The Importance of Electrocardiography in Pediatric Patients with Pulmonary Arterial Hypertension in Follow- up

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Abstract

Background: Right Ventricular (RV) hypertrophy is an adaptive response to chronic RV pressure overload in patients with pulmonary hypertension. We investigated the relationships between RV hypertrophy indicators, including electrocardiography, the percentage oxygen saturation (SaO2%), body mass index (BMI), and blood uric acid levels in patients with a biventricular structure followed up for Pulmonary Arterial Hypertension (PAH).

Materials and Methods: This retrospective study included 33 patients with confirmed systemic PAH, according to the catheterization and a negative vascular reactivity test result. Patients with single-ventricle physiology and Down's syndrome who had undergone surgery were excluded. The data of blood chemistry, hemogram, ECG, and SaO2% were collected, thus, the BMI was calculated. The patients were categorized according to SaO2 values (<90% [n=14] vs. >90% [n=19]), BMI (<18.5 [n=16] vs. >18.5 [n=17] kg/m2), PAH status (primary [n=13] vs. secondary [n=20]), and treatment regime (combination therapy [n=16] vs. monotherapy [n=17]), and the data were compared among the groups.

Results: Patients with SaO2 values of <90% and >90% differed only in terms of blood uric acid level, which was significantly higher in the patients with SaO2<90%. The V1–V2 R-waves indicating right ventricular hypertrophy were significantly higher in patients with a BMI <18.5 kg/m2. The D1 S-waves and V1–V2 R-waves were significantly higher in patients who received combination therapy compared to those receiving monotherapy.

Conclusion: Low BMI, SaO2 <90%, elevated uric acid levels, and an elevated R-wave in V1 or V2 were associated with poor functional capacity. In particular, the D1 S-wave was significantly higher in patients who received combination therapy, with a height >9 mm indicating impaired capacity. These measured markers can be used to follow-up patients with PAH.

Key Words: Children, Pulmonary arterial hypertension, S-wave.

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1- INTRODUCTION

Right Ventricular (RV) hypertrophy is an adaptive response to chronic RV pressure overload in patients with pulmonary hypertension. Electrocardiography (ECG) can be used to assess the hemodynamic effects of therapy in patients with precapillary pulmonary hypertension. The Right Ventricular Sokolow-Lyon Index (RVSLI) is an electrocardiographic indication of RV hypertrophy and may reveal the RV pressure load. This index is calculated by adding the R-wave of V1 or V2 to the S-wave of V5 or V6; an RVSLI >2.1 mV at the time of initial diagnosis is a risk factor for later cardiac disorders (1). Cachexia is a strong risk factor for cardiac failure that may be fatal; RV dysfunction is commonly associated with cachexia, often accompanied by an increased metabolic rate, impaired gastrointestinal function, and hemodynamic features triggering cardiac failure ultimately caused by pulmonary hypertension, and increased neurohumoral and cytokine responses (2).

Serum uric acid has been associated with the hypoxic state, and both increased pro-Brain Natriuretic Peptide (BNP), and uric acid levels were suggested to indicate a poor prognosis in children with PAH in studies evaluating the responses to therapy and predicting survival (3, 4). Here, we studied the relationships among RV hypertrophy evident on electrocardiography (ECG), the percentage oxygen saturation (SaO$_2$%), body mass index (BMI), and blood uric acid level in patients followed up for Pulmonary Arterial Hypertension (PAH) with biventricular structure.

2- MATERIALS AND METHODS

2-1. Study design and population

This retrospective study included 33 patients who suffered from PAH who were followed up in the pediatric cardiology outpatient clinic, Uskudar, Istanbul, Turkey, in 2016-2019. PAH was confirmed using the catheterization and a negative vascular reactivity test. The etiology was primary PAH in 13 patients and secondary PAH (associated with biventricular congenital heart disease) in 20 patients. Patients with single-ventricle physiology and those with Down's syndrome who underwent surgery were excluded. We obtained blood chemistry, hemogram, ECG, and SaO2% data, and consequently calculated the BMI.

