Correlation between Pulmonary Artery Hypertension Caused by Acyanotic CHD with Left to Right Shunt and Increased Level of Endothelin-1

Abdulkarim Abdulsalam Alfaqi*, Mohamed Osman Hafez, Besheer Abdallah Hassan, Hanan Samir Ahmed
Pediatric Department, Faculty of Medicine, Zagazig University, Egypt
***Corresponding authors:** Abdulkarim A. Alfaqi, **Mobile:** (+2)01143870952, **Email:** kareamalfaqey@gmail.com

ABSTRACT

Background: Pulmonary hypertension is defined as a resting mean pulmonary artery pressure (mPAP) of 25 mmHg or above. PAH is a frequent complication of congenital heart disease (CHD), particularly in patients with left-to-right (systemic-to-pulmonary) shunts.

Objective: The present study aimed to investigate changes in the blood level of endothelin-1 (ET-1) in patients of PAH complicated by acyanotic CHD and to detect possible correlation with different hemodynamic parameters.

Patient and methods: 48 children were recruited in Pediatric Cardiology Unit, Pediatrics Department in Zagazig University Hospitals after obtaining the required permissions and informed consent from the their caregivers. They were divided into Group (A), which included 24 children with acyanotic CHD with left to right shunt with PAH and Group B included 24 children with acyanotic CHD with left to right shunt but no PAH. All children were subjected to clinical and radiological examination, echocardiography and measurement of endothelin-1 level as well as correlation between the studied parameters were performed.

Results: the present results showed that Group A was significantly associated with previous need of hospital admission and insignificantly associated with ICU need. Endothelin-1 was significantly negatively correlated with weight and oxygen saturation (SPO_2) but significantly positively correlated with systolic blood pressure (SBP), heart rate (HR), respiratory rate (RR) and pulmonary blood pressure. Significant area under the curve (AUC) with cutoff value >1.55 with sensitivity 85.05 and specificity 91.1%.

Conclusion: Pulmonary hypertension (PAH) complicated by CHD can be predicted by estimation of endothelin-1 (ET-1) as an indicator of endothelial injury.

Keywords: CHD, Echocardiography, ET-1, PAH.

INTRODUCTION

Cyanotic heart defects are called such because they result in cyanosis, a bluish-grey discoloration of the skin due to a lack of oxygen in the body. Such defects include persistent truncus arteriosus, total anomalous pulmonary venous connection, tetralogy of Fallot, transposition of the great vessels, and tricuspid atresia [(1)].

Sometimes, congenital heart disease (CHD) improves without treatment. Most of the time CHD is serious and requires surgery and/or medications. Medications include diuretics, which aid the body in eliminating water, salts, and digoxin for strengthening the contraction of the heart. This slows the heartbeat and removes some fluid from tissues [(2)].

Pulmonary hypertension is a group of conditions with multiple causes rather than a single one. Pathogenesis and management differ among entities [(3)].

Cardiac defects resulting in left-to-right shunting cause pulmonary hypertension (PAH) because the increased pulmonary blood flow induces increases in shear stress and circumferential stretch. These haemodynamic forces within the pulmonary vessels induce endothelial dysfunction [(4)].

Therefore, this study aimed to investigate changes in the blood level of ET-1 in patients of PAH complicated by acyanotic CHD and to detect possible correlation with different hemodynamic parameters.

PATIENTS AND METHODS

A case-control study included 48 children who were presented to Pediatric Cardiology Unit, Pediatrics Department in Zagazig University Hospitals for the first time. They were divided into Group (A), which included 24 children with acyanotic CHD with left to right shunt with PAH and Group B included 24 children with acyanotic CHD with left to right shunt but no PAH.

Inclusion criteria: Patients with acyanotic congenital heart diseases with left to right shunt who were diagnosed by echocardiography aged from one month to 12 years of both gender.

Exclusion criteria:

Patients complicated by acute infection and inflammation and patients complicated by coronary heart disease, cardiomyopathy, high blood pressure and other heart diseases. Patients diseased by respiratory system diseases, hepatic diseases, chronic renal failure, cerebrovascular diseases, tumors and autoimmune diseases.

Operational design:

All participants were subjected to careful history taking, thorough clinical examination, plain X-ray chest postero-anterior view, echocardiography and measurement of endothelin-1 level.

Received: 16 /6 /2021
Accepted: 12 /8 /2021

Echocardiography investigation:

All admitted patient were subjected to transthoracic echocardiography on admission to estimate the pulmonary artery pressure noninvasively from the velocity of the tricuspid regurgitant (TR) jet using continuous wave Doppler. The echocardiography was done using the portable Echo Sonosite (Sonosite 180 Elite sonoheart, USA) to assess cardiac function.

Determination of Endothelin-1: Using a double-antibody sandwich Enzyme-Linked Immunosorbent Assay (ELISA) to assay the level of human endothelin-1 (ET-1) in samples. Add endothelin-1 (ET-1) to monoclonal antibody enzyme well, which was pre-coated with human endothelin-1 (ET-1) monoclonal antibody, incubation; then, add endothelin-1 (ET-1) antibodies labeled with biotin, and combined with Streptavidin-HRP to form immune complex then carry out incubation and washing again to remove the uncombined enzyme.

