Influence of Advancing Age on Heart Rate Variability in Beta Thalassemia Major Patients Receiving Blood Transfusions.

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ABSTRACT

The purpose of this study was to evaluate the effect of advancing age on heart rate variability (HRV) in beta(β) thalassemia major(TM) patients receiving regular blood transfusion in a hospital based comparative observational study. Day care center of S.M.S.Medical College and Hospital, Jaipur. A total of 51 confirmed beta thalassemia major patients in the age range 5-19 years were examined and the grouping was done on the basis of age. They had no symptoms and signs of cardiovascular disease as assessed clinically and by chest radiograph, routine laboratory profile and echocardiography. All patients underwent recording of impedance peripheral pulse in the right forearm for five minutes. All frequency domain HRV parameters were found to be reduced as age advanced in thalassemia patients who received regular blood transfusion. Regular iron chelation therapy along with regular blood transfusion may help/ delay iron overload which may influence cardiac autonomic balance affecting Heart rate variability.  

Keywords: Heart rate variability, thalassemia major, low frequency, high frequency.

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INTRODUCTION

Beta (β) Thalassemia is an inherited disorder of hemoglobin synthesis of β chain of globin molecule resulting in chronic hemolytic anemia [1] and requiring lifelong blood transfusion therapy for survival.

Cardiac complications represent the leading cause of mortality in patients of thalassemia major [2]. Cardiac involvement in thalassemia patients is generally characterized by iron induced ventricular dysfunctions leading to heart failure [3-5]. Before the introduction of iron chelation therapy iron overload from transfusions was a frequent cause of morbidity & mortality in thalassemia patients [6]. Iron chelation therapy begun early in life prolongs survival without cardiac disease [7].

Heart rate variability is a non invasive electrocardiographic marker reflecting the activity of sympathetic & 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 & a normal HRV [8]. In a damaged heart, the changes in the activity of afferent & efferent fibers of ANS & 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 & a reduced vagal tone may determine a marked reduction in dynamic complexity of heart rate fluctuations that would make heart period less adaptable & less able to cope up with the requirements of a continuously changing environment [9, 10].

MATERIAL & METHODS

A total of 51 β thalassemia major male patients, age ranging between 5-19 yrs were recruited from thalassemia day care center of S.M.S. Hospital, Jaipur. They were divided into three groups(5-9yrs,10-14yrs,15-19yrs) They were receiving regular blood transfusion at an interval of three weeks without iron chelation therapy. The study was performed on the day prior to receiving of blood transfusion. Written informed consent was obtained from parents of all patients & 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.

Group I- patients receiving regular blood transfusion in the age range 5-9 yrs.
Group II-patients receiving regular blood transfusion in the age range10-14yrs.
Group III- patients receiving regular blood transfusion in the age range15-19yrs.

The study was approved by the institutional ethical committee.
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°C, breathing quietly with eyes closed. The detection of impedance peripheral pulse was digitally done by Medical Analyzer, Non Invasive Vascular Monitor, and (Nivomon).

The frequency domain parameters of HRV viz Total Power (TP), High frequency (HF) Power, Low frequency (LF) Power, Low frequency normalized units (Lfnu), High frequency normalized units (HFnu) were analyzed using fast fourier transform (FFT) (Task Force, 1996) [11]. All parameters are presented as mean±SD. A ‘p’ value less than 0.05 was considered statistically significant.

Statistical analysis:

Numerical data are expressed as Mean±S.D. Statistical analysis was performed using Microsoft excels software 2003 and statistical software primer version 6. Comparison between the groups was done by one way Anova test.

RESULTS

Total power, low frequency & high frequency power in absolute terms decreased from group I to group III. High frequency power in normalized units also decreased from group I to group III. Low frequency power in normalized units & LF/HF ratio, a marker of sympathovagal balance were increased from group I to group III.

