DECREASED HEART RATE VARIABILITY IN SICKLE CELL DISEASE: EFFECT OF PULMONARY HYPERTENSION

Ferit Akgül MD.*, Talantbek Batyraliev MD.**, Ergün Seyfeli MD.*, Tunzale Seydaliyeva MD.*, Edip Gali MD***, Fatih Yalçın MD.*

*Mustafa Kemal University, Faculty of Medicine, Cardiology Department, Antakya, Turkey, **Sani Konukoğlu Medical Center, Cardiology Department, Gaziantep, Turkey, *** Department of Paediatrics, Antakya State Hospital, Antakya, Turkey

Kalp hızı değişkenliğinin (KHD) kompüturize analizi, kardiyak anatomik fonksiyonu tayin etmede non-invaziv bir yöntemdir. Azalmış KHD çeşitli hastalıklarda ve normal populasyonda, artmış mortalite hızı ile birliktedir.

Bu çalışmanın amacı, orak hücreli hastalığa (OHH) sahip olan hastalarda KHD yi ve pulmoner hipertansiyonun KHD üzerine etkisini araştırmaktır.

Biz doppler ekokardiyografiyi kullanarak OHH ya sahip 61 hastada (yaş ortalaması, 18.3±8.0 yıl) ile sağlıklı 22 bireyde (yaş ortalaması, 19.3±7.1 yıl) pulmoner arter sistolik basıncını ölçtük.

Düşük frekanslı power (DFP) ile yüksek frekanslı power (YFP) orak hücreli hastalıklı hastalarda kontrol grubuna göre düşüktü. Buna karşın düşük frekanslı power ile, yüksek frekanslı powerın oranı (DFP/YFP) orak hücreli hastalığı bulunanlarda artmış idi (p<0.0001). Orak hücreli hastalıklı hastalar arasında pulmoner hipertansiyonlu hastalar, pulmoner hipertansiyonu bulunmayan hastalardan daha düşük YFP çok daha yüksek DFP/YFP oranına sahipti (her biri için p<0.001, p<0.05). Buna rağmen, Pulmoner hipertansiyonlu ve pulmoner hipertansiyonsuz OHH lı hastalar arasında DFP yönünden fark yoktu. Kalp hastalığı preklinik devresinde olan, özellikle pulmoner hipertansi-yonu bulunan OHH hastalarda, KHD önemli ölçüde azalmıştır.

Kalp hızı değişkenliği, pulmoner hipertansiyonlu hastaların erken tanısı için bilhassa faydalı olabilir. Zira, bu hastanın kötü prognoz ve yüksek mortalite riski altında olduğuna işaret edebilir.

Anahtar kelimer: Oral hücreli hastalık, Kalp hızı değişkenliği, Pulmoner hipertansiyon

(Türk Girişimsel Kard. Der. 2011;15:151-158)

INTRODUCTION

Sickle cell disease (SCD) is a genetic disease caused by the mutation of haemoglobin A into haemoglobin S. Patients with homozygotes for haemoglobin SS genotype are prone to haemolytic anaemia and vaso-occlusive events that lead to the damage of the tissues in most organ of the body[1]. Cardiac and pulmonary involvement characterized by diastolic dysfunction and pulmonary hypertension (PHT) is common[2,3]. The patients with PHT have a high morbidity and mortality, compared with SCD patients without PHT[4,5]. Previous studies have repported that the cardiovascular autonomic function tests to be disturbed in patients with PHT[6,7]. Computerized analysis of heart rate variability (HRV) is a practical noninvasive method for studying cardiac autonomic function[8,9]. Normal heart rate variation depends on the balance between sympathetic and parasympathetic systems. A high variability in heart rate is a sign of good adaptability, implying a healthy individual with well-functioning autonomic control mechanisms. Conversely, lower variability is often an indicator of insufficient adaptability of the autonomic nervous system. In many clinical studies, the HRV has been showed to be a powerful and independent predictor of an adverse prognosis in patients with heart disease and in the general population[10,11]. Decreased HRV is associated with an increased mortality risk in patients with diabetes mellitus, hypertension, and coronary artery disease[12,13]. We hypothesized that SCD patients, especially with PHT might exhibit alterations in the activity of the autonomic nervous system that might contribute to an increased risk of death

Correspondence Address: Ferit AKGÜL MD
Mustafa Kemal Üniversitesi, Araştırma ve Uygulama Hastanesi
Bağrıyanık Mah. 31100
Antakya-Hatay/TURKEY
Tel:+90 326 2140649
Fax:+090 326 6143834
E-mail: feritakgul1@yahoo.ca
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Table 1: Clinical Characteristics of the Sickle Cell Disease Patients and Control Subjects (mean ± SD)

