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PREDICTIVE VALUE OF ENDOTHELINE-1 IN DIAGNOSIS OF PULMONARY ARTERY HYPERTENSION IN PATIENTS OF ACYANOTIC CHD WITH LEFT TO RIGHT SHUNT

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ABSTRACT

Background: Eisenmenger's syndrome represents the most advanced form of pulmonary hypertension with congenital heart disease (PAH-CHD). The current current European Society of Cardiology guidelines provide an anatomical-pathophysiological classification of the congenital left-to-right shunts associated with PAH. This study aimed to evaluate the role of Endothelin-1 (ET-1) blood level as a diagnostic marker of pulmonary hypertension in children with CHD. **Patient and methods:** A case-control study included 48 children and conducted in Pediatric Cardiology Unit, Pediatrics Department in Zagazig University Hospitals as a first time after obtaining the required permissions and informed consent from the participating patients. They were divided into Group (A) involved 24 children with acyanotic CHD with left to right shunt with PAH; Group B involved 24 children with acyanotic CHD with left to right shunt but no PAH. 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. **Results:** SBP, HR and RR were significantly higher among Group A while SPO2 was significantly lower among group A. No significant difference between groups regard distribution of type of anomalies and the majority were ASD and PDA in both groups. No significant difference between groups regard Murmur.Group A was significantly higher regard pulmonary blood pressure. Endotheline_1 was significantly higher among Group A as it was distributed as 2.31±0.76 and 1.06±0.42 respectively. **Conclusion:** ET-1 can be considered an indicator of endothelial injury and a biomarker for predicting PAH complicated by CHD and provides a new clinical thought for diagnosing PAH complicated by CHD.

Keywords: Pulmonary Hypertension**;** CHD; Endothelin-1

Introduction

Pulmonary hypertension is defined as a resting mean pulmonary artery pressure (mPAP) of 25 mm Hg or above**.**Pulmonary artery hypertension (PAH) is a frequent complication of congenital heart disease (CHD), particularly in patients with left-to-right (systemic-to-pulmonary) shunts (**1)**.

Eisenmenger's syndrome represents the most advanced form of PAH-CHD. The current European Society of Cardiology guidelines provide an anatomical–pathophysiological classification of the congenital left-to-right shunts associated with PAH (**2).**

In some instances, left-sided lesions can result in development of post-capillary pulmonary hypertension; however, this occurs much less frequently than PAH resulting from left-to-right shunts (**3).**

The development of PAH in patients with CHD is associated with increased mortality and high morbidity, reflected in a substantial increase in health service utilization (**4).**

It is commonly believed that the structural, functional and metabolic change of endothelial cell (ECs) is an important pathological feature of the pulmonary vessels of patients with PAH. ECs dysfunction has been identified to play a decisive role in mediating the structural changes in the pulmonary vasculature and in pathogenesis of PAH (**5).**

Endothelin-1 (ET-1), a 21-amino acid peptide originally isolated from the supernatants of cultured porcine aortic endothelial cells, is considered to be one of the most potent and long acting vasoconstrictors known (**6).**

Although produced mainly by ECs, ET-1 is also produced by other cell types, including vascular smooth muscle cell, fibroblasts and inflammatory cells. Several studies have indicated that ET-1 could cause vasoconstriction and vascular remodeling (**7).**

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It is known that patients with CHD-APAH have evidence of systemic inflammation and elevated serum endothelin-1 levels. The aim of the current study is to evaluate the role of ET-1 blood level as a diagnostic marker of pulmonary hypertension in children with CHD.

Patients and methods:

This case-control study was conducted in Pediatric Cardiology Unit, Pediatrics Department in Zagazig University Hospitals as a first time after obtaining the required permissions and informed consent from the participating patients. The present study recruited 48 children.

They were divided into two groups: Group (A) involved 24 children with acyanotic CHD with left to right shunt with PAH; Group B involved 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 diagnosed by echocardiography; age 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, diabetes mellitus, cerebrovascular diseases, tumors, autoimmune diseases and Down syndrome. Patients complicated by PAH caused by other factors and patients who have a major surgery recently or a history of trauma. Legal guardians unable or unwilling to give informed consent.

