Pulmonary Arterial Hypertension and The Relationship Between IGF-1, IGFBP3

Pulmoner Arteriyel Hipertansiyon ve IGF-1, IGFBP3 İlişkisi

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Geliş Tarihi/*Received:* 09.01.2015
Kabul Tarihi/*Accepted:* 06.04.2015

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ABSTRACT Objective: This study was planned to evaluate the connection between IGF-1 and IGFBP3 in congenital heart diseased children accompanying with pulmonary hypertension. **Material and Methods:** A total of 53 patients with congenital heart disease (31 female, 22 male) whose heart catheterizations were performed were evaluated. Blood samples were obtained during catheter angiocardiography for insulin like growth factor-1(IGF-1) and insulin growth factor bındıng protein-3 (IGFBP3) levels. Patients were categorised into various groups such as acyanotic and cyanotic patients; ones with pulmonary hypertension; ones with high and pulmonary vascular resistance. **Results:** Of the patients involved in the study, 31 were female and 22 were male. IGF-1 was analyzed in 37 patients (22 female, 15 male, mean age 4,74±3,98 years) and IGFBP3 was analyzed in 43 patients (22 female, 21 male, mean age 4,28±3,87 years). IG-1 levels were determined significantly low in patients with pulmonary hypertension compared to those with normal pulmonary artery pressure(p=0,021), and in the ones with high pulmonary vascular resistance compared to normal ones (p=0,022). IGFBP3 levels of patients with acyanotic pulmonary hypertension were found significantly low compared to ones with acyanotic pulmonary hypertension. IGFBP3 levels of patients with pulmonary vascular hypertension and high pulmonary resistance were found significantly low compared to ones with normal pulmonary artery pressure and resistance. **Conclusion:** Both IGF-1 and IGFBP3 levels were determined lower in children with congenital heart disease accompanied by pulmonary hypertension compared to those with normal pulmonary artery pressure.

Key Words: Pulmonary arterial hypertension, IGF-1, IGFBP3

ÖZET Amaç: Bu çalışma konjenital kalp hastalıklı çocuklarda eşlik eden pulmoner hipertansiyonla IGF-1, IGFBP3 ilişkisini değerlendirmek amacı ile planlanmıştır. **Gereç ve Yöntemler:** Konjenital kalp hastalığı olup kalp kateterizasyonu yapılmış olan toplam 53 hasta (31'i kız, 22'si erkek) değerlendirildi. İnsülin benzeri büyüme faktörü-1(IGF-1) ve insülin benzeri büyüme faktörü bağlayıcı protein-3(IGFBP3) düzeyleri kateter anjiyokardiyografi sırasında alınan kan örneklerinde çalışıldı. Hastalar asiyanotik ve siyanotik; pulmoner hipertansiyonu olanlar ve olmayanlar, pulmoner direnci yüksek ve normal olanlar olmak üzere guruplandırıldı. **Bulgular:** Çalışma kapsamına alınan hastaların 31'i kız, 22'si erkekti. IGF-1 37 (22'si kız 15'i erkek yaş ortalaması 4,74±3,98 yıl) hastada, IGFBP3 43 (22'si kız 21'i erkek, yaş ortalaması 4,28±3,87 yıl) hastada çalışıldı. IGF-1 düzeyleri pulmoner hipertansiyonu olan hastalarda olmayanlara göre (p=0,021), pulmoner direnci yüksek olanlarda normal olanlara göre(p=0,022) anlamlı şekilde daha düşük saptandı. Asiyanotik pulmoner hipertansiyonlu hastaların IGFBP3 düzeyleri asiyanotik pulmoner hipertansiyonu olmayanlara göre anlamlı derecede düşük bulundu. Pulmoner hipertansiyonlu ve pulmoner direnci yüksek olan hastaların IGFBP3 düzeyleri pulmoner hipertansiyonu olmayan ve pulmoner direnci düşük olan hastalara göre belirgin olarak düşük bulundu. **Sonuç:** Hem IGF-1 hem IGFBP3 düzeyleri pulmoner hipertansiyonun eşlik ettiği konjenital kalp hastalıklı çocuklarda pulmoner hipertansiyon olmayanlara göre daha düşük bulunmuştur.