	SCD Patients	Control Subjects	P value	SCD With PHT	SCD With PHT	P
Age (years)	18.3±8.0	19.6±7.1	NS	19.2±7.1	17.8±8.2	NS
Men/women	38:23	15:9	NS	15:7	23:16	NS
Body mass index (kg/m^2)	19.4±2.2	19.1±3.2	NS	20.2±2.5	18.6±2.2	NS
SBP (mm Hg)	99.6±9.6	102.4±9.4	NS	98.9±10.1	100.2±9.3	NS
DBP (mm Hg)	63.3±10.7	64.6±9.1	NS	62.7±11.4	63.3±10.5	NS
Heart rate (beats per minute)	75.9±13.2.	73.6± 14.5	NS	78.2±10.9	74.9±13.6	NS
Respiratory rate (breaths/min)	21.6±2.8	17.3±2.1	0.01	22.3±2.9	21.1±2.4	NS
Hydroxyurea therapy (%)	65.6	-	-	68.2	64.1	NS
>10 blood transfusions during lifetime (%)	27.9	-	-	31.8	25.6	NS
Hemoglobin (g/dl)	8.6±1.7	13.4±1.1	0.0001	8.4±1.9	8.7±1.5	NS
Hematocrit (%)	24.7±3.3	39.7±2.0	0.0001	24.3±3.7	24.9±2.4	NS
Hemoglobin F (%)	9.9±7.9	-	-	8.5±6.0	10.7±7.8	0.03
Left atrium (cm)	3.4±0.6	2.9±0.4	0.001	3.5±0.6	3.3±0.4	0.03
IVS (cm)	0.83±0.3	0.65±0.2	0.0001	0.75±0.2	0.88±0.3	0.01
LV EDD (cm)	4.8±0.6	4.4±0.5	0.008	5.0±0.6	4.6±0.5	0.01
LV ESD (cm)	2.9±0.4	2.7±0.3	0.01	3.2±0.5	2.8±0.5	0.01
LV ejection fraction (%)	71.2±5.6	71.7±4.7	NS	70.9±6.3	71.5±5.8	NS
PA systolic pressure (mmHg)	28.7±7.3	20.9±4.5	0.0001	37.8±5.4	24.1±6.9	0.0001
Oxygen saturation (%)	93.5±1.8	97.3±1.1	0.007	92.4±1.8	94.1±1.7	0.02

SCD: sickle cell disease, PHT: pulmonary hypertension, SBP: systolic blood pressure, DBP: diastolic blood pressure, LV: left ventricular, IVS: interventricular septum, EDD: end-diastolic diameter, ESD: end-systolic diameter, PA: pulmonary artery, NS: statistically not significant

in that population. So, we examined the HRV parameters in SCD patients with preclinical phase of cardiac involvement. In addition, we examined the effect of PHT on HRV parameters in SCD patients.

METHOD

A total of 61 consecutive patients with SCD were recruited from the patient population that regularly attends the Hematology Clinic of Antakya State Hospital (Antakya, Turkey). Each enrolled patient was studied in a non-crisis, steady state; had not experienced an episode of acute chest syndrome in the 6 weeks preceding enrolment. The control group consisted of 24 healthy subjects with a normal echocardiography.

All of the study subjects underwent standard 12-lead electrocardiography (PC-ECG 1200, Norav Medical Ltd., Israel). A stationary 10-minute segments of ECG was recorded from all study subjects while resting in the supine position during uncontrolled, normal breathing. Heart rate variability analysis was performed using Heart Rate Variability Software (version 4.2.0, Norav Medical Ltd., Israel). We determined the power spectrum within predefined frequency bands of interest: very-low- (<0.04 Hz), low- (0.04-0.15 Hz) and high-frequency (0.14-0.4 Hz) components, displayed in absolute values of power (milliseconds squared).

Transthoracic echocardiographic examination was performed on all patients and control subjects by using commercially available System Five echocardiography (GE Vingmed Ultrasound, Horten, Norway). All measurements were performed by the same cardiologist on frozen images from 3-5 cardiac cycles. All measurements were taken according to American Society of Echocardiographists recommendations[14].

