FREQUENCY DOMAIN INDICES OF HEART RATE VARIABILITY IN BETA THALASSEMIA MAJOR PATIENTS– A CROSS SECTIONAL STUDY

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ABSTRACT

Introduction and Objectives: Beta thalassemia is a hereditary haemolytic anaemia having overall prevalence of 3-4% in India. Appropriate therapy for this disease includes a regular monthly blood transfusion. Cardiac complications are the leading cause of death in these patients due to iron overload secondary to lifelong blood transfusions. The present study was undertaken to determine the Heart Rate Variability (HRV) in beta thalassemia major patients and to compare the mean values of frequency domain indices of heart rate variability in study and control group. **Material and Methods :** Present study was a cross sectional type of study and consisted of 50 normal subjects (control group) and 50 patients of beta thalassemia major (study group). HRV was recorded in both the groups with Medicaid Physiopac and HRV analysis was done using Kubois software version 2.1. Statistical analysis was done using Z test. **Results :** High frequency (HF) power in normalized units was reduced whereas Low frequency (LF) power in normalized units and LF/HF ratio were increased in beta thalassemia major patients as compared to control group and difference was found to be statistically significant (Z test). **Conclusion :** The present study shows that there is increased sympathetic activity and decreased parasympathetic activity in beta thalassemia major patients as compared to control group.

Key words : Beta thalassemia major, Heart rate variability, High frequency, LF/HF ratio, Low frequency.

Abbreviations : HRV, Heart Rate Variability; LF, High Frequency; Lower Frequency; HF

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INTRODUCTION

Thalassemia major is severe haemolytic anaemia that develops during the first year of life and requires life-long transfusion therapy for survival. The resultant iron overload causes severe damage of many organs [1,2]. A serious consequence of iron deposition is cardiotoxicity which is the leading cause of death among these patients. A few studies have documented initial cardiovascular dysfunction even in thalassemia major patients without clinical manifestation of heart failure [3,4].

The term Heart Rate Variability (HRV) conventionally describes the beat to beat fluctuations in the heart rate or the variations in consecutive R-R intervals. Analysis of HRV is a sensitive non-invasive tool for the assessment of cardiac autonomic regulation via sympathetic and parasympathetic nervous system. HRV analysis involves time domain and frequency domain parameters. Low frequency (LF) reflects the interaction of both sympathetic and parasympathetic nervous system whereas high frequency (HF) reflects solely the activity of the parasympathetic nervous system and LF/HF ratio is accepted as an indicator of sympathovagal balance [5].

Decreased power in the heart rate power spectrum is predictive of mortality [6]. In high risk patients, a persistent sympathetic activation and a reduced vagal tone may determine a marked reduction in dynamic complexity of heart rate fluctuations that would make heart period less adaptable and less able to cope up with the requirements of a continuously changing environment [7]. Accumulating evidence suggests that anemia may be an independent risk factor for mortality among patients with heart failure.[8] In prospective studies by Kardelen et al [9] and De Chiara et al,[10] no evidence of abnormal echocardiographic finding was shown in thalassemia major patients with reduced HRV. Therefore, a significantly reduced HRV could be an early indicator of preclinical stage of heart disease in thalassemia major patients and thus HRV might be used to assess cardiac involvement in them due to its easy access and much lower cost [11].

Thus the present study was designed to detect relationship between heart rate variability and beta thalassemia major patients receiving regular blood transfusion with or without iron chelation therapy.

STUDY DESIGN

The study design involved 100 individuals who were divided into two groups of 50 normal subjects (control group) and 50 patients of beta thalassemia major (study group) receiving regular blood transfusions between the age group of 8 to 20 years involving both, males and females. Patients with concomitant sickle cell anaemia or with associated congenital or acquired heart disease, diabetes mellitus, thyroid disorders or any other endocrine disorder or on long term medications for any other chronic disease were excluded from the study.

MATERIALS AND METHODS

The present study was a cross sectional type of study conducted in the Department of Physiology and Department of Paediatric Medicine, Grant Government Medical College, Mumbai and in the Thalassemia unit of St. George Hospital, Mumbai. Before commencement of the project, approval was taken from the Institutional Ethical Committee.

Written informed consent was taken before the clinical examination of the subject. The subjects were asked to refrain from ingesting any beverages containing caffeine and alcohol for at least 12 hours prior to the study. They were asked to report between 10 a.m to 12 p.m. in the Physiology lab after an adequate night's sleep followed by light breakfast. The subject was allowed to relax on a bed in supine position for 10 minutes and then ECG recording was done for 5 minutes in supine position using "Physiopac" by "Medicaid". The recordings of ECG of all subjects were done by the same person in order to avoid any inter-observer error. Data collected on Physiopac was analysed by Kubois software, Version 2.1.

Statistical analysis of the observations was carried out using SPSS software version. The data was expressed in terms of mean and standard deviation and statistics was determined using Z test. Statistical significance was tested at 5% & expressed in terms of 'p' value with $p<0.05$ as statistically significant.

RESULTS

Comparison of general growth parameters between study group and control group is as shown in table 1. The mean Body mass index (BMI) was 17.0152±3.2167 and 18.0585±3.7425 kg/m^2 in the study and control group respectively.