Anahtar Kelimeler: Pulmoner arteryel hipertansiyon, IGF-1, IGFBP3

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Pediatr Heart J 2015;2(2):51-5

Growth hormone(GH) is the most important hormone controlling growth. It shows its effects through somatomedins insulin like growth factor-1 (IGF-1) and insulin like growth factor-2(IGF-2). Particularly IGF-1 is effective on somatic growth. Somatomedins are present in circulation depending on binding proteins. Insulin growth factor binding protein (IGFBP3) is the most important of these proteins. It is thought that the effects of GH on somatic growth occur through stimulation and release of IGFs, which have important impacts in cell growth and reproduction, caused by autocrine and paracrine actions from liver.[1]

Obstructive congenital heart diseases with left-right shunts and high gradient leading to heart failure, particularly cyanotics, are the diseases increasing catabolic metabolism. The growth in these diseases is known to be low compared to healthy children. It was shown in previous studies that IGF-1 and IGFBP3 levels in children with congenital heart disease were lower compared to healthy ones; after surgical correction, however, IGF-1 and IGFBP3 levels increased and growth also accelerated.[2,3] Nonetheless, it has not been clarified how IGF-1 and IGFBP3 levels are affected in patients with pulmonary hypertension and who have undergone palliative treatment approaches. It is claimed that IGF-1 is effective in the development of pulmonary hypertension4,5 however there are no adequate studies conducted on this issue.

The present study was planned to evaluate the relation of IGFBP3, IGF-1 with pulmonary hypertension in children with congenital heart disease.

MATERIAL AND METHODS

A total of 53 patients [31 female, 22 male and mean age 4,31±4.19 years (5 months-16 years)] whose heart catheterization had been performed and surveiled at Gazi University Medicine Faculty Pediatric Cardiology Department were evaluated. Pressure curves of patients were written down during heart catheterization process and their hemodynamical practices were conducted. Systemic flow (Qs), pulmonary flow (Qp) values, Qp/Qs rate, pulmonary resistance (Rp), systemical resistance (Rs) values and Rs/Rp rate were calculated using Fick method.

IGF-1 (venous blood) and IGFBP3 (arterial+venous blood) levels were studied from blood samples attained in the course of catheter angiography. After centrifuging the blood samples at 3500 cycles for 10 minutes, the obtained serum was stored at -70 C°. IGF-1 and IGFBP3 levels were measured by ELISA method.

In other blood samples obtained simultaneously, however, blood gas and hemoglobin measurements were performed by using routine laboratory methods.

The patients with mean pulmonary arterial pressure >30 mmHg were regarded as having pulmonary hypertension; the ones with pulmonary resistance >2 U/m^2 were considered as having high pulmonary vascular resistance.

The cases were divided into three different groups as acyanotic and cyanotic patients; the ones with pulmonary hypertension and normal pulmonary artery pressure; the ones with high and normal pulmonary vascular resistance. In addition, acyanotic patients were divided into two groups as the ones with pulmonary hypertension and normal pulmonary artery pressure; their IGF-1 and IGFBP3 levels were compared (Table 1, Table 2).

Research ethics committee approval was obtained from faculty for the study. Permission form was obtained from the families of patients that had been informed about the study and agreed to participate.

Statistical analysis was fulfilled by utilising Minitab 13.0. The results were given as mean±standard deviation (minimum value-maximum value). $P<0.05$ was accepted as statistically significant. Student t-test was used. Pearson correlation analysis was applied to all patient groups.

RESULTS

Of the patients involved in the study, that 31 were female and 22 were male. Their mean age was 4.31±4.19 (5 months-16 years).

TABLE 1: Hemodynamic parameters of cyanotic and acyanotic patients.

	Acyanotic (n=36)	Cyanotic (n=17)	p
Hb(gr/dL)	11.91±1.89	15.01±2.81	0.000
AO O_2 sat(%)	96.2±2.19	82.47±10.68	0.000
PA O_2 sat(%)	82.91±7.72	81.93±7.15	>0.05
Qp (L/min/m²)	10.2±6.62	6.63±4.55	>0.05
Qs (L/min/m²)	4.24±1.20	4.83±3.31	>0.05
Qp/Qs	2.43±1.37	1.54±0.95	0.044
Shunt (L/min/m²)	6.00±6.19		
PAP sys (mmHg)	40.36±22.75	36.5±24.28	>0.05
PAP mean (mmHg)	28.22±19.26	30.27±20.43	>0.05
Rp (U/m²)	3.32±5.75	3.02±1.86	>0.05
LVSP (mmHg)	102.53±16.63	93.76±15.82	0.049
RVSP (mmHg)	54.28±28.22	98.65±16.67	0.000

AO: Aorta; Hb: Hemoglobin; LVSP: Left ventricular systolic pressure; PA: Pulmonary artery; PAP: Pulmonary artery pressure; Qp: Pulmonar flow; Rp: Pulmonary resistance; RVSP: Right ventricular systolic pressure; sat: Saturation; sys: Systolic; O_2: Oxygen.