Left ventricular (LV) ejection fraction was calculated using the Teichholz formula[15]. Tricuspid valve continuous-wave Doppler tracing of the tricuspid regurgitation flow was obtained and pulmonary artery (PA) systolic pressure was quantitated by adding the Bernoulli-derived pressure gradient to the estimated mean right atrial pressure[16]. The mean right atrial pressure was calculated according to the degree of collapse of the inferior vena cava with inspiration: 5 mm Hg for a collapse of at least 50 percent and 15 mm Hg for a collapse of less than 50 percent[17]. PHT was diagnosed if PA systolic pressure exceeded the upper limits of normal for age and body mass index-adjusted reference ranges[18].

Transcutaneous arterial oxygen saturation was determined by pulse oxymeter (Planar PL 1500, Beaverton, USA) in the sitting position with the oxygen saturation sensor on the right index finger.

The patients were divided into two groups regar-

Table 2: The Heart Rate Variability Parameters of the Sickle Cell Disease Patients and the Control Subjects

Parameters	SCD Patients	Control Subjects	p value
VLFP (ms^2)	194.7±131.9	220.3±144.5	0.536
LFP (ms^2)	190.7±73.3	142.1±67.9	0.02
HFP (ms^2)	194.8±91.2	314.5±88.3	<0.0001
LFP/HFP	1.26±0.8	0.64±0.7	<0.0001
Log VLFP (ms^2)	2.18±0.3	2.30±0.3	0.239
Log LFP (ms^2)	2.25±0.2	2.12±0.1	0.004
Log HFP (ms^2)	2.24±0.2	2.36±0.2	<0.0001
Log LFP / LogHFP	1.01±0.1	0.90±0.1	<0.0001

SCD: sickle cell disease, PHT: pulmonary hypertension, VLFP: very low frequency power, LFP: low frequency power, HFP: high frequency power

Table 3: The Heart Rate Variability Parameters of the Sickle Cell Disease Patients with and without Pulmonary Hypertension

Parameters	SCD Patients with PHT	SCD Patients without PHT	p value
VLFP (ms^2)	248.4±139.2	168.5±125.6	0.032
LFP (ms^2)	196.4±70.6	184.7±63.7	0.512
HFP (ms^2)	145.1±75.3	223.4±90.6	0.001
LFP/HFP	1.55±0.8	1.09±0.8	0.027
Log VLFP (ms^2)	2.34±0.3	2.10±0.2	0.004
Log LFP (ms^2)	2.26±0.2	2.24±0.2	0.647
Log HFP (ms^2)	2.12±0.2	2.31±0.2	<0.0001
Log LFP/LogHFP	1.07±0.1	0.98±0.1	0.007

SCD: sickle cell disease, PHT: pulmonary hypertension, VLFP: very low frequency power, LFP: low frequency power, HFP: high frequency power

ding the presence of PHT; 22 patients with PHT and 39 patients without PHT.

The study was approved by the local ethics committee and informed consent was obtained from the subjects, the parent(s), or both before the study.

All statistical analyses were performed using commercially available SPSS version 11.0. Because the resulting HRV spectral data had a nonlinear distribution, we transformed them into logaritmic values. Continuous variables are presented as mean ± SD. Statistical analysis was performed using unpaired student t test, Mann-Whitney U test and Chi-square test where appropriate. A P value <0.05 was considered statistically significant.

RESULTS

The SCD patients and control subjects were comparable with respect to age, sex, body mass index, heart rate, systolic and diastolic blood pressures (Table 1). The frequency of hydroxyurea therapy and blood transfusionsabove 10 units during lifetime were similar. However, respiratory rate was increased and hemoglobin and hematocrit levels were decreased in SCD patients compared with control subjects (p<0.0001). However, left atrial diameter, interventricular septum thickness, LV end-diastolic diameter (EDD), LV end-systolic diameter (ESD) and PA systolic pressure were increased in SCD patients compared with control subjects (P<0.05). There was no statistically significant difference in LV ejection fraction between SCD patients and control subjects. The arterial oxygen saturation was decreased in SCD patients compared with control subjects (P<0.01). Among SCD patients, there was no statistically significant difference in age, sex, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, LV ejection fraction, hemoglobin and hematocrit levels between SCD patients with PHT and SCD patients without PHT. The frequency of hydroxyurea therapy and blood transfusionsabove 10 units during lifetime were similar in two patient groups. However, left atrial diameter, interventricular septum thickness, LV EDD, LV ESD and PA systolic pressure were

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Figure 1: Low Frequency Power Values in Sickle Cell Disease Patients and Control Subjects