ET-1 was calculate by using the straight line regression equation of the standard curve with the standard density and the OD value with the sample OD value in the equation to calculate the sample density (USA).

Ethical approval:

The study was approved by the Ethical Committee of Zagazig Faculty of Medicine. An informed consent was obtained from the caregivers of all patients in this research. Every patient received an explanation for the purpose of the study. All given data were used for the current medical research only.

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

Data were recorded using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. Qualitative data were represented as number and percentage and quantitative continuous data were represented by mean ± SD. The used tests were Chi square test (X^2), t test, and Pearson's correlation. A receiver operating characteristic (ROC), was created and sensitivity and specificity were calculated. P value was set at <0.05 for significant results and <0.001 for high significant result.

RESULTS

The current study showed no significant difference between groups as regard age and sex distribution (Table 1).

Table (1) Age and sex distribution between studied groups

			Group A	Group B	t/ X^2	P
Age (years)			6.45± 2.14	6.87± 1.80	0.728	0.470
Sex	**Male**	**N**	13	12		
		%	54.2%	50.0%		
	Female	**N**	11	12	0.083	0.773
		%	45.8%	50.0%		
Total		**N**	24	24		
		%	100.0 %	100.0 %		

Group A was significantly associated with previous need of hospital admission (Table 2).

Table (2) Previous need of hospital admission and ICU need distribution between studied groups

			Group		X^2	P
			Group A	Group B		
Previous hospital admission	**No**	**N**	12	21	7.85	0.005 *
		%	50.0%	87.5%		
	Yes	**N**	12	3		
		%	50.0%	12.5%		
Intensive Care Unit	**No**	**N**	17	22	3.41	0.064
		%	70.8%	91.7%		
	Yes	**N**	7	2		
		%	29.2%	8.3%		
Total		**N**	24	24		
		%	100.0 %	100.0 %		

*: Significant difference

Group A was significantly higher than group B as regard pulmonary blood pressure and endothelin-1 (Table 3).

Table (3) Pulmonary blood pressure and endothelin-1 distribution between studied groups

	Group A	Group B	t	P
PUL-BP	54.08±5.79	30.20±3.64	17.086	<0.001 **
Endothelin-1	2.31±0.76	1.06±0.42	6.968	<0.001 **

**: Highly significant difference

Endothelin-1 was significantly negatively correlated with weight and SPO_2 but significantly positively correlated with SBP, HR, RR and pulmonary blood pressure (Table 4).

Table (4) Correlation of endothelin-1 with other parameters

		Endothelin_1
Age	**r**	-0.165
	P	0.261
Weight	**r**	-0.353*
	P	0.014
Height	**r**	-0.276
	P	0.057
BMI	**r**	0.071
	P	0.633
SBP	**r**	0.358*
	P	0.012
DBP	**r**	0.064
	P	0.664
HR	**r**	0.470**
	P	0.001
RR	**r**	0.461**
	P	0.001
SPO_2	**r**	-0.418**
	P	0.003
PUL_BP	**r**	0.800**
	P	<0.001

Significant area under the curve (AUC) with cutoff value, sensitivity and specificity are shown in table 5.

Table (5) Area under curve, cutoff value and validity

Area under the curve	Cutoff value	P	95% Confidence Interval		Sensitivity	Specificity
			Lower Bound	Upper Bound		
0.914	>1.55	<0.01**	0.831	0.997	85.0%	91.1%

DISCUSSION

Congenital heart disease (CHD) is the most common congenital cardiovascular anomaly. It is the most common congenital disease that affects 8 out of every 1000 births or around 40,000 births every year in the United States. Prevalence of neonates born with CHD compared to total birth rate increases each year, accompanied by an increase in adult patients with CHD. According to its clinical manifestations, CHD is divided into acyanotic and cyanotic type [(5)].

Acyanotic type is the most common case found in CHD. The three most common incidence of acyanotic CHD are Ventricular Septal Defect (VSD) (30%), Atrial Septal Defect (ASD) (19%), and Patent Ductus Arteriosus (PDA) (19%). The incidence of acyanotic CHD is more common than cyanotic CHD with a ratio of acyanotic CHD reaching 79% of all CHD, or about 3 to 4 times more than cyanotic CHD [(6, 7)].

Pulmonary arterial hypertension (PAH) is a complex and rapidly progressive disorder. The pathophysiology of PAH is multifactorial, and endothelial dysfunction considered its key element. Remodeling of the pulmonary vessel wall, vasoconstriction, and thrombosis contribute to increased pulmonary vascular resistance [(7)]. Pulmonary hypertension is often developed in patients with CHD and considered as the most common complication that occurs in patient with acyanotic CHD. Though PAH is a common complication of left-to-right shunts, the pathogenesis of CHD complicated with PAH is not yet be fully elucidated [(8)]. Thus, the current study aimed to investigate changes in the blood level of ET-1 in patients of PAH complicated by acyanotic CHD and to detect possible correlation with different hemodynamic parameters.