TABLE 2: Hemodynamic parameters of acyanotic patients with pulmonary hypertension and normal pulmonary artery pressure.

	Pulmonary Hypertension (n=20)	Normal pulmonary artery pressure (n=16)	p
Hb(gr/dL)	11.08±1.79	12.39± .81	0.044
AO O_2 sat(%)	95.67±2.74	96.48±1.86	>0.05
PA O_2 sat(%)	84.17±8.36	82.26±7.47	>0.05
Qp (L/min/m²)	14.23±7.92	6.63±4.55	0.004
Qs (L/min/m²)	4.79±1.18	3.93±1.12	0.038
Qp/Qs	2.96±1.90	2.12±0.86	>0.05
Shunt (L/min/m²)	9.57±8.70	3.99±2.83	0.007
PAP sys (mmHg)	63.00±23.27	27.57±7.01	0.000
PAP mean (mmHg)	47.15±20.67	17.52±5.04	0.000
Rp (U/m²)	6.14±8.97	1.72±1.15	0.024
LVSP (mmHg)	98.77±12.21	104.65±18.60	>0.05
RVSP (mmHg)	68.23±23.94	46.39±27.83	0.023

AO: Aorta; Hb: Hemoglobin; LVSP: Left ventricular systolic pressure; PA: Pulmonary artery; PAP: Pulmonary artery pressure; Qp: Pulmonar flow; Rp: Pulmonary resistance; RVSP: Right ventricular systolic pressure; sat: Saturation; sys: Systolic; O_2: Oxygen.

IGF-1 was analyzed in 37 patients (22 female, 15 male, mean age 4,74±3,98 years) and IGFBP3 was studied in 43 cases (22 female, 21 male, mean age 4,28±3,87 years).

17 patients (9 female, 8 male; 4,22±2.2 years) In cyanotic group and 36 patients (15 female, 21 male; 4,83±2,87 years) in acyanotic group were evaluated. Hemodynamic values of groups were given in Table 1. When patients were classified into groups as those with pulmonary hypertension and normal pulmonary artery pressure, there were 23 (10 female, 13 male; 3,21±3,21 years) in pulmonary hypertension group and 30 (14 female, 16 male; 6,62±4,44 years) in normal pulmonary artery pressure. Although the mean ages of cyanotic and acyanotic patients were similar (4,22±2.2 years and 4,83±2,87 years), mean age of the patients with pulmonary hypertension was significantly lower than those with normal pulmonary artery pressure ($p<0.05$).

Hemodynamic data of 20 patients with acyanotic pulmonary hypertension (12 male, 8 male, mean age 3,68±3.56 years) and 16 normal pulmonary artery pressure patients (9 male, 7 female, mean age 4,99±2.56 years) were compared in Table 2.

No significant difference was established between groups in terms of their age and gender. IGF levels of all patient groups and their comparison are given in Table 3. IGF-1 levels in patients with pulmonary hypertension were determined significantly lower than those with normal pulmonary artery pressure ($p=0.021$), similarly lower IGF-1 levels were found in those with high pulmonary vascular resistance compared to those with normal pulmonary vascular resistance ($p=0.022$) (Table 3).

IGFBP3 levels were determined similar in systemic venous blood and pulmonary artery samples obtained simultaneously (Table 4). No significant difference was determined between IGFBP3 levels of cyanotic and acyanotic patients (Table 4). IGFBP3 levels of patients with acyanotic pulmonary hypertension were found significantly low compared to acyanotic patients and normal pulmonary artery pressure (Table 4). IGFBP3 levels of patients with pulmonary hypertension and high pulmonary vascular resistance were detected significantly low compared to those with normal pulmonary artery pressure and low pulmonary vascular resistance (Table 4).

In all patient groups, IGF-1 and IGFBP3 values, age, weight and height percentiles and corre-

TABLE 3: IGF-1 levels of patient groups.

	IGF-1 (V) (ng/ml)	p
Acyanotic (n=36)	47.5±68.8	>0,05
Cyanotic (n=17)	83.3±126.1	
Acyanotic PAH (+)(n=15)	23.7±55.9	>0,05
Acyanotic PAH (-) (n=10)	81.4±73.3	
Ones with PAH (n=20)	28.6±53.1	0,021
Ones with no PAH (n=17)	93.5±109.7	
High Pulmonary Resistance (n=14)	41.8±80.5	0,022
Normal Pulmonary Resistance (n=19)	78.8±99.8	

PAH: Pulmonary arterial hypertension; IGF-1: Insulin like growth factor; V: Venous blood; IGF-1: insulin like growth factor-1.

lation analyses of hemodynamic parameters were evaluated. Correlation of IGF-1, IGFBP3 values with age (r:0.33, r:0.36) was not determined. A significant negative correlation of IGF-1 and IGFBP3 values was respectively determined with weight percentiles (r:-0.64, r:-0.66), height percentiles (r:-0.67, r:-0.70), and oxygensaturation (r:-0.72, r:-0.74) and pulmonary resistance (r:-0.87, r:-0.81).