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.

Echocardiography investigeation: 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) to assess cardiac function.

Determination of Endothelin-1: Using a double-antibody sandwich Enzyme-Linkd 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 is 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 andwashing again to remove the uncombined enzyme.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.

Statistical analysis:

Data collected using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance; difference and association of qualitative variable by Chi square test (X2). Differences between quantitative independent groups by t test, correlation by Pearson's correlation. P value was set at <0.05 for significant results &<0.001 for high significant result.

Results:

The present study showed age was distributed as 6.45±2.14 and 6.87±1.80 respectively with no significant difference between groups also there was no significant difference regard sex distribution **(Figure 1)**. Weight was significantly lower at group A, height and BMI also were lower among Group A but not significantly **(Figure 2)**. SBP, HR and RR were significantly higher among Group A while SPO2 was significantly lower among group A **(Table 1)**. No significant difference between groups regard distribution of type of anomalies and the majority were ASD and PDA in both groups **(Table 2)**. Cough and chest infection were associated with Group A but not significantly while Dyspnea was significantly associated with Group A **(Table 3)**. No significant difference between groups regard Murmur **(Table 4)**.Group A was significantly higher regard pulmonary blood pressure **(Figure 3)**. Endotheline_1 was significantly higher among Group A as it was distributed as 2.31±0.76 and 1.06±0.42 respectively **(Figure 4)**.

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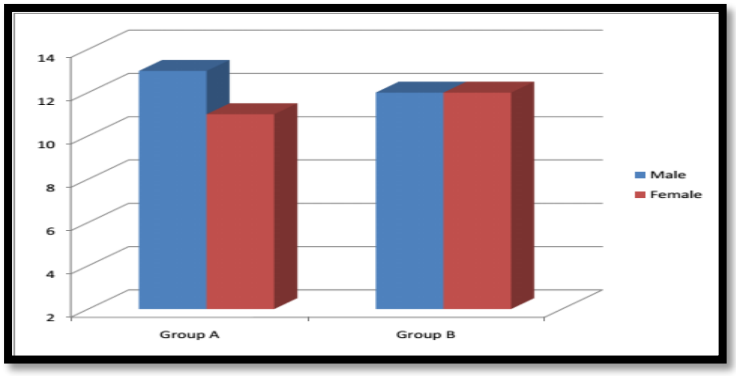

Figure (1): Age and sex distribution between studied groups

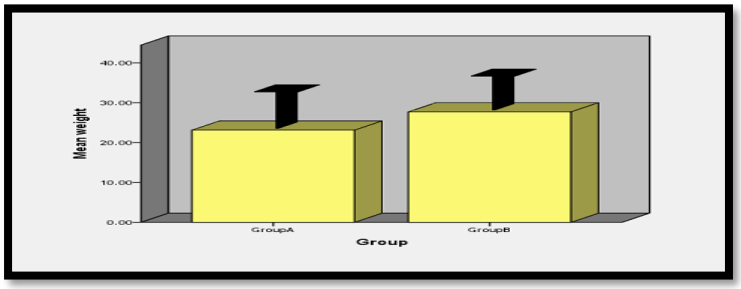

Figure (2): Anthropometric parameters distribution between studied groups.