Our study showed no significant difference between groups as regard age and sex distribution. While, **Parinding** [(9)] showed distribution of sex in CHD patients who developed pulmonary hypertension was divided into 68% (60 cases) female and 32% (28 cases) male. **Tjan *et al.*** [(10)] found a similar sex distribution where a significant proportion of CHD patients who developed pulmonary hypertension were female (68%), around 2 times more than male (32%). This difference in distribution among pulmonary hypertension severity can be due to patients' age distribution which is still quite young so that the burden of the shunt is still mild [(9)].

In our study, endothelin-1 was significantly higher among Group A. Vascular adventitial fibroblasts are able to synthesize and release ET-1 in response to angiotensin II and transforming growth factor-β (TGF-

β), which contributed to extracellular matrix protein secreted by vascular adventitial fibroblasts in turn, contracted extracellular matrix, and further aggravated PAH. Thus, ET-1 played important biological effects in the pathogenesis of PAH [(11)].

In our study, endothelin-1 was significantly negatively correlated with weight and SPO_2 but was significantly positively correlated with SBP, HR, RR and pulmonary blood pressure. ROC curve for endothelin-1 regarding pulmonary hypertension found significant AUC with cutoff value >1.55 with sensitivity of 85.05 and specificity of 91.1%.

Barman [(12)] declared that ET-1 enhanced the production of 1,2-diacylglycerol, which endogenously activated protein kinase C (PKC) in ECs. So ET-1 causes pulmonary vasoconstriction via PKC activation, which may further induce increase in circulating endothelial cells (CECs) in PKC mediated Ca^{2+} sensitization to cause vascular contraction.

Lai *et al.* [(13)] determined correlations between the parameters measured under routine cardiac catheterization and ET-1 production in CHD patients. ET-1 production displayed significant positive correlations with pulmonary artery systolic pressure as well as mean pulmonary artery pressure. Also, the volume of left-to-right shunt positively correlated with the level of ET-1. They suggested that CHD complicated with PAH is associated with increased ET-1 production. ET-1 could be used as a clinical biomarker to define medical strategies for control of PAH.

CONCLUSION

We can conclude that pulmonary hypertension (PAH) complicated by CHD can be predicted by estimation of endothelin-1 (ET-1) as an indicator of endothelial injury.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Rubin L, Badesch D (2005):** Evaluation and management of the patient with pulmonary arterial hypertension, Annals of Internal Medicine, 143(4): 282–292.
2. **Burstein D, Shamszad P, Dai D (2019).** Significant mortality, morbidity and resource utilization associated with advanced heart failure in congenital heart disease in children and young adults. American Heart Journal, 209: 9-19.
3. **Oishi P, Datar S, Fineman J (2017):** Pulmonary hypertension. Pediatric Critical Care Medicine, 17: 263-281.
4. **Diller G, Gatzoulis M (2007):** Pulmonary vascular disease in adults with congenital heart disease. Circulation, 115(8): 1039–1050.
5. **Mai C, Correa A, Kirby R *et al.* (2015):** Assessing the practices of population-based birth defects surveillance programs using the CDC Strategic Framework, 2012. Public Health Reports, 130(6): 722-730.
6. **Khan M (2011):** Congenital Heart Disease in Encyclopedia of Heart Diseases. Amsterdam: Elsevier; Pp. 355-368. https://www.elsevier.com/books/encyclopedia-of-heart-diseases/khan/978-0-12-406061-6
7. **Marelli A, Therrien J, Mackie A *et al.* (2009):** Planning the specialized care of adult congenital heart disease patients: from numbers to guidelines; an epidemiologic approach. American Heart Journal, 157(1): 1-8.
8. **De Luca G, Venegoni L, Iorio S (2010):** Platelet distribution width and the extent of coronary artery disease: results from a large prospective study. Platelets, 21:508–514.
9. **Parinding A (2016):** Gambaran Kasus Penyakit Jantung Bawaan di RSUD Abdul Wahab Sjahranie Samarinda. Samarinda: FK Unmul. https://e-journal.unair.ac.id/CCJ/article/download/21364/12345
10. **Tjan V, Purwandini D, Purnamasari C (2020):** Pulmonary hypertension in patient with acyanotic congenital heart defects in Abdul Wahab Sjahranie General Hospital, Samarinda from 2015-2016. Cardiovascular Cardiometabolic Journal, 2: 45-49.
11. **Shao D, Park J, Wort S (2011):** The role of endothelin-1 in the pathogenesis of pulmonary arterial hypertension. Pharmacol Res., 63: 504-511.
12. **Barman S (2007):** Vasoconstrictor effect of endothelin-1 on hypertensive pulmonary arterial smooth muscle involves Rho-kinase and protein kinase C. Am J Physiol Lung Cell Mol Physiol,, 293: L472-479.
13. **Lai W, Mertens L, Cohen S *et al.* (2015):** Echocardiography in pediatric and congenital heart disease: from fetus to adult. 2nd edi., Wiley-Blackwell. Pp. 928. https://www.abebooks.com/9780470674642/Echocardiography-Pediatric-Congenital-Heart-Disease-0470674644/plp