Blood chemical parameters were measured using the enzymatic photometric test using a fully automated biochemistry analyzer, and hematological parameters were estimated using a routine automated hematological analyzer. We recorded blood uric acid and albumin levels, the hemoglobin (Hb), Mean Corpuscular Volume (MCP), Mean Platelet Volume (MPV), and Red Blood Cell Distribution Width (RDW) from complete blood counts.

BMI was calculated as weight in kilograms divided by height in square meters. Patients were classified as underweight (BMI <18.5 kg/m2), normal (18.5–25), overweight (25–30), and obese (>30). Cyanosis was defined as a SaO2 <90%. The patients were divided into groups based on a SaO2 (<90%, >90%), BMI (<18.5, >18.5 kg/m2), and primary and secondary PAH; and those receiving combination therapy and monotherapy. Afterward, the groups were compared.

2-2. Measurement

ECG: The electrodes were placed as follows: V1 on the fourth intercostal space at the right sternum, V2 on the fourth intercostal space at the left sternum, V3 directly between V2 and V4 leads, V4 on the fifth intercostal space on the left midclavicular line, V5 on the anterior axillary line at the same level as V4, and V6 on the midaxillary line at the same

level as V5. A 12-lead standard ECG (10 mm = 1 mV, 25 mm/s) was acquired in the supine position during quiet respiration. The RVSLI was calculated by adding the S-wave in V5 or V6 (whichever was wider) to the R-wave in V1 or V2 (whichever was wider). A QRS axis of + 90° to ± 180° and − 90° to ± 180° was regarded as a right axis and right superior axis deviation, respectively (1). The length of the S-wave in D1 was recorded for each patient (**Figure.1**).
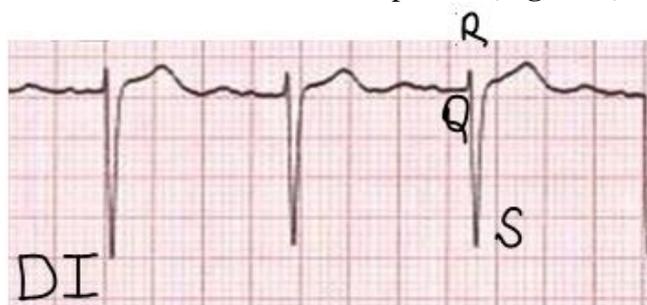
Fig.1: ECG waves in lead D1.

2-3. Ethical Consideration

This study was approved by the Ethics Committee of Istanbul Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital (approval number, 28001928-508.01).

2-4. Statistical Analysis

SPSS forV.15.0 for Windows (SPSS, Chicago, IL, USA) was employed for all statistical analyses. Descriptive data were expressed as means ± standard deviations of numerical variables. Most comparisons between the groups were performed using Student's *t*-tests, although the Mann-Whitney U test was employed in the case of abnormal distribution of variables. The Kruskal-Wallis test was used to determine whether differences between continuous variables were significant. If the overall P-value was significant, the Mann-Whitney U test was performed to evaluate the differences further. All categorical variables were compared using the Chi-squared test. P <0.05 indicates statistical significance.

3- RESULTS

The mean age was 5.16±4.16 years (range 4.5–18 years), and the mean BMI was 19.56±5.01 kg/m2 (range 12.9 to 32.5 kg/m2). 16 patients were male (48%), and 17 female (52%). Patients with SaO2 <90% and >90% differed only in terms of blood uric acid level, which was significantly higher in the patients with SaO2 <90% (n=14) (**Table.1**). R-waves in V1–V2 (indicating RV hypertrophy) were significantly higher in patients with a BMI <18.5 kg/m2 (n=16), as was the RVSLI (**Table.2**). The serum albumin level and SaO2% were lower in patients with secondary compared to primary PAH (**Table.3**). A comparison of patients in terms of functional capacity NYHA II who were receiving combination therapy or monotherapy showed the significantly higher D1 S-waves and V1–V2 R-waves in the former patients (**Table.4**). In particular, the D1 S-wave was significantly higher in patients receiving combination therapy (n=16). There was no significant difference in terms of sex and patients with BNP levels of >100 and <100 pg/mL.