Table (1): Vitals parameters distribution between studied groups:

	Group A	Group B	t	P
SBP	95.21±3.09	92.20±1.95	4.017	0.00**
DBP	62.12±3.82	61.08±3.58	0.239	0.769
HR	117.91±4.56	105.41±8.77	6.189	0.00**
RR	39.20±4.18	32.79±3.64	5.666	0.00**
SPO2	96.21±1.05	97.83±1.09	4.565	0.00**

Table (2):Type of congenital anomalies distribution between studied groups

			Group		X^2	P
			Group A	Group B		
Congenital Anomalies	ASD	N	9	6		
		%	37.5%	25.0%		
	AVSD	N	2	3		
		%	8.3%	12.5%		
	PDA	N	8	9	0.95	0.81
		%	33.3%	37.5%		
	VSD	N	5	6		
		%	20.8%	25.0%		
Total		N	24	24		
		%	100.0%	100.0%		

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Table (3): Clinical picture distribution between studied groups

			Group		X^2	P
			Group A	Group B		
Cough	-VE	N	17	21	2.02	0.15
		%	70.8%	87.5%		
	+VE	N	7	3		
		%	29.2%	12.5%		
Chest infection	-VE	N	18	22	2.40	0.12
		%	75.0%	91.7%		
	+VE	N	6	2		
		%	25.0%	8.3%		
Dyspnea	-VE	N	18	23	4.18	0.041*
		%	75.0%	95.8%		
	+VE	N	6	1		
		%	25.0%	4.2%		
Total		N	24	24		
		%	100.0%	100.0%		

Table (4): Murmur distribution between studied groups:

			Group		X^2	P
			Group A	Group B		
Systolic murmur	-VE	N	0	0	0.00	1.0
		%	0.0%	0.0%		
	+VE	N	24	24		
		%	100.0%	100.0%		
Diastolic murmur	-VE	N	13	14	0.085	0.77
		%	54.2%	58.3%		
	+VE	N	11	10		
		%	45.8%	41.7%		
Total		N	24	24		
		%	100.0%	100.0%		

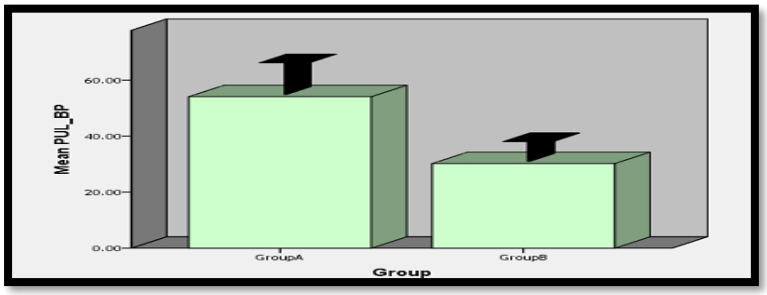

Figure (3): Pulmonary blood pressure distribution between studied groups

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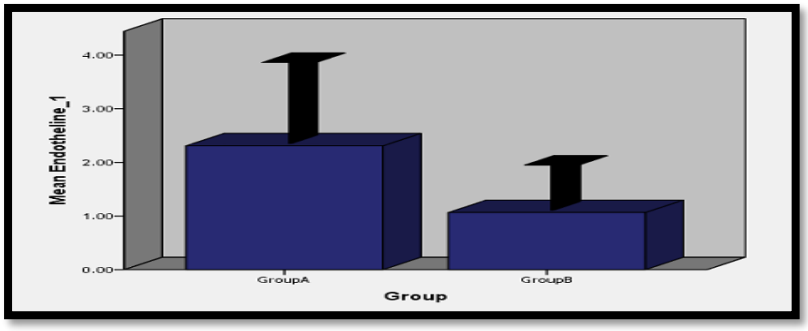

Figure (4): Endotheline-1 distribution between studied groups

DISCUSSION

Pulmonary hypertension prevalence reached around 15 cases per million people **(8)**. **Peacock et al. (9)** showed that around 5% of adult CHD patients developed pulmonary hypertension and the estimated pulmonary hypertension cases as a complication of CHD can reach around 1.6 to 12.5 cases per each million population. **Parinding (10)** showed a record of 374 patients diagnosed with pulmonary hypertension, and there were a total of 88 patients diagnosed with pulmonary hypertension due to CHD.

