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Research Article

HEART RATE VARIABILITY ANALYSIS IN PATIENTS WITH BETA THALASSEMIA MAJOR

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ABSTRACT
Cardiac complication is one of the major causes of death in patients of thalassemia major. Heart rate variability (HRV) is a non invasive index of neural modulation of heart rate. In this hospital based observational study 30 patients of beta thalassemia major age matched with control subjects, free of any signs of cardiovascular disease were evaluated for HRV. All cases and controls underwent recording of impedance peripheral pulse in the right forearm for five minutes. All frequency and time domain parameters were significantly lower in the study group than the control group ($p<0.001$).

Key Words: *Heart Rate Variability, Thalassemia Major*

INTRODUCTION
Beta (β) Thalassemia is an inherited disorder of hemoglobin synthesis of β chain of globin molecule resulting in chronic hemolytic anemia and requiring life long blood transfusion therapy for survival Shrier (1997). Cardiac complications represent the leading cause of mortality in patients of thalassemia major Borgna *et al.,* (1998). Cardiac involvement in thalassemia patients is generally characterized by iron induced ventricular dysfunctions leading to heart failure Ehlers *et al.,* (1980); Spirito *et al.,* (1990) and Hahalis *et al.,* (2005).

Before the introduction of iron chelation therapy, iron overload from transfusions was a frequent cause of morbidity and mortality in thalassemia patients Engle (1980). Death was often due to cardiac failure which typically began before the patient reached 20 years of age. Iron chelation therapy begun early in life prolongs survival without cardiac disease Olivieri *et al.,* (1994).

Heart rate variability is a non invasive electrocardiographic marker reflecting the activity of sympathetic and vagal components on the sinus node of the heart. In a normal heart with an integer ANS there will be continuous physiological variations of the sinus cycles reflecting a balanced sympathovagal state and a normal HRV Ravenswaaij *et al.,* (1993). In a damaged heart, the changes in the activity of afferent and efferent fibers of ANS and in the local neural regulation will contribute to the resulting sympathovagal imbalance reflected by a diminished HRV. 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 Goldberger (1996) and Bigger *et al.,* (1996).

MATERIALS AND METHODS
30 β thalassemia major patients, age ranging between 5-20 yrs of both sexes were recruited from thalassemia day care center of S.M.S. Hospital, Jaipur. 23 healthy control subjects, ages matched were selected from amongst the children of S.M.S. Medical College staff and students. The study was performed on the day prior to receiving of blood transfusion in the morning between 10a.m. to 12 noon. The study was approved by institutional ethical committee. Written informed consent was obtained from parents of all patients and from patients above 18 yrs of age. The inclusion criteria for patient selection were, confirmed TM patients receiving blood transfusion. Exclusion criteria were, patients having any acute or chronic illness, patients receiving medication which may affect autonomic functions and patients

having symptoms and signs of heart disease as assessed clinically, by routine laboratory profile and echocardiography.

Heart Rate Variability Measurement

Impedance peripheral pulse in the right forearm was recorded in the supine posture for 5 minutes after 5 minutes of supine rest in a quiet environment at a room ambient temperature of 24-25^{0}C, breathing quietly with eyes closed. The detection of impedance peripheral pulse was digitally done by Medical Analyzer, Non Invasive Vascular Monitor (Nivomon).

The frequency domain parameters of HRV viz total power(TP), high frequency(HF)power, low frequency (LF)power in absolute and normalized units, and LF/HF ratio were analyzed using fast fourier transform (FFT).The time domain parameters used in the analysis of HRV were the standard deviation of all normal R-R intervals (SDNN),square root of mean of sum of the squares of differences between adjacent R-R intervals (RMSSD), and percentage of NN50 count of all R-R intervals (PNN50) (Task Force, 1996).