Table-1: Comparison of groups with an oxygen saturation <90% to those with an oxygen saturation >90%.

Variables	Saturation <90%, (n=14)	Saturation >90%, (n=19)	P-value
ECG-DI S-wave amplitude	10.25±6.20 mm	11.85±6.30 mm	NS
V1 or V2 R-wave amplitude	19.50±10.40 mm	23.15±16.09 mm	NS
V5 S-wave amplitude	13.38±9.94 mm	15.54±12.97 mm	NS
V1-2 R-+V5 S-wave sum	32.88±11.88 mm	38.69±21.43 mm	NS
QRS angle	171.25±83.25°	120.54±38.11°	NS
Uric acid level (mg/dL)	6.35±1.51	4.68±1.24	**0.03**
RDW (%)	15.75±2.41	14.97±1.96	NS
MPV (fL)	9.84±2.18	9.46±1.36	NS

NS: Not significant. ECG: Electrocardiography, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume.

Table-2: Comparison of patients with a BMI <18.5 to those with a BMI >18.5 kg/m^2.

Variables	BMI <18.5, (n=16)	BMI >18.5, (n=17)	P-value
ECG-DI S-wave amplitude	12.90±6.69 mm	9.73±5.51 mm	NS
V1 or V2 R-wave amplitude	28.50±16.64 mm	15.64±7.56 mm	**0.03**
V5 S-wave amplitude	17.40±14.41 mm	12.27±8.53 mm	NS
V1-2 R0+V5 S-wave sum	45.90±20.39 mm	27.91±11.10 mm	**0.02**
QRS angle	144.40±70.33°	136.45±57.90°	NS
Hb (g/dL)	13.75±2.51	16.06±3.78	NS
MCV (fL)	80.73±8.34	87.24±9.37	NS
RDW (%)	15.49±2.24	15.07±2.09	NS
MPV (fL)	9.56±1.99	9.67±1.44	NS
Albumin (g/dL)	4.18±0.39	4.19±0.36	NS
Uric acid (mg/dL)	4.71±1.54	5.72±1.44	NS
SaO$_2$%	91.60±6.93	87.64±12.18	NS

BMI: Body mass index, ECG: Electrocardiography, MCV: Mean Corpuscular Volume, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume, NS: not significant.

Table-3: Comparison of patients with primary and secondary PAH.

Variables	Primary PAH, (n=13)	Secondary PAH, (n=20)	P-value
ECG-DI S-wave amplitude	12.57±5.28 mm	10.57±6.64 mm	NS
V1 or V2 R-wave amplitude	28.29±20.23 mm	18.50±8.89 mm	NS
V5 S-wave amplitude	16.43±12.99 mm	13.86±11.40 mm	NS
V1-2 R-+V5 S-wave sum	44.71±22.45 mm	32.36±15.02 mm	NS
QRS angle	128.29±47.48°	146.21±69.80°	NS
Hb (g/dL)	14.27±2.14	15.30±3.87	NS
MCV (fL)	85.11±3.65	83.65±11.22	NS
RDW (%)	14.24±1.17	15.78±2.33	NS
MPV (fL)	9.94±1.27	9.44±1.90	NS
Albumin (g/dL)	4.40±0.19	4.07±0.39	**0.03**
Uric acid (mg/dL)	4.64±1.38	5.60±1.56	NS
O_2 saturation (%)	96.57±1.71	86.00±10.59	**0.01**

ECG: Electrocardiography, MCV: Mean Corpuscular Volume, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume, NS: Not significant.