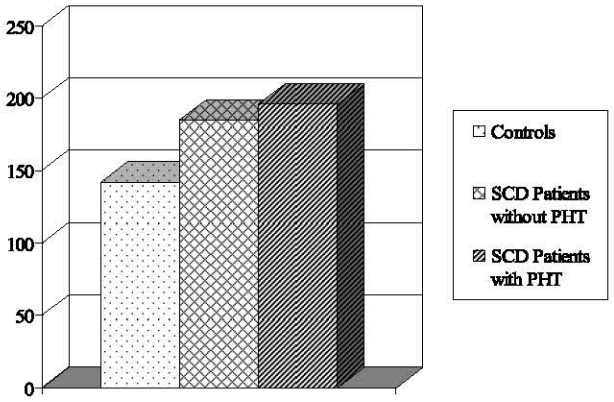


Figure 2: High Frequency Power Values in Sickle Cell Disease Patients and Control Subjects

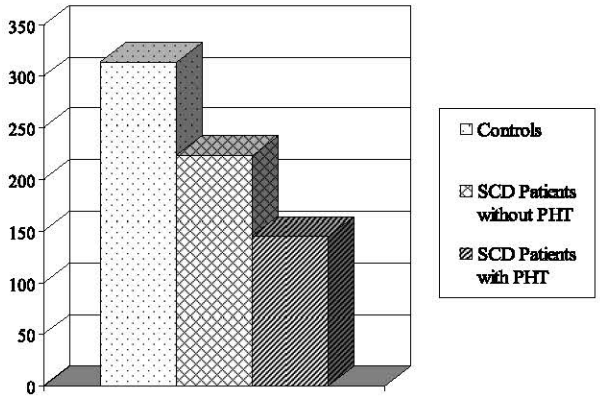
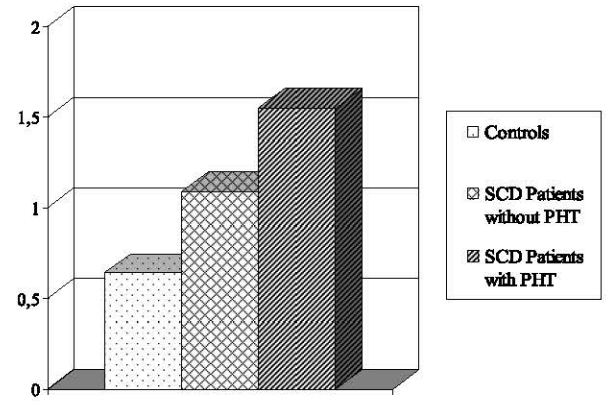


Figure 3: The Ratio of Low Frequency Power to High Frequency Power in Sickle Cell Disease Patients and Control Subjects



increased and hemoglobin F and arterial oxygen saturation levels were decreased in SCD patients with PHT compared with SCD patients without PHT (P<0.05).

The results for the HRV analysis of SCD patient groups and control subjects are shown in Table 2, Table 3, Figure 1, Figure 2 and Figure 3. There was no statistical difference in very low frequency power (VLFP) and LogVLFP between SCD patients and control subjects. Low frequency power (LFP), low frequency power to high frequency power ratio (LFP/HFP), LogLFP and LogLFP/HFP were increased in SCD patients compared to control subjects (p<0.05, Table 2). However, high frequency power (HFP) and LogHFP were decreased in SCD patients compared to control subjects (P<0.05).

The results in Table 3 show that VLFP, LFP/HFP, LogVLFP and LogLFP/HFP were statistically significantly higher in SCD patients with PHT than in SCD patients without PHT (p<0.05). However, HFP and LogHFP were significantly lower in SCD patients with PHT compared to SCD patients without PHT (p<0.05). There was no statistically significant difference in LFP and LogLFP between SCD patients with PHT and SCD patients without PHT.

DISCUSSION

HRV is a practical and noninvasive method for investigating the sympathetic and parasympathetic functions of the autonomic nervous system[8,9]. It is not dependent on patient's cooperation and is more sensitive than the conventional reflex tests of autonomic nervous system[19,20]. HRV is composed of several different frequencies power. Low-frequency power reflect the modulation of sympathetic and parasympathetic tones, whereas high-frequency power reflect pure parasympathetic tone[21,22]. Although the precise physiologic meaning of very-low-frequency power is not completely understood, it has been suggested that very-low-frequency power is influenced by thermoregulation, fluctuation in the renin-angiotensin system and function of peripheral chemoreceptors[23]. The decreased in HRV has been considered a marker for poor prognosis in some diseases and in the general population[10-13].