DISCUSSION

A part of congenital heart diseases could have the way for postnatal growth retardation.[6,7] In congenital heart diseases in which especially pulmonary blood flow increases and congestive heart failure accompanies, growth retardation is more apparent.[2,8,9] It is thought that growth retardation develops in congenital heart diseased children with numerous effects such as malnourishment, malabsorption, non-utilizable foods in anoxic setting, accelerated basal metabolism rate, increased recreation oxygen consumption[10,11] and increased nutritional need. Therefore, congenital heart diseased children show chronic malnutrition clinically characterized by decreased fatty tissue, delicate muscle mass and growth retardation.[12] While basal growth hormone (GH) levels increases in the setting of malnutrition caused by chronic diseases, the IGF-1 levels decrease.[13] It was determined that despite increased GH levels in children with congenital heart disease, IGF-1 levels were low and growth retardation is seen.[2,14]

It is also known that GH and somatomedins (IGF-1, IGF-2) have primary effects on the structure of cardiovascular system and functions.[15,16] Cardiomyopathy, cardiomegaly and ventricular hypertrophy are seen in growth hormone excessiveness.[15] In addition to this, it is suggested that IGF-1 mediated mechanisms may play role in the development of pulmonary arterial hypertension.[4,5]

Florentina and Leanne showed in their research carried out on rats that IGF-1 increased intracellular Ca level by activating T type calcium

TABLE 4: IGFBP3 levels of patient groups.

	IGFBP3 (A) (ng/ml)	IGFBP3 (V) (ng/ml)	P
Acyanotic (n=36)	2591±1280	2538±1237	>0.05
Cyanotic (n=17)	2402±1515	2280±1579	>0.05
p	>0.05	>0.05	
Acyanotic PAH (+) (n=15)	2591±1280	2538±1237	>0.05
Acyanotic PAH (-) (n=12)	2402±1515	2280±1579	>0.05
p	0.002	0.007	
Ones with PAH (n=24)	2013±918	2017±887	>0.05
Ones with no PAH (n=97)	3217±1513	2280±1579	>0.05
p	0.003	0.016	
High Pulmonary Resistance (n=24)	2065±988	2078±1103	>0.05
Normal Pulmonary Resistance (n=19)	2984±1539	2911±1511	>0.05
p	0.035	0.059	

A: Artery; V: Vein; PAH: Pulmonary arterial hypertension; IGFBP3: Insulin growth factor binding protein.

channels activation and caused pulmonary artery smooth muscle cell proliferation.[4].Jin et al, however, claimed that IGF-1 prevents apoptosis in pulmonary artery smooth muscle cells via inducible nitric oxide synthase and plays a role in pulmonary hypertension mechanisms.[5]

We displayed in this study that IGF-1 and IGFBP3 levels in children with congenital heart disease and pulmonary hypertension were significantly low compared to children with normal pulmonary artery pressure. IGF levels in congenital heart diseased children were reviewed in limited number of studies.[2,3] Findings that we obtained contributed to results of these studies. Since blood samples of our patients were the samples attained during catheter angiography, we could not compare them with those of healthy control group. We speculate somatomedin levels in patients with pulmonary hypertension were lower compared to those with normal pulmonary artery pressure and IGF-1 does not have a primary role in the development of pulmonary hypertension even it mediates proliferation in pulmonary vascular smooth muscles.[4,5] On the contrary, IGF and IGFBP3 levels are low secondary to malnutrition and chronic disease in these patients. Having significant negative correlation of somatomedin levels determined in our study with both weight, height percentiles and pulmonary resistance levels of patients supports this condition.

When IGF-1 values were compared among PAH+ and PAH- patients, the diference was considerable although it did not reach statistical significance. Similar outcome was noticed between cyanotic and non-cyanotic patients. This situation is probably due to the small number of the cohort and non-normal distribution of the group.

As a result, IGF-1 and IGFBP3 levels were established low in congenital heart diseased children with pulmonary hypertension compared to those with normal pulmonary artery pressure. This finding could be related to growth retardation and malnutrition that are more apparent in patients with pulmonary hypertension. Further studies are needed to clarify the role of IGF-1 in the development of pulmonary hypertension.

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