Table-4: A comparison of patients receiving combination therapy and monotherapy.

Variables	Combination therapy, (n=16)	Monotherapy, (n=17)	P-value
ECG-DI S-wave amplitude	15.20±6.46 mm	7.64±2.90 mm	**0.005**
V1 or V2 R-wave amplitude	28.70±17.04 mm	15.45±6.29 mm	**0.036**
V5 S-wave amplitude	14.60±11.68 mm	14.82±12.27 mm	NS
V1-2 R+V5S	43.30±21.69 mm	30.27±12.44 mm	NS
QRS angle	157.20±48.89°	124.82±71.67°	NS
Hb (g/dL)	14.79±2.96	15.11±3.84	NS
MCV (fL)	82.18±9.66	85.92±9.01	NS
RDW (%)	15.49±2.29	15.07±2.03	NS
MPV (fL)	9.79±1.84	9.44±1.61	NS
Albumin (g/dL)	4.15±0.38	4.21±0.36	NS
Uric acid (mg/dL)	5.36±1.93	5.19±1.22	NS
O_2 saturation (%)	86.20±12.16	92.55±6.75	NS

ECG: Electrocardiography, MCV: Mean Corpuscular Volume, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume, NS: Not significant.

4- DISCUSSION

Follow-up of patients with PAH should include measurement of easily accessible markers that can predict prognosis and guide treatment decisions. ECG can usefully investigate the hemodynamic effects of therapy in patients with precapillary pulmonary hypertension. Hemodynamic improvements evident after therapy may be due to the reduction in the amplitude of the V1 R-wave, and decrease in the maximum R-wave in V1 or V2, and the S wave in the max-D1–aVL–S-wave

interval in V1. In patients with PAH, a decrease in the amplitude of the V1 R-wave was associated with the highest survival rate (2), the presence of qR in V1 was a risk factor of mortality (5). The amplitude of V1 R-wave andV6 S-wave correlated with the mean pulmonary arterial pressure (6). Sato et al. (7) studied 112 PAH patients and found that the ECG parameters changed 3 months after therapy was commenced; a ≥1-mm decrease in the amplitude of the V1 R-wave was associated with optimal survival. In a study conducted on 145 patients with suspected PAH, mean age of 58.4±17.5 years, the depths of the V5 S-wave (0.42 mv), and the V4 negative T-wave (–0.28 mV) independently predicted a pulmonary arterial pressure ≥25 mmHg; whereas a deep V5 S-wave and a wide negative T-wave in terms of the precordial derivations served as simple, useful ECG parameters during clinical screening for PAH (8).

A right axis deviation evident on ECG is associated with a 93% positive predictive value for PAH. The absence of a right axis deviation, N-terminal-proBNP level <333 pg/mL, and a SaO$_2$ ≥95.5%were associated with a negative predictive value of 96% for PAH (9). In astudy (10), 93% of patients under 18 years with PAH exhibited abnormal ECG findings (RV hypertrophy in 78% and right axis deviation in 52%). Right atrial dilation combined with RV hypertrophy was associated with a positive predictive PAH value of 33%, a negative predictive value of 95%, a sensitivity of 92%, and a specificity of 48%. In the present study, the R-waves in V1 or V2, and the RVSLI were significantly higherin patients with BMI values <18.5 kg/m^2. The V1–V2 R-wave and D1 S-wave were significantly higher in patients on combination therapy compared to those receiving monotherapy. In particular, the depth of the D1 S-wave was associated with functional capacity, with a value >9 mm indicating impaired

capacity. The serum uric acid level is associated with hypoxia, and increases in the levels of both N-terminal-proBNP and uric acid are indicators of poor prognosis in children with PAH; these indicators are useful when evaluating the responses to therapy and predicting survival (3, 4). In a study on adults, the mean serum uric acid level was 7.8 mg/dL (range 5.8–9.2 mg/dL) in patients with severe RV dysfunction, 5 mg/dL (range 3.5–6.95 mg/dL) in patients with moderate dysfunction, and 4.7 mg/dL (range 3.87–5.82 mg/dL) in those with mild dysfunction. The serum uric acid level was correlated with pulmonary arterial systolic pressure and WHO functional class. A level >5.7 mg/dL afforded a sensitivity of 76.6% and a specificity of 71.4% in terms of predicting RV dysfunction (11).