Numerical data are presented as mean±SD. Statistical analysis was performed using Microsoft excel software, Microsoft corporation USA 2003.Comparison of HRV indices between the two study groups was evaluated using 'Z' test for equality of variance. Statistical significance was assigned at $p<0.05$.

RESULTS CONCLUSION

The analysis of heart rate variability might be helpful to detect cardiac complications in the preclinical stage of cardiac involvement. Total power, low frequency and high frequency power in absolute terms, high frequency power in normalized units were significantly reduced in β thalassemia major patients (p value <.001).Low frequency power in normalized units and LF/HF ratio, a marker of sympathovagal balance were significantly increased in thalassemics (p value<.001).The time domain parameters viz SDNN, RMSSD, PNN50 were also significantly reduced in thalassemics. (p value<.001)(Table 1).

Table 1: Comparison of mean of various parameters of HRV between control and thalassemia patients by 'Z' test

S.N.	Parameters	Mean±S.D Cases (n=30)	Control (n=23)	p Value	Significance
1	Total Power (ms^2)	382.30±178.52	1768±995.89	<.001	HS
2	LF Power (ms^2)	104.53±59.22	313.15±186.34	<.001	HS
3	HF Power (ms^2)	61.10±51.57	713.63±442.27	<.001	HS
4	LF/HF ratio	2.27±1.20	0.49±0.19	<.001	HS
5	LFnu (%)	65.88±10.25	31.68±8.16	<.001	HS
6	HFnu (%)	34.11±10.25	68.10±8.53	<.001	HS
7	SDNN (ms)	0.033±0.01	0.064±0.02	<.001	HS
8	RMSSD (ms)	0.03±0.02	0.071±0.03	<.001	HS
9	PNN50 (%)	0.05±0.05	0.32±0.15	<.001	HS

***LF** – Low frequency, **SDNN** – Standard deviation of R-R intervals over the selected time interval, **HF** – High frequency, **RMSSD** – Square root of mean of sum of the squares of differences between, **Nu** – Normalized unit, adjacent RR intervals, **PNN50** – percentage of NN50 count of all R-R intervals*

DISCUSSION

The reduced HRV expression in β thalassemia major patients can be interpreted as evidence of early cardiac autonomic neuropathy in these patients.

The Total power and SDNN are indicators of both sympathetic and parasympathetic activity. The HF Power, RMSSD and PNN50 values are reliable indicators of parasympathetic activity. LF Power and LF/HF ratio provides an adequate reflection of sympathetic activity. Reduced HRV which reflects both sympathetic and parasympathetic activities predict increased risk for subsequent cardiac events.

The reduced HRV expression and impaired sympathovagal balance may be explained by chronic anemia which leads to a persistent sinus tachycardia and a sustained decrease in autonomic fluctuations. The expansion of blood volume during transfusion could represent an uncontrolled stimulation of cardiac receptors with sympathetic afferents leading to a further decrease in vagal modulation of heart rate Veglio *et al.,* (1998). It could also be explained by transfusional iron overload which may lead to deposition of iron in cardiac myocytes and myocardial fibrosis causing heterogeneous ventricular depolarization causing abnormal excitability of iron loaded heart cells Franzon *et al.,* (2004).

An increase in the cellular iron content is also believed to drive an increase in the formation of OH^- radical, a highly reactive oxygen species (ROS) from H_2O_2 which is suggested to be the main cause of damage associated with iron overload Weinberg (1990). Thus chronic iron overload may lead to development of cardiomyopathy manifested by ventricular arrhythmias and heart failure.

Thus our observations indicate that reduced HRV parameters which reflect impaired activity of both sympathetic and parasympathetic nervous system, predict increased risk for subsequent cardiac events in young β thalassemia major patients.

Quantification of myocardial iron content using magnetic resonance imaging is costly and not widely available. Therefore all β Thalassemia major patients should be screened for cardiac autonomic dysfunctions using heart rate variability analysis. Regular iron chelation therapy in young β thalassemia major patients may predict a better outcome.

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