Table 1 : General growth parameters

	Study group (MEAN±S.D)	**Control group (MEAN±S.D)**
Mean age (yrs)	13.42±4.43	14.84±3.92
Mean height (cm)	133.45±16.271	148.61±18.052
Mean weight (kg)	31.05±10.908	41.1±13.892
Mean BMI (kg/m^2)	17.0152±3.2167	18.0585±3.7425

(BMI – Body mass index)

Mean resting heart rate of study and control groups was 101.30±11.48 and 83.97±11.48 beats per minute respectively and the difference was statistically significant (Table 2). High frequency power in normalized units was lower in β thalassemia major patients whereas low frequency power in normalized units and LF/HF ratio were increased in thalassemics and the difference was found to be statistically significant (Table 2).

Table 2 : HRV analysis using Kubois software, version 2.1 (mean ± S.D.) & Statistical analysis using 'Z' test

Parameters	**Study group (MEAN± S.D)**	**Control group (MEAN± S.D)**	**P value**	**Significance**
HR(/m	101.302	83.9728	<0.000	Statist

in)	±11.48754	6±11.48754	1	ically significant
LF(n.u.)	67.288±9.111322	52.506±7.378773	<0.0001	Statistically significant
HF(n.u.)	32.96939±9.111322	47.39592±7.378773	<0.0001	Statistically significant
LF/HF Ratio	2.282265±1.012221	1.162878±0.349402	<0.0001	Statistically significant

(HR – heart rate, LF – low frequency, HF – High frequency, n.u. – normalised units)

DISCUSSION

The present research was undertaken to study the heart rate variability in beta thalassemia major patients. In the present study resting heart rate of study group was higher than control group and the difference was statistically significant. This is in accordance with the study done by Lakhotia et al[12], who suggested that anaemic patients have lower basal parasympathetic outflow resulting in the increase in heart rate as a compensatory mechanism to hypoxia. Increase in heart rate may be also because of increased in sympathetic activity as shown by Yokusoglu et al[13]. He observed that in patients with iron deficiency anaemia the parasympathetic activity decreases, whereas sympathetic activity increases and this autonomic imbalance lead to altered electrophysiological activity of the heart . The increase in sympathetic activity is due to the decreased levels of haemoglobin leading to hypoxia, which is sensed through carotid bodies[14].

In contrast, Veglio et al [15],observed lower heart rates and diminished sympathetic activity in anaemic patients with thalassemia major as indicated by lower plasma norepinephrine levels compared with the control group. Also Spirito et al [16] reported that there were no differences in heart rates in thalassemia cases when compared with controls.

High frequency power in normalized units was significantly reduced in beta thalassemia major patients. Low frequency power in normalized units and LF/HF ratio, a marker of sympathovagal balance were significantly increased in thalassemics. Our findings are in accordance with the findings of Jyotsna et al who had shown that the total power, low frequency and high frequency power in absolute terms, high frequency power in normalized units were significantly reduced in beta thalassemia major patients (p value <.001). Low frequency power in normalized units and LF/HF ratio were significantly increased in thalassemics (p value<.001) [17].

Our study is also in correlation with the studies done by Rutjanaprom et al [18] and Franzoni et al [19] who showed that frequency domain HRV parameters in the thalassemia major group were significantly lower than control groups. It is also supported by Kumfu et al [20] who showed that LF／HF ratio in thalassemic mice was higher than those in the wild type.

The HRV findings of this study indicate that parasympathetic activity is decreased whereas sympathetic activity is increased in the study group as compared to control group [5]. Apart from chronic anaemia this may also be due to transfusional iron overload which may lead to deposition of iron in cardiac myocytes and myocardial fibrosis causing heterogeneous ventricular depolarization leading to abnormal excitability of iron loaded heart cells [19].

Iron overload cardiomyopathy (IOC) results from the accumulation of iron in the myocardium, and it is the leading cause of death in patients receiving chronic blood transfusion therapy [21]. Cardiac magnetic resonance T2* (CMR T2*) has become a widely used tool for its accurate and non-invasive technique to measure iron deposition in heart [22]. However its usage is currently limited because of its cost and availability. Therefore cardiacT2 MRI might not be a practical method for early detection of cardiac iron status in thalassemia major patients in developing countries [23].

Serum ferritin has also been used for decades as a predictor of iron overload status in clinical

practice due to its strong correlation with hepatic iron [24,25] , representing an indirect index for estimating the total body iron stores. It is inexpensive and accessible worldwide. However increased level of serum ferritin is not specific to iron overload condition since its level can also be increased in other conditions such as inflammation, collagen diseases, hepatic diseases, and malignancy [26].

It has been documented that adequate medical therapy can reverse IOC when it is diagnosed before end-stage heart failure occurs [27]. Thus HRV can be used as an alternative approach to assess cardiac involvement for early detection of IOC.

CONCLUSION

Our study showed increased sympathetic activity and decreased parasympathetic activity in study group as compared to control group and the difference was found to be statistically significant. This may be because of chronic anaemia and cardiac autonomic dysfunction secondary to iron overload cardiomyopathy due to repeated blood transfusion which remains the main stay of treatment in patients of thalassemia major. HRV being simple and non-invasive technique could be used in screening of beta thalassemia major patients for early detection of iron overload cardiomyopathy resulting in cardiac autonomic dysfunction.

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