Hyperuricemia is common in those with inoperable defects featuring left-right shunting (12). Another study found that a uric acid cut-off of 425.5 μmol/L predicted prognosis (sensitivity 50%, specificity 72%) (13). Uric acid levels are elevated in patients under increased oxidative stress, and those with vascular or cardiac dysfunction, chronic heart failure, cyanotic congenital heart disease, and PAH. They may also increase in patients exhibiting renal failure, gout, and insulin resistance. Uric acid is a useful biomarker during the follow-up of pediatric patients with PAH, as the abovementioned problems are rare in childhood. Close monitoring of uric acid levels yields important information on disease status (14).

In the present study, the uric acid levels were significantly higher in patients with a SaO$_2$ <90% than in those with a SaO$_2$ >90% (6.35±1.51 and 4.68±1.24 mg/dL, respectively). We attributed this finding to high uric acid levels with hypoxemia rather than poor functional capacity. Growth is impairedchildren with PAH is associated with congenital heart disease, although the extent of impairment is not

related to the cause of PAH, but rather to disease duration and severity. BMI can thus be used to monitor the clinical condition (15). Mortality and morbidity decrease with increasing BMI in patients with heart failure and an increased BMI protects patients against death in PAH(16). Elevated tumor necrosis factor-α and troponin T levels have been reported in patients with a low BMI, associated with high systolic pulmonary arterial pressure (17). Moreover, we found that both an R-wave in V1 or V2 (indicating RV hypertrophy) and the RVSLI were higher in patients with a low BMI, suggesting that such patients had more severe PAH. The blood albumin level and SaO2% were significantly lower in patients with secondary PAH compared to the primary PAH. We concluded that these findings were the result of high pressure from birth and the mixing of desaturated and saturated blood in patients with secondary PAH.

4-1. Study Limitations

A larger sample size would be preferable, and it would be useful to compare the effects of therapeutic changes in patients at high risk.

5- CONCLUSION

SaO2 <90%, an elevated uric acid level, and an elevated R-wave in V1 or V2 were associated with a poor prognosis. In particular, the D1 S-wave was significantly higher in the patients receiving combination therapy, with a height >9 mm indicating impaired capacity. The combined evaluation of these parameters during follow-up would improve disease management.

6- WHAT IS ALREADY KNOWN?

Right Ventricular (RV) hypertrophy is an adaptive response to chronic RV pressure overload in patients with Pulmonary Arterial Hypertension (PAH).

Electrocardiography (ECG) can assess the hemodynamic effects of therapy in patients with precapillary pulmonary hypertension. In patients with PAH, a decrease in the amplitude of the V1 R-wave is associated with the highest survival rate, and the presence of qR in V1 is a risk factor for mortality. The V1 R-wave and V6 S-wave amplitudes were correlated with mean pulmonary arterial pressure.

7- WHAT THIS STUDY ADDS?

The S-wave was significantly higher in patients receiving combination therapy, with a height >9 mm indicating impaired capacity. These easily accessible markers can be used to follow-up patients with PAH.

8- CONTRIBUTORS CREDIT

Taliha Oner, Pınar Dervisoglu and Ahmet Celebi: Dr. Oner, Dr Dervisoglu and Dr. Celebi conceptualized and designed the study, drafted the initial manuscript, and carried out the initial analyses, reviewed and revised the manuscript and approved the final manuscript as submitted.

9- ACKNOWLEDGEMENTS

10- CONFLICT OF INTEREST: None.

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