(Table I) Comparison between the three groups by applying one way Anova Test showed a ‘p’ value highly significant for Total Power, Low frequency absolute power, Significant ‘p’ value for high frequency absolute power, low and high frequency normalized units and not significant ‘p’ value for LF/HF ratio (Table II)

Table 1: Comparison of Mean of various frequency domain parameters of Heart Rate Variability in different age groups of Beta Thalassemia major Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>5-9 years(n=17) mean±SD</th>
<th>10-14 yrs(n=17) mean±SD</th>
<th>15-19 yrs(n=17) mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Power (ms²)</td>
<td>2907±1830.36</td>
<td>1652.12±1794.61</td>
<td>437.07±231.97</td>
</tr>
<tr>
<td>LF Power (ms²)</td>
<td>607.78±467.79</td>
<td>321.73±297.53</td>
<td>131.14±105.83</td>
</tr>
<tr>
<td>HF Power (ms²)</td>
<td>875.38±565.67</td>
<td>663.14±896.06</td>
<td>88.57±75.71</td>
</tr>
<tr>
<td>LF nu(%)</td>
<td>43.97±14.44</td>
<td>48.90±22.18</td>
<td>61.92±8.73</td>
</tr>
<tr>
<td>HF nu(%)</td>
<td>56.03±14.44</td>
<td>51.10±22.18</td>
<td>38.08±8.73</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>0.93±0.57</td>
<td>1.65±1.73</td>
<td>1.79±0.78</td>
</tr>
</tbody>
</table>
Table 2: Inter age group comparison of various frequency domain parameters of Heart rate variability by one way Anova test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>F value</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Power</td>
<td>11.058</td>
<td>0.001</td>
<td>HS</td>
</tr>
<tr>
<td>LF Power</td>
<td>8.672</td>
<td>0.0006</td>
<td>HS</td>
</tr>
<tr>
<td>HF Power</td>
<td>7.047</td>
<td>0.002</td>
<td>Sig</td>
</tr>
<tr>
<td>LF nu</td>
<td>5.314</td>
<td>0.008</td>
<td>Sig</td>
</tr>
<tr>
<td>HF nu</td>
<td>5.314</td>
<td>0.008</td>
<td>Sig</td>
</tr>
<tr>
<td>LF/HF Ratio</td>
<td>2.645</td>
<td>0.081</td>
<td>NS</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The reduced HRV expression in β thalassemia major patients who received regular blood transfusion but no iron chelation therapy could be interpreted as evidence of early cardiac autonomic neuropathy.

The Total power is indicator of both sympathetic & parasympathetic activity. The HF Power is reliable indicator of parasympathetic activity. LF Power & LF/HF ratios provide an adequate reflection of sympathetic activity. Reduced HRV which reflects both sympathetic & parasympathetic activity predict increased risk for subsequent cardiac events.

The reduced HRV expression & impaired sympathovagal activity may be explained by chronic anemia which leads to a persistent sinus tachycardia & a sustained decrease in autonomic fluctuations.

It is evident from our observations that patients who received regular blood transfusion but no iron chelation therapy, with advancing age showed reduced HRV parameters which supports the explanation that deposition of iron in cardiac myocytes & myocardial fibrosis may cause heterogeneous ventricular depolarization & could lead to abnormal excitability of iron loaded heart cells [12].

It has been reported that iron reduces the number of functional cardiac sodium channels & enhances the inactivated state of functional channels causing reduction in overshoot of cardiac action potential in iron loaded cardiac myocytes [13]. Iron has been reported to produce peroxidative damage to DNA [14] & also damages membrane lipids & proteins [15, 16]. In cultured rat cardiomyocytes invitro treatment with iron altered membrane fatty acids & suppressed mitochondrial respiratory enzymes with a concomitant reduction in cellular ATP [17, 18].

The decrease in ATP might alter phosphorylation of Sodium channel protein which affects steady state inactivation & recovery from inactivation [19, 20].

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 H2O2 which is suggested
to be the main cause of damage associated with iron overload [21]. This is also thought to be one of the main mechanisms by which iron overload leads to heart impairment [22, 23].

Thus chronic iron overload may lead to development of cardiomyopathy manifested by ventricular arrhythmias & heart failure. Iron loaded cardiomyocytes may have an abnormal excitability reflected as altered HRV as evidenced by this study. Thus our observations indicate that reduced HRV parameters which reflect impaired activity of both sympathetic & parasympathetic nervous system, predict increased risk for subsequent cardiac events in young β thalassemia major patients.

The deposition of iron in cardiac myocytes leading to cardiac autonomic dysfunction can result into sudden appearance of arrhythmias & may prove fatal.

Quantification of myocardial iron content using magnetic resonance imaging is costly & not widely available. Therefore all β Thalassemia major patients should be screened for cardiac autonomic dysfunctions using heart rate variability analysis to detect cardiac complication in the pre clinical stage of cardiac involvement.

REFERENCES