Endothelin-1 (ET-1) is a middle molecule and most of it is secreted in the lungs by the endothelium and smooth muscles of airway epithelium. ET-1 is also found circulating in the plasma. The activity of endothelin-1 is mediated by two different receptors, namely, ETA and ETB. ETA is inside the smooth muscle cells of the pulmonary vascular bed while ETB is located inside the smooth muscle cells of the pulmonary vascular system as well as inside the endothelial cells **(11)**.

It seems that the endothelin receptor mediates a potent vasoconstrictive response through G-protein-coupled phospholipase C activation that ends in 1,4,5-inositol triphosphate formation and leads to increased level of intracellular Calcium ion **(12)**.

The endothelin receptor seems to express its effects on the endothelial cells, which would mediate pulmonary artery dilatation, through nitric oxide and prostacyclin production. Although some evidence has shown that the endothelin receptor could possibly exert its vasoconstrictive effects in hypoxic conditions, its mechanism is not fully elucidated **(13)**.

Since the discovery of ET-1, **Masaki and Sawamura (14)** performed a study because of its prolonged vasoconstrictive effect even after a single-dose injection to rats. It has been shown that ET-1 has an important role in stabilizing the blood pressure. Also, ET-1 causes bronchoconstriction and pulmonary artery hypertension.

It is known that patients with CHD-PAH have evidence of systemic inflammation and elevated serum endothelin-1 levels. But, few studies discussed the role of endothelin-1 in diagnosis of PAH caused by CHD as a whole. Therefore, the aim of the present study was to investigate changes in the blood level of ET-1 in children of PAH complicated by CHD.

In our study, age was distributed as 6.45±2.14 and 6.87±1.80 respectively with no significant difference between groups. This goes in disagreement with a study conducted by **Yıldız et al. (15)**. Also, **Tjan et al. (16)** saw that age distribution was predominantly in children (56%) than adults (44%). The youngest patient who was diagnosed with acyanotic CHD and developed pulmonary hypertension was only 2 months old.

Also, we found no significant difference regard sex distribution. This was in agreement with **Arslan et al. (17)** study on 57 cases that revealed that no defference in sex distribution. But, this was not in agreement with a study conducted by **Güvenc et al. (18)** where there was significant different in sex distribution.

In our study, SBP, HR and RR were significantly higher among Group A, while SPO2 was significantly lower among group A. This is was against the results obtained by a study done by **Arslan et al. (17)**, where there was no significant different in heart rate between groups.

We found no significant difference between groups regarding distribution of type of anomalies and the majority were ASD and PDA in both groups. Cough and chest infection were associated with Group A but not significantly, while Dyspnea was significantly associated with Group A. **Tjan et al. (16)** distributed patients across the various type of acyanotic CHD. More than half of enrolled patients (58%) presented with ASD, followed by VSD (21%), and PDA (21%).

Group A was significantly higher regarding pulmonary blood pressure. This goes in contrast with a study done by **Yıldız et al. (15)**, where there was no significant difference between systolic and diastolic blood pressure in different groups. **Güvenc et al. (18)** that showed that systolic PAP was

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significantly higher in the PH group (70.16 ± 24.09 mm Hg) compared to the controls (22.77 ± 4.29; $p < 0.001$).

In our study, endothelin-1 was significantly higher among Group A as it was distributed as 2.31±0.76 and 1.06±0.42 respectively. **Li et al. (5)** investigated changes in the level of endothelin-1 (ET-1) in peripheral venous blood of the patients with congenital heart disease (CHD) complicated with pulmonary artery hypertension (PAH). They have considered ET-1 as a potent vasoconstrictive peptide that shows a widespread tissue distribution and many actions. They demonstrated that ET-1 production in the group of moderate-severe PAH was significantly higher than those in the group of mild PAH and the group of CHD without PAH. Meanwhile, secretion of ET-1 in the group of mild PAH was also significantly higher than those in the group of CHD without PAH and the control group.

CONCLUSION

Our study revealed that ET-1 can be considered an indicator of endothelial injury and a biomarker for predicting PAH complicated by CHD, and provides a new clinical thought for diagnosing PAH complicated by CHD.

No conflict of interest.

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