CTGF is involved in normal physical condition, but also participates in pathological processes such as angiogenesis and wound healing, as well as extracellular matrix production, adhesion, proliferation and apoptosis ***(Hishikawa et al., 1999).***

More importantly, there are several observations that CTGF is intimately correlated with pulmonary vascular remodeling ***(Lee et al., 2005).*** Many studies performed by Lee and Wang et al at rats, found CTGF contributed to the proliferation of pulmonary artery smooth muscle cells these results suggest that CTGF should play an important role in the development of pulmonary vascular remodeling ***(Lee et al., 2011, Wang et al., 2012).***

Plasma CTGF levels are shown to be useful in diagnosing heart failure ***(Behnes et al., 2014),*** idiopathic pulmonary fibrosis ***(Kono et al., 2011),*** and correlate with the severity of fibrotic diseases ***(Dziadzio et al 2005).*** We therefore hypothesize that secreted CTGF levels could be a clinical biomarker in children with PAH associated with CHD (PAH–CHD).

Right heart catheterization (RHC) is the gold standard method for diagnosis of PAH and an important tool for testing the eligibility of patients with CHD to undergo operations for correction of heart defects. However, it is an invasive test and not always practical for repeated ongoing evaluation ***(Lowe et al., 2011).***So, accurate noninvasive assessment of PAH is desirable both for diagnostic purposes and to assess response to therapy. Doppler echocardiography (D-ECHO) has become the most important and routinely applied noninvasive imaging technique for the diagnosis and follow-up of patients with CHD and is recommended as the initial noninvasive modality in the screening and evaluation of PAH***(Barts et al., 2004, Mjami et al., 2011).***

AIM OF THE WORK

The aim of this study is to assess plasma connective tissue growth factor(CTGF)levels in children with CHD and study its role in assessment of PAH that can be promising diagnostic and prognostic biomarkers for PAH in children with CHD.

Also, to assess the diagnostic accuracy of Doppler ECHO as noninvasive technique in detecting PAH in patients with CHD and its value in detecting the ventricular remodeling and diastolic dysfunction induced by PAH to some extent.

Chapter 1

Normal Development of The Heart

The primitive heart tube is initially straight, and the atrial portion receives venous blood from both the left and right sinus venosus. The straight heart tube begins to loop inside the pericardial sac when the embryo is about 11 somites, or 15 days. The atrioventricular junction comes to lie to the left side of the pericardial cavity. In the primitive heart, there is a single atrium, single atrioventricular connection, and single ventricle communicating by an outflow (infundibulum or conus) to the undivided truncus arteriosus ***(Moorman et al., 2010)***.

As the heart progresses from the straight tube stage and with the proximal and distal ends more or less fixed, the tube grows and loops anteriorly. In normal hearts, the looping is anterior and to the right, termed by Van Praagh a D-(Dextro = right) loop. This usually results in the right ventricle being on the right with the aorta posterior and rightward of the pulmonary artery. The aorta is connected to the left ventricle and the main pulmonary artery to the right ventricle ***(Van Praagh et al., 1990).***

At day 22, the circulatory system is bilaterally symmetrical with paired vessels on each side and the heart consisting of a simple tube located in the midline of the body