In literature, there are are several small studies have found decreased HRV in selected patients who have anemia[24-26]. However, our study is the first work which described a loss in HRV in young adult SCD patients compared with subjects with normal haemoglobin. Indeed, this is the first study which reported the decreased HRV in SCD patients with

PHT compared to SCD patients without PHT.

The main findings of the present study were that patients with SCD, even without clinical signs of cardiac functional involvement, have reduced LFP and HFP in patients with SCD compared with control subjects. These findings are in accordance with previous reports that indicating abnormal cardiovascular autonomic tests in SCD patients[26,27]. Romero Mestre JC et al. reported that 58.3% of SCD patients had cardiovascular autonomic dysfunction based on abnormal values for at least two cardiovascular autonomic function tests[28]. In another study conducted by Romero-Vecchione E et al. reported that SCD patients had a defective sympathetic activity of heart and arteries[27].

The lower values of LFP and HFP in SCD patients compared to control might suggest both lower sympathetic and vagal activity in the patient group. The higher LF/HF ratio found in SCD patients could suggest an impairment of sympathovagal balance mainly due to a lower autonomic parasympathetic activity. VLF values that are supposed to be affected by temperature regulation and humoral systems were not different between the patients with SCD and healthy controls.

The exact mechanism responsible for the decrease in HRV is not known. We think there are several pathophysiologic changes that might be responsible for decrease in HRV in SCD patients. In SCD, capillaries are often packed with sickled erythrocytes leading to microcirculatory alterations[28]. Microcirculatory changes could result in myocardial ischemia[29]. This hypothesis is supported by myocardial perfusion scintigraphy studies which have showed high incidence of perfusion abnormalities in patients with SCD[30,31]. Previous studies concerning HRV analysis in coronary artery disease have showed that HRV was effected in case of myocardial ischemia[32,33]. So, SCD associated myocardial ischemia may cause decrease in HRV. Furthermore, hypoxia could cause impairment in electrophysiological function of nerves[34]. Since the arterial oxygen saturation of our SCD patients was significantly lower than that of normal control, it seemed possible that chronic hypoxia might cause hypoxic damage to the nerve which in turn could lead to decreased cardiac sympathetic and vagal activity in SCD patients. In a previous study conducted by Stewart et al. have shown that subclinical parasympathetic autonomic neuropathy was a feature of hypoxic chronic obstructive pulmonary Disease and the degree of parasympathetic autonomic dysfunction correlated significantly with arterial partial pressure of O_2[34]. In the reports of Scalvini et al. and Stein et al. some indices of HRV mediated by parasympathetic tone or by both sympathetic and parasympathetic tone in chronic obstructive pulmonary Disease patients were found to be lower than those of the control subjects[35,36].

These studies suggested that the vagal activity of chronic obstructive pulmonary Disease patients was related to the oxygenation status of the patients. Furthermore, subclinical microvaso-occlusion of capillaries by sickled cells may occur in any part of the nervous system. These microvaso-occlusion also might cause autonomic dysfunction in SCD patients.

Previous studies have showed that HRV parameters were associated with LV mass[37]. As our patients with SCD had increased ventricular diameter and interventricular septum thickness compared with healthy controls, the HRV in our patients may be partially due to ventricular dilation and increased septum thickness. Postmortem studies have shown degenerative changes of myocardium and cardiac conduction system in SCD[38]. These degenerative changes may affect HRV as in the case of myocardial infarction[39].

PHT is a frequent complication of SCD[2,40]. Patients with PHT have a much higher mortality rate than those without PHT[40,41]. Our findings, decreased HFP and increased LFP/HFP ratio in SCD patients with PHT compared with patients without PHT were consistent with previous studies which documented that PHT had high mortality[40,42]. Autonomic dysfunction in patients with PHT may favor the development of arrhythmias and mortality[43,44].

We don't know the exact mechanisms responsible for the decrease of HRV in patients with PHT compared with patients without PHT. We suppose that the pathophysiological changes that decrease HRV could be more severe in SCD patients with PHT than SCD patients without PHT.

The HRV can be influenced by the medication of the patients and the circadian rhythm[45].

However, none of the patients in our study was on any medication that effect HRV and to minimize the potential impact of circadian rhythm HRV, the electrocardiography signals of all subjects were picked up at 3-4 p.m. in this study.

CONCLUSION

HRV is significantly decreased in SCD patients in a preclinical stage of heart disease, especially those with PHT. HRV may be particularly useful in early detection of PHT and differentiate the patients might be at risk for worse prognosis and high mortality. Fur-

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ther studies should be performed to clarify the mechanism of decreased HRV in SCD.

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